Malignant Transformation of Liver Cysts Into Cholangiocarcinoma During Follow-up: Potential Dangers of Liver Cysts

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Case Report

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Abstract

Background: The liver cyst is a common disease in hepatobiliary surgery. Most patients have no apparent symptoms and are usually diagnosed accidentally during imaging examinations. The vast majority of patients with liver cysts follow a benign course, with very few serious complications and rare reports of malignant changes.

Case Presentation: We present two cases of liver cysts that evolved into intrahepatic tumors during the follow-up process. The first patient had undergone a fenestration and drainage operation for the liver cyst, and the cancer was found at the cyst's position in the third year after the procedure. Microscopically, bile duct cells formed the cyst wall. Tumor cells can be seen on the cyst wall and its surroundings to form adenoid structures of different sizes, shapes, and irregular arrangements, some of which are arranged in clusters. The second patient was regularly rechecked after discovering liver cysts, and a new mass appeared very close to the cyst. The clinical manifestations and laboratory examinations of the two patients lacked specificity, the preoperative diagnosis was unclear, and the postoperative pathology confirmed cholangiocarcinoma.

Conclusions: Our cases indicate that liver cysts may lead to the occurrence of malignant intrahepatic cholangiocarcinoma. Therefore, follow-up of particular liver cysts is necessary, and the differential diagnosis of the intrahepatic cystic tumors needs to include cholangiocarcinoma.

Introduction

The simple liver cyst is a common disease in hepatobiliary surgeons' daily clinical practice, with a reported incidence ranging from 2.5–18%(1, 2). Most patients with liver cysts are asymptomatic, and their cysts are usually found accidentally after imaging examinations. Generally recommended such patients for clinical observation without intervention(3). Some patients with symptoms are mostly caused by cysts compressing surrounding tissues. Other liver cysts complications include obstruction of inferior vena cava or common bile duct, portal vein occlusion and varices, intracystic hemorrhage, cyst rupture, and infection(4). The clinical course of almost all liver cysts is benign. Reports of malignant transformation of simple liver cysts are extremely rare. In this study, we reported two cases of cholangiocarcinoma, they were initially found to have simple liver cysts. During the observation period, examination revealed a tumor that grew at the location of the cysts. To the best of our knowledge, only a few cases of cholangiocarcinoma closely related to liver cysts were reported in English literature(5–8). The present report is the first to describe the malignant change of simple liver cysts that became cholangiocarcinoma during follow-up.

Case Presentation

Case 1

A 64-year-old woman sought medical care in September 2020 due to abdominal swelling in the upper right abdomen for one week. She reported a history of liver cysts and received cysts fenestration and drainage three years ago. On admission, no positive result of the abdominal examination. Liver function, blood coagulation, and tumor markers are all normal. Computed Tomography(CT) showed a slightly lower density nodule located in the left inner lobe. MRI revealed the mass with noticeable enhancement in the arterial phase and no decrease in the degree of enhancement in the delayed phase. We traced the patient's previous examinations and found that the site of the left inner lobe mass was once two liver cysts. CT image in July 2017 showed several low-density nodules in the left inner lobe (Fig. 1). These cysts had undergone fenestration surgery three years ago.

During the operation, the mass was located at the edge of the left inner lobe, below the sickle ligament, partly protruding from the liver capsule, and the surrounding adhesions were prominent. Found liver blood vessels to be tortuous and dilated, considering that large-scale resection may lead to uncontrollable bleeding, surgeons performed local tumor resection. Open the resected liver tissue, the mass was gray and white(Fig. 2). Pathological results confirmed the tumor was cholangiocarcinoma(Fig. 3). The patient received Lenvatinib treatment after surgery and not found significant recurrence in the follow-up.

Case 2

In August 2017, a 65-year-old woman came to Zhongnan Hospital of Wuhan University for a medical examination. The patient reported a history of liver cysts. Abdominal CT revealed multiple cysts in the liver, the maximum diameter is 4.2cm×3.6cm, with no other abnormalities. The patient regularly reviewed in our hospital since then. Re-examination in August 2019 showed that the cyst had increased to 4.9cm×4.5cm, no malignant lesions were found. In September 2020, the abdominal CT demonstrated a new solid lesion adjacent to the anterior cysts(Fig. 1).

On admission, physical examination touched the enlarged liver 2cm below the costal margin without tenderness. Hematology analysis revealed normal blood coagulation and liver function, the patient also had normal levels of AFP and CEA, but the levels of CA125, CA153 and CA19-9 were elevated. Enhanced MRI of liver tumor-specific contrast demonstrated a lobular cystic, solid mass in the lower right posterior lobe. Positron emission tomography(PET/CT) considered the lesion a malignant tumor(Fig. 1).

The tumor was found in the lower right posterior lobe at surgery and had adhesion to the lateral peritoneum. It was removed successfully under ultrasound positioning. The resected tumor was a solid cystic mass, the inner wall of the cavity is gray and smooth, the solid mass is grayish-white and dark-yellow in section, with a slightly stiff texture(Fig. 2). Fibrous tissue hyperplasia in the remaining liver tissue's portal area is accompanied by chronic inflammatory cell infiltration. The pathology report revealed a diagnosis of poorly differentiated cholangiocarcinoma. Immunohistochemistry showed positivity for CK7 and CK19(Fig. 4). The patient developed lung metastasis two months after the operation and subsequently received immunization and targeted therapy. Her condition has improved, and she is still alive. The clinical characteristics of the two cases are shown in Table 1.

Table 1
The clinical characteristics of the two cases.

	Case 1	Case 2
Gender	Female	Female
Age, years	64	66
Adjacent Cyst Size, cm	6.8×6.8	4.8×4.3
Cyst Number	> 3	> 3
AST/ALT,U/L	33/27	40/28
TBIL/DBIL, μmol/L	17.0/3.0	9.2/1.7
PT/APTT, sec.	12.3/40.3	12.5/28.4
AFP/CEA, ng/ml	5.90/3.05	1.63/5.98
CA125, U/mL	13.0	675.00
CA153, U/mL	10.3	38.22
CA19-9, U/mL	< 2.00	2865.00
Tumor Size, cm ³	5×3.6×3.4	7×6×4.5
Tumor Number	Single	Single
Tumor Location	S4	S6
Immunohistochemistry		
AFP	-	+
Arginase	-	-
CD34	-	-
CK7	+	+
CK19	+	+
Glypican-3	-	-
Hepatocyte	-	-
<i>Supplement</i>	MUC1(+),HSP70(+)	Ki-67(Positive rateAbout70%)
Portal Vein Invasion	-	-
Splenomegaly	-	-

*Both patients had no history of alcohol consumption, estrogen use, hepatolithiasis, and history of hepatitis B and/or hepatitis C infection.

	Case 1	Case 2
Treatment	Surgery&Immunotherapy	Surgery&Immunotherapy
Outcome	No progress after operation, survival	Postoperative lung metastasis, survival with tumor
*Both patients had no history of alcohol consumption, estrogen use, hepatolithiasis, and history of hepatitis B and/or hepatitis C infection.		

Discussion

The simple liver cyst is a type of non-parasitic liver cyst (NPLC). NPLC also includes traumatic liver cysts such as serous hematoma and neoplastic liver cysts such as intraductal papillary neoplasm of the bile duct (IPNB), mucinous cystic neoplasm of the liver (MCN-L), biliary hamartomas, and biliary cystadenoma. Besides, infectious liver cysts, Caroli disease, and Polycystic liver disease (PCLD) are all intrahepatic cystic diseases. Among these diseases, IPNB, MCN-L, biliary cystadenoma, and Caroli disease have been reported to have cancer risk, IPBN and MCN-L are considered precancerous lesions of intrahepatic cholangiocarcinoma(9).

Simple liver cysts are considered to be congenital abnormalities in the development of liver structures. They seem to have an origin over biliary ducts that have not undergone involution, and that by slowly dilating produce the cystic lesions, the cysts do not communicate with the bile duct(10). Reports of malignant transformation of simple liver cysts are infrequent. *Azizah, N. and F.J. Paradinas* reported two simple cysts and adenocarcinoma cases to coexist closely in the liver, the authors believe that the two patients are cholangiocarcinoma through multi-angle comparison and proposed that cystadenocarcinoma and cholangiocarcinoma coexisting with simple cysts should be treated as two separate concepts. They also cited several other similar cases in the article. Due to the age of publication, it is difficult to determine the specific circumstances of these cases(5). *Kokubo, T. et al.*, and *Lee, S.K. et al.* respectively reported two cases of intrahepatic cholangiocarcinoma with liver cysts, but these two patients were considered as tumors causing cystic degeneration, which were not the same as the situation in this report(6, 7). A patient-reported by *Kaneko, T. et al.* was initially diagnosed with a giant liver cyst, the tumor progressed rapidly after puncture and drainage. This case was considered to be a cholangiocarcinoma in the form of a cyst(8). The conditions of the above patients with cholangiocarcinoma all show the characteristics of high correlation with liver cysts, but it is still challenging to determine the occurrence sequence of tumor and cyst.

Our first case had undergone cyst fenestration and drainage for liver cysts. The third year after the operation, a tumor was found at the cyst site where the fenestration was once, and the excised tumor showed cholangiocarcinoma. Another case was found to have liver cysts many years ago and insisted on re-examination. Her condition progressed to a neoplastic lesion within a year. She was diagnosed with cystadenocarcinoma before the operation, and the pathological result was eventually confirmed as cholangiocarcinoma. We have not found similar liver cysts progression reports to intrahepatic

cholangiocarcinoma in the available published English literature. Only sporadic reports of other pathological malignancies developed from liver cysts: *Hayashi I. et al.* showed a mucoepidermoid carcinoma arising from a preexisting cyst of the liver(11), *Ameriks J. et al.* reported a case of malignant nonparasitic cyst of the liver, but the specific pathological type has not been determined(12), other reports showed that liver cysts can developed into cystadenocarcinoma(13, 14). Besides, *Xiao, J. et al.* showed a case of hepatic squamous cell carcinoma(SCC) with liver cysts in a study on the liver's primary SCC. In their article, the authors list chronic inflammation of the congenital cysts of the liver cysts associated with infection and/or stones as one of the causes of malignant transformation(15). The continuous stimulation of chronic inflammation leading to malignant transformation may also serve as an explanation for the course of our patients. The lesion may be caused by the constant compression of the cysts on the surrounding bile ducts. Another possible hypothesis is that the tumor originated from the cyst's lining and showed a pattern of intracystic hyperplasia, such cysts may have cellular components derived from the bile duct.

Among the risk factors for the onset of cholangiocarcinoma, the bile-duct cyst is an established high-risk factor(16, 17). Previous studies have shown that choledochal cysts are the most relevant among many high-risk factors for cholangiocarcinoma, The incidence of malignant biliary tumors arising from choledochal cysts ranging from 2.5–26%(17, 18). Reflux of pancreatic enzymes, bile stasis, and increased concentration of intraductal bile acids are thought to play an essential role in the carcinogenesis of the biliary tract(19). This possibility does not seem to exist in our cases. In our cases, the cysts were located at the hepatic hilum's distal end, and there was no prominent bile component. Our cases' condition seems to be more prone to the fact that the bile duct structure's expansion formed the cyst cavity. It can be seen under the microscope that the cysts lining contains bile duct cells; the pathological results of case 2 showed the covered columnar epithelial cells had a minor abnormality. On the other hand, the cysts' long-term stimulation to the surrounding small bile ducts may also lead to carcinogenesis.

The clinical manifestations and laboratory examinations of our case lack specificity, therefore, we believe that the imaging examination has important reference value for discovering the malignant transformation of liver cysts. Doctors should pay special attention to regular review for patients with large volumes, multilocular structures, and multiple cysts. During follow-up, if the cyst is found to be significantly enlarged recently, the thickness of the cyst is uneven, and nodules are found in the cyst wall or inside the cyst, it is necessary to take into account the possibility of malignant cysts.

In conclusion, our cases indicate that liver cysts may deteriorate into intrahepatic cholangiocarcinoma. Patients with multiple liver cysts, giant liver cysts, liver cysts with volume changes during follow-up and patients after fenestration of the cysts should be paid special attention. Regular follow-up and timely monitoring of changes in the patient's condition should be performed. Simultaneously, for patients with atypical imaging findings and complicated liver cysts, the differential diagnosis of intrahepatic cholangiocarcinoma needs to be considered.

Abbreviations

CT

Computed Tomography; MRI:magnetic resonance imaging; AFP:alpha-fetoprotein; CEA:carcinoembryonic antigen; CA125:carbohydrate antigen 125; CA153:carbohydrate antigen 153; CA19-9:carbohydrate antigen 19 – 9; CK7:Cytokeratin 7; CK19:Cytokeratin 19; AST:Aspartate aminotransferase; ALT:Alanine aminotransferase; TBIL:total bilirubin; DBIL:Direct Bilirubin; PT:Prothrombin time; APTT:activated partial thromboplastin time; CD34:cell antigen 34; MUC1:mucoprotein 1; HSP70:Heat Shock Protein 70.

Declarations

Acknowledgement

None.

Authors' contributions

Study concepts and design: WHT, LFS. Histologic analysis and interpretation: LFS, LKL. Manuscript preparation: LFS. Manuscript review: YYF, WHT. All authors reviewed the clinical course during follow-up and the microscopic slides of their resection specimens. All authors read and approved the final manuscript.

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Availability of data and materials

Clinical details - including preoperative investigations, intraoperative situation, and post-surgical management - of both cases were collected. All these data were anonymous.

Ethics approval and consent to participate

Not applicable

Consent for publication

All authors consent to the publication of the manuscript in Diagnostic Pathology.

Competing interests

None.

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Figures

Figure 1

Imaging findings. Case 1: A. multiple cysts in the liver; the cyst indicated by the white arrow has been fenestrated(CT, 2017/07/28). B. a slightly low/density nodule with an unclear boundary in the live's left inner lobe(CT, 2020/09/15). C. a slightly higher T2 signal shadow mixed in the left inner lobe(MRI, 2020/09/18). Case 2: D. multiple cysts in the right lobe of the liver, about 42mm×36mm in size(CT, 2017/08/20). E. the size of the cyst increased to about 49mm×45mm(CT, 2019/08/30). F. the liver's right lobe showed a low/density shadow with a cross-sectional size of about 75mm×53mm, and more low/density areas were seen inside(CT, 2020/09/02). G-I. the MRI and PET/CT images at 2020/09/05.

Figure 2

Gross examination of the resected specimen (Each square side is 1cm). A. the tumor of case 1 is grayish/brown after the cut. B. the resected tumor of case 2 was a solid cystic mass; the inner wall of the cavity is gray and smooth, the solid mass is grayish/white and dark/yellow in section, with a slightly stiff texture.

Figure 3

Microscopic findings of the case 1 resected specimen. Hematoxylin and eosin staining: A($\times 20$, $\times 40$). Bile duct cells formed the cyst wall. Tumor cells can be seen on the cyst wall and its surroundings to form adenoid structures of different sizes, shapes, and irregular arrangements, some of which are arranged in clusters. B($\times 40$, $\times 100$). The transition between neoplastic glands and dilated bile ducts. C($\times 40$, $\times 100$). Classic pathological image of cholangiocarcinoma: a large number of tubular malignant glands with surrounding fibrous interstitial hyperplasia.

Figure 4

Microscopic findings of the case 2 resected specimen. Hematoxylin and eosin staining(×40, ×100): A. Visible cyst wall formed by bile duct cells, hyaline degeneration of the cyst wall, irregular glandular infiltrating growth around the cyst wall, interstitial fibrosis, mucus degeneration, and inflammatory cell infiltration. B. Tumorous glands invade the liver parenchyma. Immunohistochemistry(×100): C. CK7 is diffusely positively expressed in the cytoplasm of bile duct cysts and neoplastic glandular epithelial cells. D. CK19 is diffusely positively expressed in the cytoplasm of neoplastic glandular epithelial cells and negatively expressed in peripheral hepatocytes.