



Unexpected discovery of intrahepatic cholangiocarcinoma during follow-up in two cases of liver cysts: case report

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Background: The liver cyst is commonly treated by hepatobiliary surgery. Generally, most patients show no apparent symptoms and often get diagnosed accidentally during the imaging examinations. In addition, most patients with liver cysts follow a benign course, with fewer severe complications and rare occurrences of malignant changes. Therefore, based on disease characteristics and healthcare costs, long-term regular follow-up of liver cysts are rarely performed clinically.

Case Description: Here, we reported two previously treated or observed cases for liver cysts, where intrahepatic neoplastic lesions were found unexpectedly at the liver cyst during follow-up. These two patients' clinical manifestations and laboratory examinations lacked specificity with unclear pre-operative diagnosis, whereas the post-operative pathology confirmed cholangiocarcinoma. One of the patients was a 64-year-old female with right upper abdominal distension. She underwent cyst fenestration for a liver cyst 3 years ago. In the latest admission, imaging examination revealed a tumor in the left inner lobe of the liver. The tumor was located in the exact fenestration location, and the pathological diagnosis of cholangiocarcinoma was made after surgical resection. The patient received Lenvatinib post-operatively and had no recurrence during the follow-up. Another patient, a 68-year-old woman, was asymptomatic, but the liver margin was palpable under the ribs on her physical examination. She had a previous diagnosis of liver cysts and was on regular yearly follow-up. In the last follow-up, a tumor was found close to a cyst. It was diagnosed as intrahepatic cystadenocarcinoma before surgery; however, the pathological features after surgical resection were more consistent with the cholangiocarcinoma. The patient had lung metastases 2 months after the surgery, but her condition improved after receiving targeted therapy and immunotherapy. Moreover, she is alive to this day.

Conclusions: We reported 2 cases of intrahepatic cholangiocarcinoma discovered accidentally during the follow-up of hepatic cysts. The location of the malignant tumor coincided with the location of the cyst, making the clinical differential diagnosis problematic. Therefore, it is necessary to be vigilant about the possibility of combined malignant tumors for the follow-up of complex cysts, as early detection and treatment may help improve the prognosis of these patients. After surgery, multimodal therapy, including chemotherapy, immunotherapy, and targeted therapy, is helpful.

Keywords: Liver cysts; intrahepatic cholangiocarcinoma; case report

Submitted Oct 29, 2021. Accepted for publication Feb 17, 2022.

doi: [10.21037/tcr-21-2373](https://doi.org/10.21037/tcr-21-2373)

View this article at: <https://dx.doi.org/10.21037/tcr-21-2373>

Introduction

With a reported incidence from 2.5% to 18%, the liver cyst is a common disease treated by hepatobiliary surgeons in routine clinical practice (1,2). Most patients with liver cysts are asymptomatic, while cysts are usually accidental during imaging examinations. The general recommendation for such patients is clinical observation without any intervention (3). Only some patients exhibit the symptoms, mostly originating from the cyst's compression to the surrounding tissues. The liver cysts can also lead to the complications such as obstruction of inferior vena cava or common bile duct, portal vein occlusion with varices, intra-cystic hemorrhages, cyst rupture, and infection (4). The clinical course of almost all liver cysts is benign, but the occasional rare occurrence of malignant transformation of liver cysts is also reported. Intrahepatic cholangiocarcinoma accounts for a low proportion of primary liver cancer and has a high degree of malignancy. In the current case report, we discussed two cases of cholangiocarcinoma, which had initial findings of multiple liver cysts. During the observation period, the examination revealed the growth of the tumor at the location of the cysts. These two cases clinical manifestations and laboratory examinations lacked specificity with unclear pre-operative diagnosis, whereas the post-operative pathology confirmed cholangiocarcinoma. To the best of our knowledge, only a handful of cases of cholangiocarcinoma, closely related to liver cysts, are reported in English literature (5-8). The location of the malignant tumor coincided with the site of the cysts in our cases, making clinical differential diagnosis challenging. Our observations raise two clinical concerns, namely, what type of patients with liver cysts require regular follow-up and whether there is a possible correlation between the occurrence of intrahepatic cholangiocarcinoma with liver cysts. We present the following case in accordance with the CARE reporting checklist <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2373/rc>.

Case presentation

We reported two previously treated or observed cases for liver cysts, where intrahepatic neoplastic lesions were found unexpectedly at the liver cyst during follow-up. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained

from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Case 1

A 64-year-old woman sought medical care in September 2020 due to the abdominal swelling in the upper right quadrant of the abdomen for 1 week. She had a history of liver cysts, for which she received cysts fenestration and drainage 3 years ago. At admission, no positive result of the abdominal examination was detected. Also, the patient presented with normal liver function, blood coagulation, and tumor markers levels. However, the liver's computed tomography (CT) showed a slightly lower density nodule at the left inner lobe. Further, magnetic resonance imaging (MRI) examination revealed the mass with noticeable enhancement in the arterial phase with no decrease in the degree of enhancement for the delayed phase. While examining the patient's previous examinations found that the left inner lobe mass site once had two liver cysts. The CT images of July 2017 showed several low-density nodules in the left inner lobe (*Figure 1*). These cysts were treated with fenestration surgery 3 years ago. The post-operative pathological images showed that the inner wall of the cyst was partially lined up with monolayer cubic epithelium. The epithelial cells were well differentiated without atypia. The cyst wall fibrous tissue proliferated with hyalinosis, calcification, and local chronic inflammatory cell infiltration, was consistent with the pathological features of the simple liver cyst (*Figure S1*).

During the latest surgery, the mass was located at the edge of the left inner lobe, below the sickle ligament, partly protruding from the liver capsule, with the surrounding prominent adhesions. Liver blood vessels were tortuous and dilated. Considering the large-scale resection complication of uncontrollable bleeding, surgeons opted for local tumor resection. After opening the resected liver tissue, the mass appeared gray and white (*Figure 2*). The pathological results confirmed that the tumor was cholangiocarcinoma (*Figure 3*); therefore, the patient received Lenvatinib treatment after the surgery and did not show any recurrence in the follow-up visits.

Case 2

In August 2017, a 65-year-old woman visited Zhongnan Hospital of Wuhan University for a medical examination. The patient reported a prior history of liver cysts. During

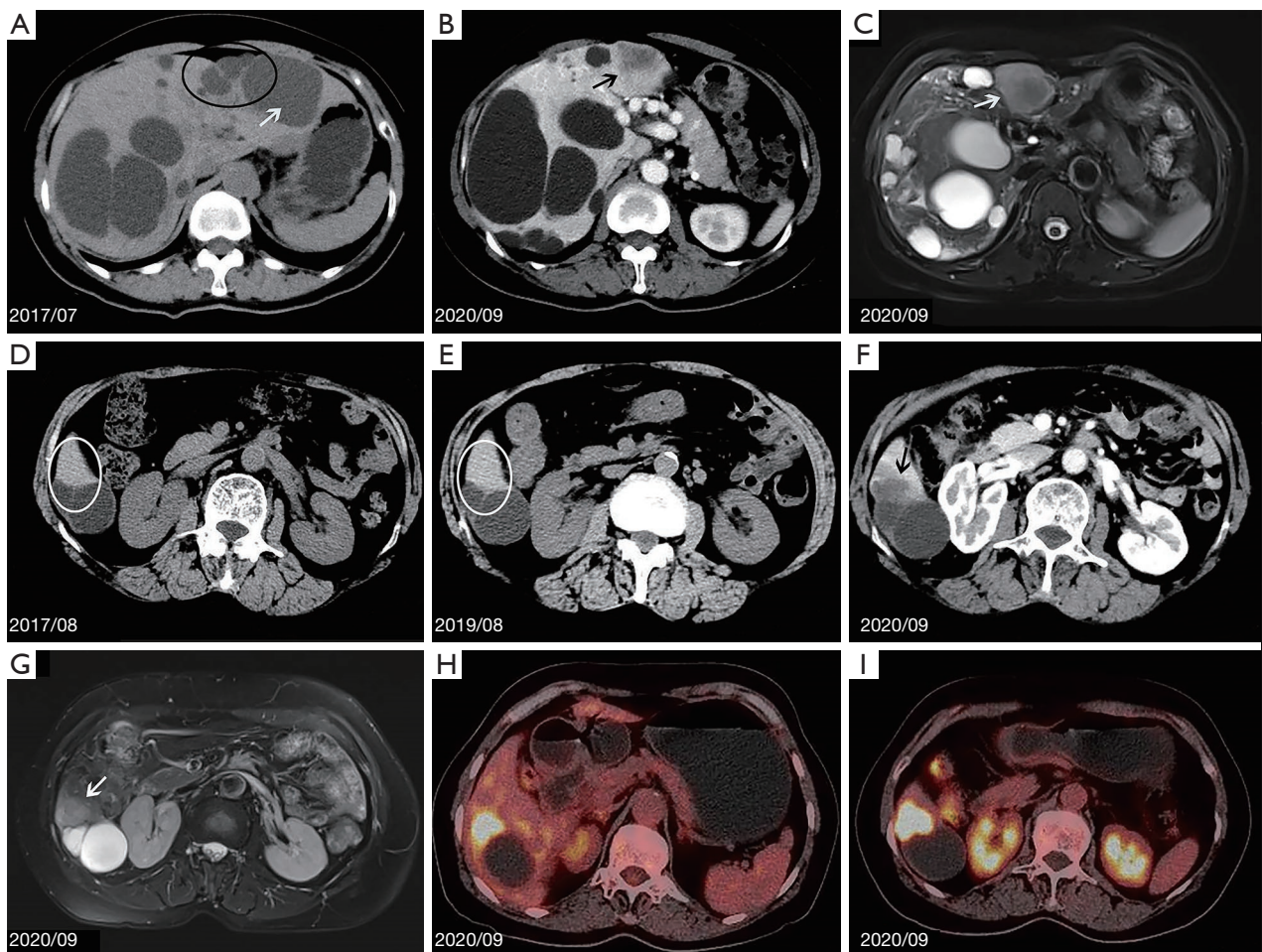


Figure 1 Imaging findings. Case 1: (A) multiple cysts in the liver; the cyst indicated by the white arrow has been fenestrated, and the site marked by the black circle was found to have a neoplastic lesion three years after the patient underwent fenestration of the liver cyst (CT, 2017/07/28); (B) a slightly low-density nodule by the black arrow with an unclear boundary in the liver's left inner lobe (CT, 2020/09/15); (C) a marginally higher T2 signal shadow mixed in the left inner lobe as indicated by the white arrow (MRI, 2020/09/18). Case 2: (D) multiple cysts in the right lobe of the liver, about 42 mm × 36 mm in size (CT, 2017/08/20); (E) the size of the cyst increased about 49 mm × 45 mm (CT, 2019/08/30); (F) the liver's right lobe showed a low-density shadow with a cross-sectional dimension of about 75 mm × 53 mm, and many low-density areas were seen inside the tumor (CT, 2020/09/02); (G-I) the MRI and PET/CT images at 2020/09/05. The white circles in (D,E) were the border of the hepatic cyst and the normal liver at examinations in 2017 and 2019, respectively. At the same location, a tumor adjacent to the anterior cysts indicated by the arrows in (F,G) was found at the follow-up examination in 2020. CT, computed tomography; MRI, magnetic resonance imaging.

the visit, abdominal CT revealed multiple cysts in the liver, with the largest cyst measuring 4.2 cm × 3.6 cm in diameter, with no additional abnormalities. The patient has regularly been reviewed in our hospital since then. The re-examination in August 2019 showed that the cyst size was increased to 4.9 cm × 4.5 cm, but no malignant lesions were found. However, in the follow-up of September 2020, the abdominal CT revealed a new solid lesion adjacent to the

anterior cysts (Figure 1).

On admission, physical examination revealed the enlarged liver without tenderness, 2 cm below the costal margin. Hematology analysis showed normal blood coagulation, liver function, alpha-fetoprotein (AFP), and carcinoembryonic antigen (CEA), but the levels of carbohydrate antigen (CA)125, CA153, and CA19-9 were found to be elevated. Further, enhanced MRI of liver

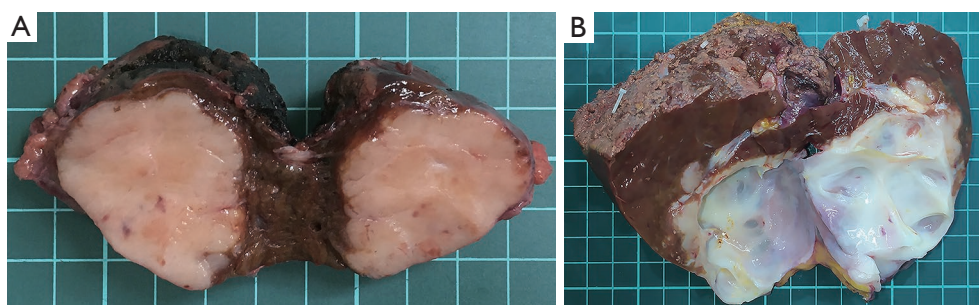


Figure 2 Gross examination of the resected specimen. (A) The tumor of case 1 was grayish/brown after the cut. (B) The resected tumor of case 2 was a solid cystic mass, and the inner wall was gray and smooth. The solid mass was grayish/white and dark/yellow in section, slightly stiff texture (each square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

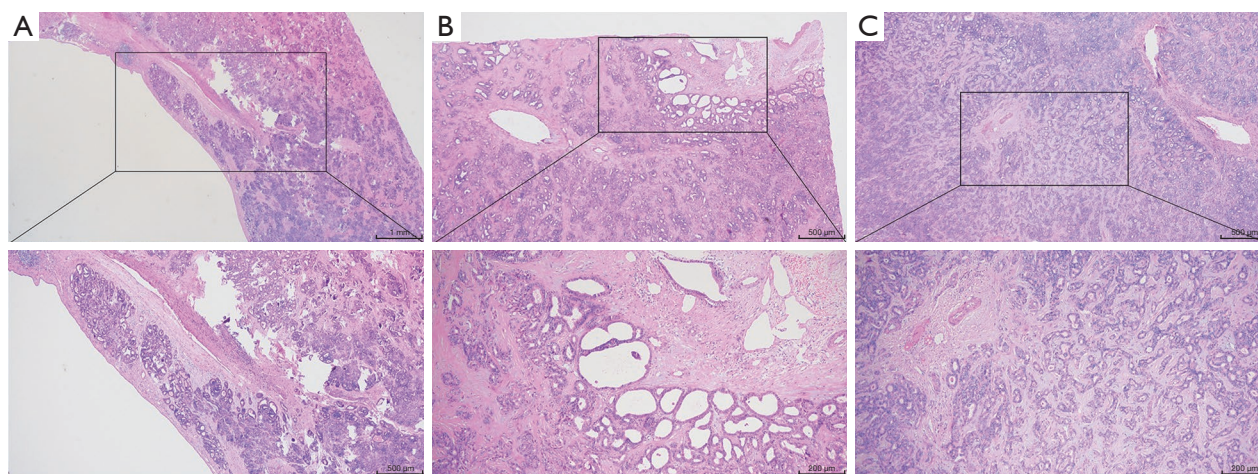


Figure 3 Microscopic findings of the case 1 resected specimen. Hematoxylin and eosin staining: (A) bile duct cells formed the cyst wall. Tumor cells can be seen on the cyst wall and its surroundings, creating adenoid structures of different sizes, shapes, and irregular arrangements, some of which are arranged in clusters ($\times 20$, $\times 40$); (B) the transition between neoplastic glands and dilated bile ducts ($\times 40$, $\times 100$); (C) classic pathological image of cholangiocarcinoma: many tubular malignant glands with surrounding fibrous interstitial hyperplasia ($\times 40$, $\times 100$).

tumor-specific contrast demonstrated a lobular cystic, solid mass in the lower right posterior lobe. Finally, positron emission tomography (PET)/CT confirmed the lesion as a malignant tumor (Figure 1).

The tumor was found in the lower right posterior lobe and had adhesion to the lateral peritoneum during surgery. However, it was removed successfully under ultrasound positioning. The resected tumor was a solid cystic mass, with the cavities gray and smooth inner wall, whereas the solid mass was grayish-white and dark yellow in section, with a slightly stiff texture (Figure 2). Fibrous tissue hyperplasia in the remaining liver tissue's portal area accompanied the infiltrating chronic inflammatory

cell. The pathology report revealed a diagnosis of a poorly differentiated cholangiocarcinoma, while the immunohistochemistry showed positivity for cytokeratin 7 (CK7) and CK19 (Figure 4). The patient developed lung metastasis 2 months following the surgery, for which she received targeted and immunotherapy. Her condition has improved, and she is still alive. The clinical characteristics of the two cases are shown in Table 1.

Discussion

Liver cysts can be classified into parasitic and non-parasitic liver cysts (NPLC). NPLCs include traumatic liver cysts

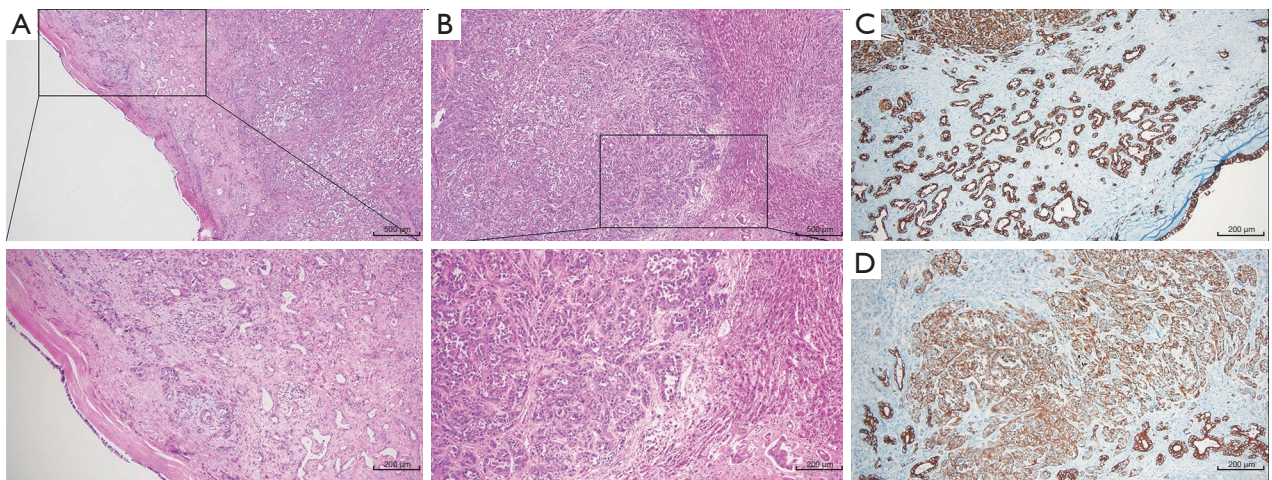


Figure 4 Microscopic findings of the case 2 resected specimen. Hematoxylin and eosin staining ($\times 40$, $\times 100$): (A) visible cyst wall formed by bile duct cells, hyaline degeneration of the cyst wall, irregular glandular infiltrating growth around the cyst wall, interstitial fibrosis, mucus degeneration, and inflammatory cell infiltration; (B) tumorous glands invading the liver parenchyma. Immunohistochemistry ($\times 100$): (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 neoplastic glandular epithelial cells and negatively expressed in the peripheral hepatocytes. CK7, cytokeratin 7; CK19, cytokeratin 19.

such as serous hematoma and neoplastic liver cysts like 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) fall under intra-hepatic cystic diseases. Among these, IPNB, MCN-L, biliary cystadenoma, and Caroli disease carry cancer transitioning risk, whereas IPNB and MCN-L are considered as pre-cancerous lesions of intrahepatic cholangiocarcinoma (9). In case 1, the pathological results confirmed a simple liver cyst following the first fenestration. However, if the cyst had been cystadenoma, its cancerousness might have significantly increased. Therefore, it is essential to distinguish the tumor for assessing cancer risk in these patients.

Liver cysts are generally considered congenital abnormalities during the development of liver structures. They all seem to have an origin over biliary ducts that did not undergo involution. Its slow dilation produces cystic lesions, as the cysts do not communicate with the bile duct (10). Reports of malignant correlation of liver cysts are of rare occurrence. However, Azizah and Paradinas reported two simple cysts and adenocarcinoma cases to coexist closely in the liver. The authors suggested that the two patients had cholangiocarcinoma through multi-angle comparison. They also proposed that the cystadenocarcinoma and

cholangiocarcinoma coexisting with simple cysts should be treated with the two separate concepts (5). Further, Kokubo *et al.* and Lee *et al.* reported two cases of intrahepatic cholangiocarcinoma with liver cysts. Still, these two patients' tumors were considered to have undergone cystic degeneration. Therefore, the situation was not comparable to the current report (6,7). A patient-reported by Kaneko *et al.* was initially diagnosed with a giant liver cyst, where the tumor progressed rapidly following the puncture and drainage. This case was later diagnosed as cholangiocarcinoma in the form of a cyst (8). Therefore, the conditions of the above patients with cholangiocarcinoma demonstrated the characteristics of high correlation with liver cysts. However, it is still challenging to determine the order for the cysts and the tumor.

Our first case had undergone fenestration with drainage for liver cysts, with the post-operative pathological diagnosis of the simple liver cyst. In the third year following the surgery, a tumor was excised, found at the cyst site where fenestration was done previously. The tumor was eventually confirmed to be cholangiocarcinoma. Multiple liver cysts were detected years ago in the second case, but they progressed to a neoplastic lesion upon re-examination within a year. She was diagnosed with cystadenocarcinoma before the surgery, and the pathological result further confirmed it as cholangiocarcinoma. In these two cases,

Table 1 The clinical characteristics of the two cases

Characteristics	Case 1*	Case 2*
Gender	Female	Female
Medical history	Liver cysts received cysts fenestration and drainage 3 years ago	Liver cysts, regular review, a solid lesion adjacent to the anterior cysts appeared in 1 year
Current information		
Age, years	64	66
Adjacent cyst size, cross-sectional, cm ²	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, s	12.3/40.3	12.5/28.4
AFP/CEA, ng/mL	5.90/3.05	1.63/5.98
CA125, U/mL	13.00	675.00
CA153, U/mL	10.30	38.22
CA19-9, U/mL	<2.00	2,865.00
Tumor size, cm ³	5.0×3.6×3.4	7.0×6.0×4.5
Tumor number	Single	Single
Tumor location	S4	S6
Treatment	Surgery & immunotherapy	Surgery & immunotherapy
Pathological diagnosis	Intrahepatic cholangiocarcinoma	Intrahepatic cholangiocarcinoma
Immunohistochemistry		
AFP	–	+
Arginase	–	–
CD34	–	–
CK7	+	+
CK19	+	+
Glypican-3	–	–
Hepatocyte	–	–
Supplement	MUC1 (+), HSP70 (+)	Ki-67 (positive rate about 70%)
Portal vein invasion	–	–
Splenomegaly	–	–
Outcome	No progression after operation, survival	Post-operative lung metastasis, survival with tumor

*, patients had no history of alcohol consumption, estrogen use, hepatolithiasis, or history of hepatitis B, hepatitis C infection. AFP, alpha-fetoprotein; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; CA153, carbohydrate antigen 153; CA19-9, carbohydrate antigen 19-9; CD34, cell antigen 34; CK19, cytokeratin 19; CK7, cytokeratin 7; DBIL, direct bilirubin; HSP70, heat shock protein 70; MUC1, mucoprotein 1; PT, prothrombin time; TBIL, total bilirubin.

the tumor location is highly correlated with the location of the cyst, but we did not find any similar available published English literature. However, sporadic publications of liver cysts transitioning into other pathological malignancies have been reported: Hayashi *et al.* showed a mucoepidermoid carcinoma arising from a preexisting cyst of the liver (11); Ameriks *et al.* reported a case of malignant non-parasitic cyst of the liver, but the specific pathological type was not determined (12); other reports showed that the liver cysts could be developed into cystadenocarcinoma (13,14). Besides, Xiao *et al.* showed a case of hepatic squamous cell carcinoma (SCC) with liver cysts in a study on the liver's primary SCC, where they listed chronic inflammation of the congenital liver cysts associated with the infection and/or stones as one of the prime causes of malignant transformation (15). The continuous stimulation of chronic inflammation leading to the malignant transformation might be a possible explanation for the course of our patients. The lesion can emerge due to 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 shows a pattern of intra-cystic hyperplasia. Such cysts may have cellular components derived from the bile duct.

Bile-duct cyst is an established high-risk factor among the risk factors for the onset of cholangiocarcinoma (16,17). Previous studies have shown that the choledochal cysts are the most relevant among many high-risk factors for cholangiocarcinoma, with the incidence of malignant biliary tumors arising from choledochal cysts ranging from 2.5% to 26% (17,18). Besides, reflux of pancreatic enzymes, bile stasis, and increased concentration of intraductal bile acids can play an essential role in the carcinogenesis of the biliary tract (19). However, this possibility does not seem to exist in our cases. In the present case discussions, the cysts were located at the hepatic hilum's distal end, with no prominent bile component. Moreover, in our cases, the bile duct structure's expansion to form the cyst cavity was more prominent. As seen under the microscope, the cysts lining had bile duct cells. Furthermore, the pathological results of case 2 showed minor abnormality in the covered columnar epithelial cells. On the other hand, the cyst's long-term stimulation to the surrounding small bile ducts might have initiated carcinogenesis.

Our cases clinical manifestations and laboratory examinations lack specificity; however, the imaging examinations show a higher reference value for diagnosing the disease. Patients with large volumes, multilocular structures, and multiple cysts may require additional

attention in clinical practice. If the cyst is significantly enlarged recently, with uneven thickness, nodules in the wall, or inside the cyst, it is necessary to consider the possibility of malignancy.

In summary, we have discussed two cases of liver cysts that may be related to the occurrence of intrahepatic cholangiocarcinoma as a point of interest in the clinical work of liver surgery. Therefore, we suggest that the patients with multiple liver cysts, giant liver cysts, liver cysts with changes in volume, and patients who have the above conditions and have undergone cyst fenestration surgery, must pay attention to their follow-up. Simultaneously, for liver tumor patients with complicated liver cysts and atypical imaging findings, differential diagnosis of intrahepatic cholangiocarcinoma needs to be considered.

Acknowledgments

The authors would like to thank all the reviewers who participated in the review and MJEditor (www.mjeditor.com) for its linguistic assistance during the preparation of this manuscript.

Funding: This work was supported by the Cancer Research and Translational Platform Project of Zhongnan Hospital of Wuhan University (ZLYNXM202004), the Translational Medicine and Interdisciplinary Research Joint Fund Project of Zhongnan Hospital of Wuhan University (ZNJC201918), and a grant from the National Key Research and Development Program of China (SQ2019YFC200078/02).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2373/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-21-2373/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as

revised in 2013). Written informed consent was obtained from the patients for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Cite this article as: Liu FS, Li KL, He YM, Zhang ZL, Yuan YF, Wang HT. Unexpected discovery of intrahepatic cholangiocarcinoma during follow-up in two cases of liver cysts: case report. *Transl Cancer Res* 2022;11(4):935-942. doi: 10.21037/tcr-21-2373

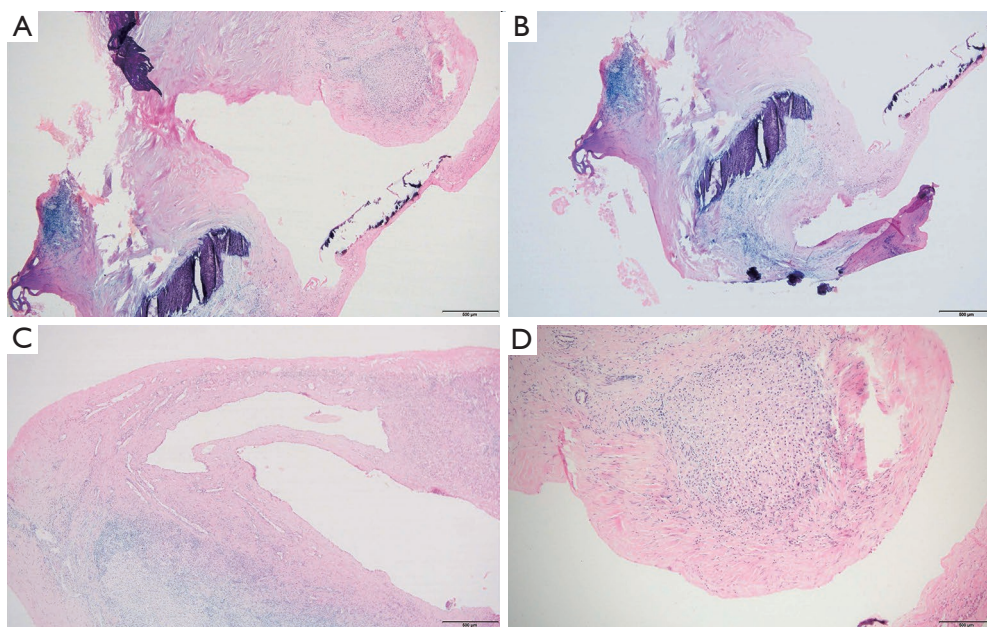


Figure S1 Pathological pictures of cyst wall tissue after fenestration of liver cyst in case 1 3 years ago. (A,B) The cyst wall presents fibrous tissue proliferation with hyaline degeneration and calcification, and chronic inflammatory cell infiltration can be seen locally; (C) the inner wall of the cyst is locally lined with a single layer of squamous epithelium, with normal epithelial cell morphology and no atypia; (D) residual normal hepatocytes and bile canaliculi can be seen around the cyst wall. Scale bar: 500 µm.