

# Ultrasonographic findings of intrahepatic lymphoepithelioma-like cholangiocarcinoma associated with Epstein–Barr virus

## Two cases report

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### Abstract

**Rationale:** Epstein–Barr virus (EBV)-related lymphoepithelioma-like cholangiocarcinoma (LELCC) is an extremely rare primary liver tumor with nonspecific clinical manifestations. The clinicopathological features of EBV-associated LELCC have been reported in a few cases. But reports of the tumor's imaging characteristics, particularly ultrasonographic findings, are very rare.

**Patient concerns:** The first patient was a 64-year-old man with left upper quadrant pain and no nausea and dizziness for about 3 months. The second patient was a 40-year-old man, had an incidental finding of a hepatic tumor in a routine health checkup at a local hospital.

**Diagnoses:** In the first patient, the abdominal ultrasound demonstrated a slightly heterogeneous hypoechoic nodule in segment 3 of the liver. The nodule was about 2.0 cm × 1.7 cm in size, with a clear margin and regular shape. Color Doppler flow imaging (CDFI) revealed no blood flow signals in this nodule. According to the clinical information and imaging features, it was difficult to determine the diagnosis of the nodule. In the second patient, gray-scale ultrasound revealed a slightly heterogeneous hypoechoic mass measuring 3.5 cm × 2.5 cm with well-defined margin and regular shape at the superior segment of the left hepatic lateral lobe. There was a blurry hypoechoic halo around the mass. In contrast-enhanced ultrasound (CEUS), the mass was homogeneous hyperenhancement in the arterial phase. In the portal phase and late phase, the center enhancement of the mass washed out gradually, presenting hypoenhancement. Therefore, the tumor was diagnosed as malignancy.

**Intervention:** Finally, a laparoscopic left hepatic lateral lobectomy was performed in the first patient. The second patient underwent a left hepatectomy with cholecystectomy.

**Outcomes:** The first patient has been alive without recurrence or distant metastases for 11 months since the surgery. The second patient received routine follow-up after surgery. Until now, he has been tumor-free for 32 months.

**Lessons:** We mainly focus on the ultrasound characteristics of EBV-associated LELCC, especially its enhancement patterns on CEUS, which may provide valuable information for diagnosis of the LELCC. When a liver tumor with typical CEUS patterns of malignancy is found in middle-aged adults with EBV positive, the possibility of EBV-related LELCC should be considered.

**Abbreviations:** AFP = alpha-fetoprotein, AJCC/UICC = American Joint Committee on Cancer /Union for International Cancer Control, CA 19-9 = carbohydrate antigen 19-9, CDFI = color Doppler flow imaging, CEA = carcinoembryonic antigen, CECT = contrast-enhanced computed tomography, CEMRI = contrast-enhanced magnetic resonance imaging, CEUS = contrast-enhanced ultrasound, CK = cytokeratins, CT = computed tomography, EBER = EBV-encoded RNA, EBV = Epstein–Barr virus, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, ICC = intrahepatic cholangiocarcinoma, ISH = in situ hybridization, LELCC = lymphoepithelioma-like cholangiocarcinoma, LELCs = lymphoepithelioma-like carcinomas, MRI = magnetic resonance imaging.

**Keywords:** contrast-enhanced ultrasound, Epstein–Barr virus, lymphoepithelioma-like cholangiocarcinoma, ultrasonographic findings

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## 1. Introduction

Lymphoepithelioma-like carcinomas (LELCs) are tumors with morphologic characteristics similar to the undifferentiated nasopharyngeal carcinomas that arise outside the nasopharynx. These tumors are mostly associated with the Epstein–Barr virus (EBV), and have been found in various anatomical locations including the stomach, salivary gland, skin, thymus, and lung.<sup>[1–5]</sup> Primary LELC in the hepatobiliary tract, however, is extremely rare. Lymphoepithelioma-like cholangiocarcinoma (LELCC), which is a rare variant of intrahepatic cholangiocarcinoma (ICC), was first described in 2001 by Jeng et al.<sup>[6]</sup> Up to now, only 40 cases have been reported in the English literature, and 80.0% (32/40) of these cases were related to EBV.<sup>[6–23]</sup> However, the role of EBV is still unclear in the pathogenesis of ICC. Recently, Sun et al<sup>[16]</sup> reported that EBV-positive ICC may be divided into 3 different histopathological types according to the host cellular immune reaction and tumor cellular differentiation: typical LELC, LELCC, and conventional-type ICC. And LELCC is the most common subtype.

Previous reports have mainly focused on the clinicopathological features of LELCC. Among imaging features, the findings on computed tomography (CT) and magnetic resonance imaging (MRI) have been mentioned in a few cases.<sup>[6,9–12,14,15,17]</sup> However, the sonographic features of LELCC are rarely reported.<sup>[6,11,14,15,17]</sup> Because clinical symptoms and laboratory tests are nonspecific for diagnosing LELCC, imaging features of this extremely rare tumor are important for its identification. In this study, we describe the B-mode ultrasound and contrast-enhanced ultrasound (CEUS) findings of LELCC associated with EBV in 2 male patients. To the best of our knowledge, this report is the first to describe the CEUS pattern of EBV-related LELCC.

## 2. Case presentation

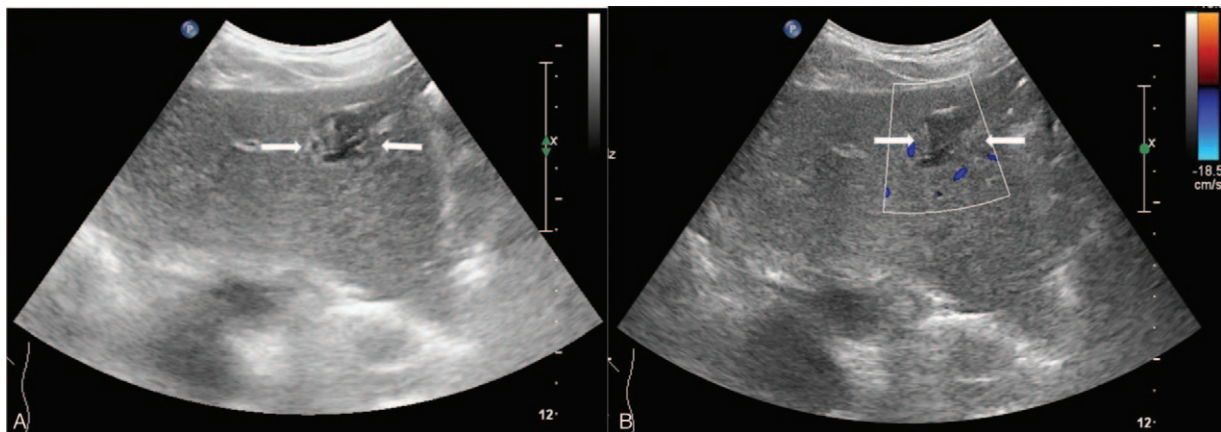
### 2.1. Case 1

The first patient was a 64-year-old man with left upper quadrant pain and no nausea and dizziness for about 3 months. He underwent an abdominal contrast-enhanced CT (CECT) at a local hospital, which revealed a 2.3 cm × 1.7 cm hypodense nodule with unclear margin in the inferior segment of the left hepatic lateral lobe. The nodule had isoenhancement in the arterial phase and slight hypoenhancement in the portal phase. The patient came to our

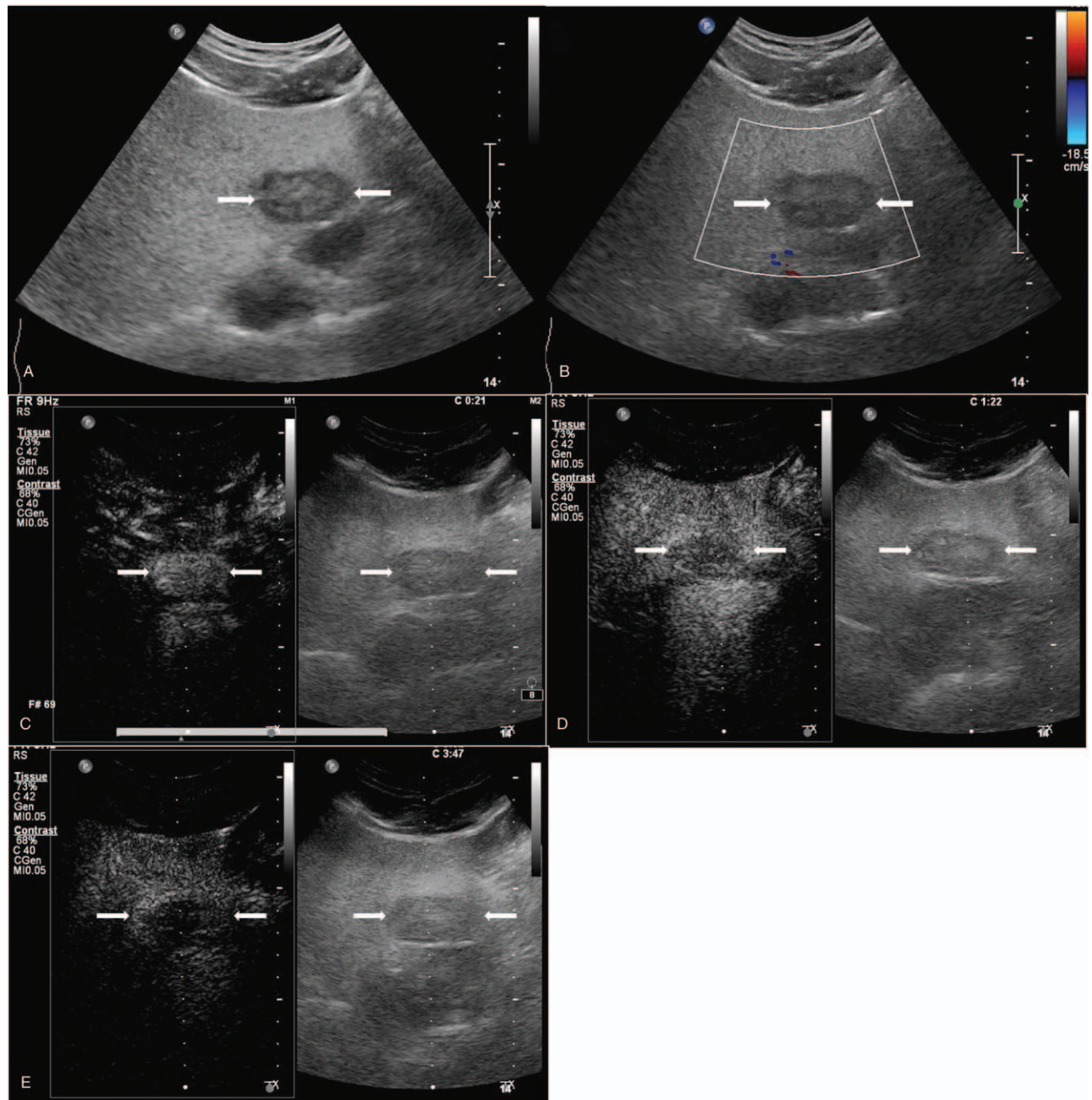
hospital for a second opinion. His physical examination did not reveal any abnormalities. The laboratory tests showed that the serum hepatitis B virus (HBV) surface antigen was positive, and the antihepatitis C virus (HCV) antibody was negative. The liver function tests and serum tumor markers, including the clinical chemistry profile, alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), were within normal range. Abdominal ultrasound demonstrated a slightly heterogeneous hypoechoic nodule in the background of normal hepatic parenchyma in segment 3 of the liver (Fig. 1A). The nodule was about 2.0 cm × 1.7 cm in size, with a clear margin and regular shape. Color Doppler flow imaging (CDFI) revealed no blood flow signals in this nodule (Fig. 1B). According to the clinical information and imaging features, it was difficult to determine the nature of the nodule before surgery. In the end, a laparoscopic left hepatic lateral lobectomy was performed. During operation, a solid tumor measuring about 2.0 cm was found in segment 3 of the liver. The tumor was firm, well-demarcated, and gray-white in color with an integrated capsule. Intraoperative ultrasound showed no metastatic lesions in other hepatic lobes. And the background liver was not cirrhotic. According to the 8th edition of American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM staging system for ICC,<sup>[24]</sup> the tumor was classified as stage IA (T1a N0 M0). The patient has been alive without recurrence or distant metastases for 11 months since the surgery.

### 2.2. Case 2

A 40-year-old man had an incidental finding of a hepatic tumor in a routine health checkup at a local hospital. The patient was a chronic HBV carrier without any symptoms for more than 6 months. He was referred to our hospital for further diagnosis and treatment. The laboratory test results indicated that: the serum level of CA19-9 was 53.45 U/mL (reference range <22 U/mL); the serum levels of AFP, CEA and the liver function tests were within normal ranges; and the anti-HCV antibody, EBV early antigen IgG antibody and EBV viral capsid antigen IgA antibody were negative. Real-time fluorescence detection was negative for the amplification of EBV DNA. Gray-scale ultrasound image revealed a slightly heterogeneous hypoechoic mass measuring 3.5 cm × 2.5 cm with well-defined margin and regular shape at the superior segment of the left hepatic lateral lobe (Fig. 2A).



**Figure 1.** EBV-related LELCC of Case 1 on B mode and CDFI images. (A) A 2.0 cm × 1.7 cm slightly heterogeneous hypoechoic nodule located at the inferior segment of the left hepatic lateral lobe. (B) CDFI revealed no blood flow signals in the nodule. CDFI = color Doppler flow imaging, EBV = Epstein–Barr virus, LELCC = lymphoepithelioma-like cholangiocarcinoma.



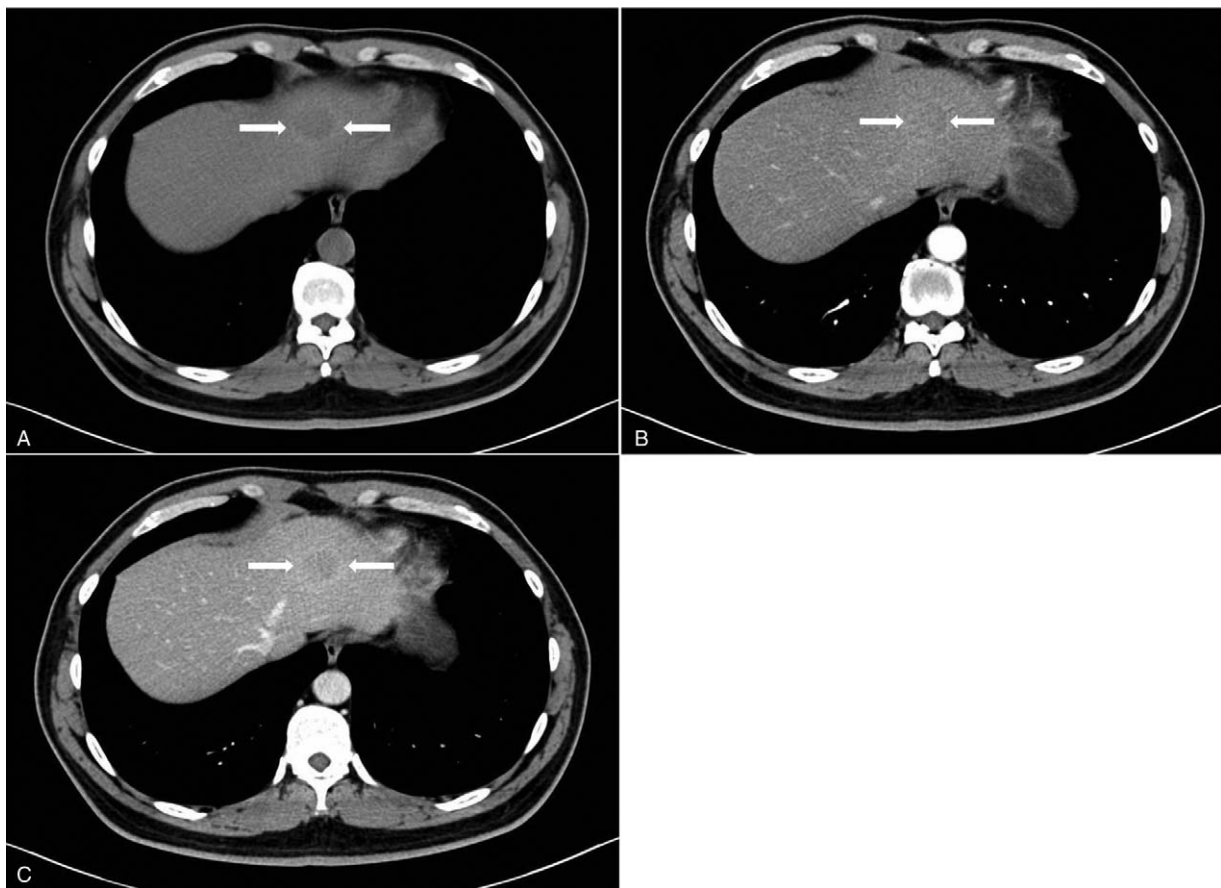
**Figure 2.** EBV-related LELCC of Case 2 on B mode, CDFI and CEUS images. (A) A 3.5cm × 2.5cm slightly heterogeneous hypoechoic mass with peripheral hypoechoic halo located at the superior segment of the left hepatic lateral lobe. (B) CDFI revealed no blood flow signals in the mass. (C) The mass showed homogeneous hyperenhancement in the arterial phase. (D) The central enhancement washed out gradually, presenting hypoenhancement, and the periphery demonstrated rim-like slight hyperenhancement in the portal phase. (E) In the delayed phase, the enhanced presentation of the mass was similar to the portal phase. CDFI=color Doppler flow imaging, CEUS=contrast-enhanced ultrasound, EBV=Epstein-Barr virus, LELCC=lymphoepithelioma-like cholangiocarcinoma.

There was a blurry hypoechoic halo around the mass. CDFI showed no blood flow signals in the mass (Fig. 2B). The background liver showed fat infiltration. The patient underwent CEUS examination for further diagnosis. A 1.2 mL ultrasound contrast agent SonoVue (Bracco, Milan, Italy) suspension was injected through the cubital vein followed by a flush with 5 mL saline. An iU22 ultrasound system (Royal Philips, The Netherlands) equipped with a C5-1 (1–5 MHz) transducer was used for real-time contrast-specific imaging at low mechanical index (the mechanical index setting was 0.05). Using surrounding

liver parenchyma as a reference, the mass was homogeneous hyperenhancement in the arterial phase (Fig. 2C). In the portal phase and late phase (Fig. 2D and E), the center enhancement of the mass washed out gradually, presenting hypoenhancement, while the periphery demonstrated rim-like slight hyperenhancement. Therefore, the tumor was diagnosed as malignant by CEUS.

In addition, CECT was performed on this patient using a 64-channel multislice CT scanner (Royal Philips, The Netherlands) with iodinated contrast agent Ultravist (Bayer Schering Pharma,





**Figure 3.** EBV-related LELCC of Case 2 on CECT images. (A) Noncontrast CT showed a 3.0 cm × 2.8 cm slight hypodense mass with peripheral rim-like hyperdense in the segment 2 of the liver. (B) In the arterial phase, the periphery of the mass demonstrated slight hyperenhancement like a bright ring, the centripetal was isoenhancement. (C) The mass was slight hypoenhancement with peripheral rim-like hyperenhancement in the portal phase. CDFI = color Doppler flow imaging, CECT = contrast-enhanced computed tomography, CT = computed tomography, EBV = Epstein-Barr virus, LELCC = lymphoepithelioma-like cholangiocarcinoma.

Berlin-Wedding, Germany). CECT showed a 3.0 cm × 2.8 cm slightly hypodense mass with peripheral rim-shape hyperdense and ill-defined margin in segment 2 of the liver (Fig. 3A). In the arterial phase, the peripheral part of the mass demonstrated slight hyperenhancement like a bright ring, the centripetal part of the mass was isoenhancement (Fig. 3B). The periphery of the mass still showed slight hyperenhancement, but the center washed out to hypoenhancement in the portal phase (Fig. 3C). The patient underwent a left hepatectomy with cholecystectomy. A 3.0 cm, circumscribed, firm, and gray-white tumor in the left hepatic lateral lobe was discovered during surgery. A part of tumor protruded into the liver surface, without necrosis and hemorrhage. According to the 8th edition of AJCC/UICC TNM staging system for ICC,<sup>[24]</sup> the tumor was staged as IA (T1a N0 M0). The patient received routine follow-up after surgery. Until now, he has been tumor-free for 32 months.

In this paper, ethical approval was not necessary, as this article is a case report, which is based on the clinical information of the patient. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

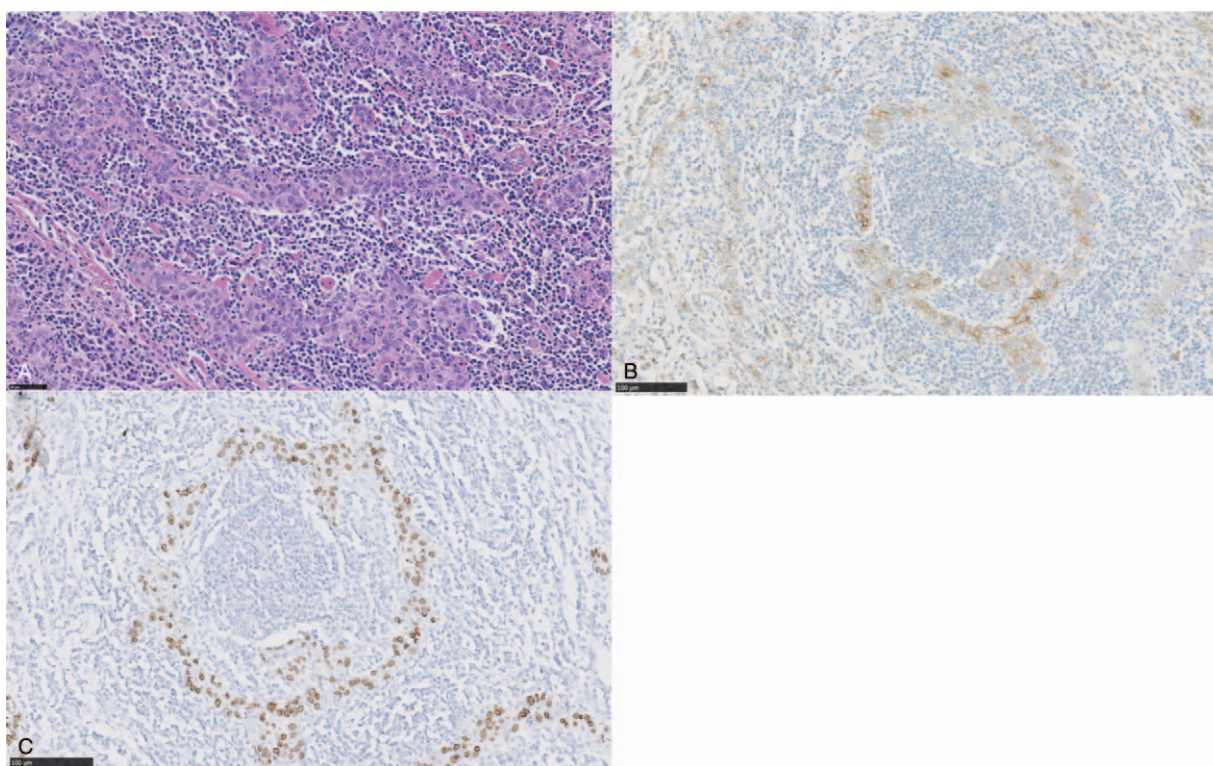
### 3. Pathologic findings

Microscopy revealed that both tumors had similar histological characteristics. They were composed of moderately differentiated

glandular cells forming adenocarcinoma with dense lymphoplasmacytic infiltration (Fig. 4A). Immunohistochemical staining showed positive for biliary-type cytokeratins (CK7, CK19) (Fig. 4B), and negative for CK20, AFP and hepatic marker HepPar-1 in tumor cells. In situ hybridization (ISH) test using EBV-encoded RNA (EBER) showed strong positive nuclear signal in the tumor cells (Fig. 4C), but not in the surrounding non-neoplastic liver tissue. From the pathologic features, EBV-related LELCC was diagnosed in both patients.

### 4. Discussion

LELCC is a rare variant of ICC. Chronic viral hepatitis, such as HBV and HCV, has been confirmed as one of the etiologic factors for ICC.<sup>[25]</sup> But according to previous studies, only 44.1% (15/34) and 9.4% (3/32) of LELCCs were HBV and HCV positive, respectively.<sup>[6–23]</sup> About 80.0% of LELCCs were associated with EBV infection, and the majority of these cases were discovered in the oriental countries.<sup>[11,26]</sup> Despite these findings, the roles of EBV, HBV and HCV remain unknown in the tumorigenesis and development of LELCC. EBV-positive LELCCs were mainly found in middle-aged females: the ratio of female to male was about 3.13:1, the range of age was 19 to 71 years (mean age, 53.39 years).<sup>[6–16]</sup> No preference in the tumor location was found between the left and the right hepatic lobe. Clinical symptoms



**Figure 4.** Pathologic findings of EBV-related LELCC. (A) The tumor was composed of moderately differentiated glandular cells forming adenocarcinoma with dense lymphoplasmacytic infiltration (H&E stain,  $\times 40$ ). (B) Immunohistochemical staining showed that CK7 was positive ( $\times 20$ ). (C) In situ hybridization (ISH) test using EBV-encoded RNA (EBER) showed strong positive in the tumor cells ( $\times 25$ ). EBER = EBV-encoded RNA, EBV = Epstein-Barr virus, LELCC = lymphoepithelioma-like cholangiocarcinoma.

were nonspecific, usually found incidentally or abdominal pain. In our study, EBV and HBV were both positive in these 2 Chinese patients. Clinical information was similar to previous reports with the difference that the gender of both patients was male. The prognosis of EBV-associated LELCC after surgery is still controversial. Some studies reported that the clinical outcomes of patients with EBV-associated LELCC were better than conventional type of ICC.<sup>[10]</sup> But other studies thought that there was no significant difference of prognosis between these 2 types of carcinomas.<sup>[16]</sup>

There were few previous reports describing the imaging features of EBV-associated LELCC, especially on the ultrasound findings. Up to now, only 4 reported cases described gray-scale ultrasound image features: 3 cases were hypoechoic, and 1 was mixed echoic.<sup>[6,11,14,15]</sup> In our study, both tumors were slightly heterogeneous hypoechoic, well-defined, and had regular shape. Case 2 had a blurrily hypoechoic halo. The heterogeneous echogenicity may relate to the different pathologic components and size of the tumor, but these features are nonspecific for diagnosing EBV-related LELCC.

It is well known that CEUS can be used to discriminate malignant from benign focal liver lesions. However, to the best of our knowledge, our report is the first to depict the CEUS features of LELCC. In the arterial phase, the tumor showed homogeneous hyperenhancement, and the enhancement gradually washed out, characterized by interior hypoenhancement and periphery rim-like slight hyperenhancement in the portal and late phases. CECT findings of this tumor were similar to the CEUS in our study. The common characteristic was peripheral hyperenhancement like a bright ring in the portal and delayed phase. Our patient image

features were also similar to the contrast-enhanced MRI (CEMRI) characteristics of Liao et al<sup>[15]</sup> study. The authors of this previous study thought that the peripheral rim-like hyperenhancement represented the delayed fibrous capsule enhancement.<sup>[15]</sup> As the contrast agents used in ultrasound, CT, and MRI have different enhanced principles, it is unclear whether the same enhancement patterns in different imaging modalities represent the same pathological components. The peripheral rim-like enhancement or halo sign on imaging may also indicate tumor infiltration or pseudocapsule.

In our study, patients had histories of chronic B hepatitis with a normal serum level of AFP and slightly elevated serum level of CA19-9. The tumor showed hyperenhancement in the arterial phase and hypoenhancement in the late phase by CEUS. According to the WFUMB-EFSUMB guidelines for CEUS in liver,<sup>[27]</sup> these are typical CEUS patterns of hepatocellular carcinoma (HCC). In the meantime, there was a hypoechoic halo around the tumor, and this imaging characteristics may overlap with metastasis. Therefore, EBV-associated LELCC could be misdiagnosed as HCC or metastases. Clinical history and laboratory tests may be used to help differentiate the diagnosis, and metastases also tended to wash out faster and more marked in the portal and delayed phases on CEUS.<sup>[28]</sup> Nevertheless, it remains difficult to distinguish typical HCC and LELCC by CEUS. So tumor biopsy may still be needed in order to make definite diagnosis before surgery.

In conclusion, EBV-associated LELCC is a rare subtype of ICC, which is mainly found in middle-aged females. The preoperative imaging diagnosis of LELCC is still a challenge for radiologists. CEUS may provide valuable information for diagnosing LELCC.

When a liver tumor with typical CEUS patterns of HCC is found in middle-aged women with EBV positive, the possibility of EBV-related LELCC should be considered.

### Author contributions

**Funding acquisition:** Wenwu Ling.

**Resources:** Changli Lu, He Huang.

**Supervision:** Yan Luo, Shigao Chen.

**Writing – original draft:** Wenwu Ling, Tingting Qiu.

**Writing – review & editing:** Wenwu Ling, Qiang Lu, Chengwu Huang, Ping Gong.

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