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CASE REPORT

# Lymphoepithelioma-Like Intrahepatic Cholangiocarcinoma Associated with Epstein–Barr Virus and Hepatitis Virus: Case Report and a Literature Review

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**Background:** Lymphoepithelioma-like carcinoma of the liver is a rare primary malignancy of the liver. The identification of lymphoepithelioma-like cholangiocarcinoma is very limited as there are currently very few reports of such cases. Although previous studies have reported the lymphoepithelioma-like cholangiocarcinoma pathologic features, few studies have revealed the clinic features, imaging characteristics, and clinical course and outcomes. This study was analyzed from multiple aspects such as contrast-enhanced ultrasound, magnetic resonance imaging, and pathological characteristics, aiming to improve the comprehensive understanding of this rare subtype of disease.

**Case Presentation:** A 43-year-old female with a history of hepatitis B for over 20 years presented with a lesion found in the right lobe of her liver. After discussion by a multidisciplinary team (MDT), malignant tumors cannot be excluded based on contrast-enhanced ultrasound and MRI. Thus, we decided to perform surgery for the patient. Postoperative pathology confirmed lymphoepithelioma-like intrahepatic cholangiocarcinoma. After 3 months of follow-up, the patient was still alive and no recurrence was observed.

**Conclusion:** The purpose of this article is to describe a rare case of lymphoepithelioma-like intrahepatic cholangiocarcinoma and analyze its contrast-enhanced ultrasound and contrast-enhanced MRI features, which will be helpful for physicians in diagnosing this disease. From the perspective of CEUS, the wedge-shaped highly enhanced area around the lesion in the arterial phase appears to be inflammatory but looks malignant based on the extremely fast washout. The lesion showed a low signal on T1WI, a high signal on T2WI and DWI, and an abnormal perfusion shadow can be seen behind the lesion. In particular, this subtype of cholangiocarcinoma has a good prognosis, the clinician should improve the recognition of the disease to strive for early diagnosis and therapy.

**Keywords:** lymphoepithelioma-like carcinoma, intrahepatic cholangiocarcinoma, contrast-enhanced ultrasound, magnetic resonance imaging, epstein-barr virus

## Background

Lymphoepithelioma-like carcinoma (LELC) is a tumor composed of undifferentiated epithelial cells with obvious lymphocyte infiltration. It was first reported to occur in the nasopharynx, and subsequently related cases were also reported in the lung, breast, prostate, bladder, uterus, liver, and other locations[1,2] LELC primary in the liver can be further divided into lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC) and lymphoepithelioma-like intrahepatic cholangiocarcinoma (LEL-ICC). LEL-ICC is a rare variant of intrahepatic cholangiocarcinoma (ICC) first described in 2001 by Jeng et al.[3] However the identification of LEL-ICC is very limited as there are currently very few reports of such cases. Although previous studies have reported the LEL-ICC pathologic features, few studies have revealed the clinic features, imaging characteristics, and clinical course and outcomes. This study was analyzed from multiple aspects such as contrast-enhanced ultrasound, magnetic resonance imaging, and pathological characteristics, aiming to improve the comprehensive understanding of this rare subtype of disease.



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## Case Presentation

A 43-year-old female came to the outpatient department of Hebei General Hospital and complained of a lesion found in the right lobe of her liver during her last check-up 15 days ago. Further inquiry revealed no specific symptoms and a history of hepatitis B for over 20 years. Physical examinations discovered no abnormality.

The serum tumor marker of alpha-fetoprotein (AFP) was within the reference range. Blood tests showed negative of HBsAb and HBeAg, but positivity of HBsAg, HBeAb, and HBcAb. HBV DNA was $5.29\times10^4$IU/mL. Other viral (HCV/HIV) serology tests all tested negative. The serologic tests including assessment of hepatic fibrosis and liver function were normal (Table 1).

Abdominal ultrasound demonstrated a slightly heterogeneous hypoechoic nodule in the background of normal hepatic parenchyma in the right lobe of the liver (Figure 1). The nodule was about 19.9mm×14.2mm in size, with a clear margin.

The patient underwent contrast-enhanced ultrasound (CEUS) examination for further diagnosis. A 1.1mL ultrasound contrast agent SonoVue suspension was injected. Arterial phase: the lesion began to show slight hyperenhancement at the 11th second, with a wedge-shaped high hyperenhancement around the lesion. The hyperenhancement reaches its peak in the 14th second, with a range of approximately 45.5mm×29.2mm. The lesion had a clear boundary with a normal vascular pattern. After 22 seconds, the lesion was rapidly washout from the center, and the boundary gradually became unclear. Portal phase: The lesion is further washout and shows low enhancement; Delayed phase: The lesion continues to washout and shows low enhancement (Figure 2).

The Magnetic resonance imaging (MRI) revealed a high-intensity mass on T2-weighted (Figure 3A), a low-intensity mass on T1-weighted images (Figure 3B), and a high-intensity mass on diffusion-weighted images (Figure 3C), which was located in the right lobe of the liver with an estimated magnitude of 18mm×14 mm; a clear margin was also observed. (Gadobenate Dimeglumine) Gd-BOPTA-enhanced MRI revealed heterogeneous enhancement with a vague margin in the arterial phase and contrast medium washout in the portal and delayed phases (Figure 3D-F). The lesions appear as low signal intensity in the hepatobiliary phase and capsular (pseudocapsule) enhancement (Figure 3G).

After discussion by a multidisciplinary team (MDT), malignant tumors cannot be excluded based on contrast-enhanced ultrasound and MRI. Thus, we decided to perform surgery for the patient. The patient underwent laparoscopic tumor resection. The operation lasted for 1.5 hours, and the intra-operative blood loss was about 200 mL. The post-

**Table 1** Laboratory Data

| | Result | Reference | Unit |
|---|---|---|---|
| AFP | 1.220 | <7 | ng/mL |
| HbsAg | >250 | <0.05 | IU/mL |
| HbsAb | 1.68 | <10 | mIU/mL |
| HbeAg | 0 | <0.59 | IU/mL |
| HbeAb | >4.5 | <0.15 | PEIU/mL |
| HbcAb | >45 | <0.7 | PEIU/mL |
| HBV DNA | 52,900 | 50 | IU/mL |
| HCV-Ab | 0.05 | <1 | s/co |
| ALT | 16.3 | 7–40 | U/L |
| AST | 20.3 | 13–35 | U/L |
| CK-MB | 39.8 | 0–19 | U/L |
| Hyaluronic acid | 56.87 | <100 | ng/mL |
| Laminin | 29.93 | <50 | ng/mL |
| Collagen | 27.88 | <30 | ng/mL |
| Collagen IV | 14.91 | <30 | ng/mL |

**Abbreviations**: AFP, alpha-fetoprotein; HbsAg, Hepatitis B surface antigen; HbsAb, Hepatitis B surface antibody; HbeAg, Hepatitis B e antigen; HbeAb, Hepatitis B e antibody; HbcAb, Hepatitis B core antibody; HBV DNA, Hepatitis B virus DNA; HCV-Ab, Hepatitis C virus antibody; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; CK-MB, Creatine kinase-MB.

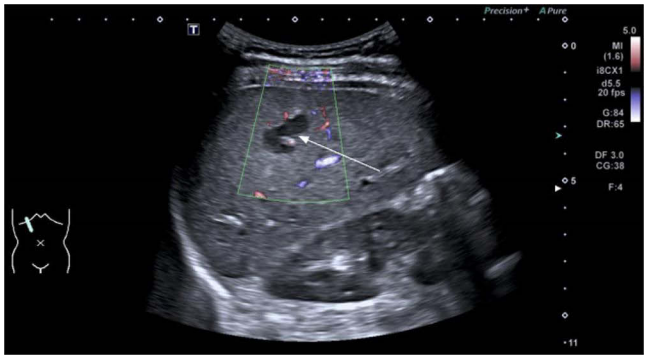

**Figure 1** Abdominal ultrasound before surgery. A 19.9mm×14.2mm heterogeneous hypoechogenic nodule (white arrow) located at the right lobe of the liver.

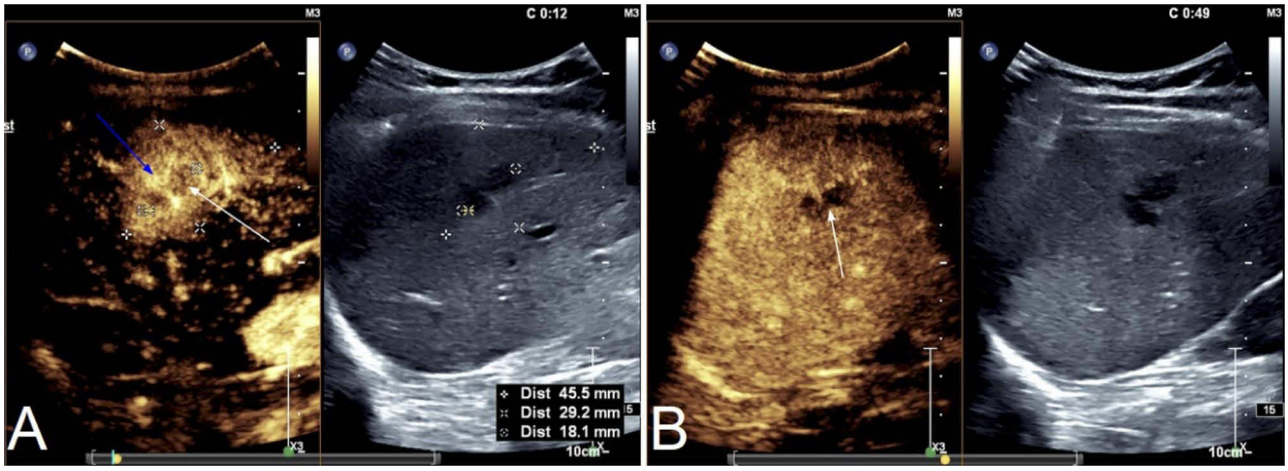


**Figure 2** Contrast-enhanced ultrasound (CEUS)before surgery. CEUS showed the lesion (white arrow) was heterogeneous low hyperenhancement and a wedge-shaped high hyperenhancement (blue arrow) around the lesion in the arterial phase (**A**). The lesion (white arrow) was rapidly washout from the center in the Portal phase (**B**).

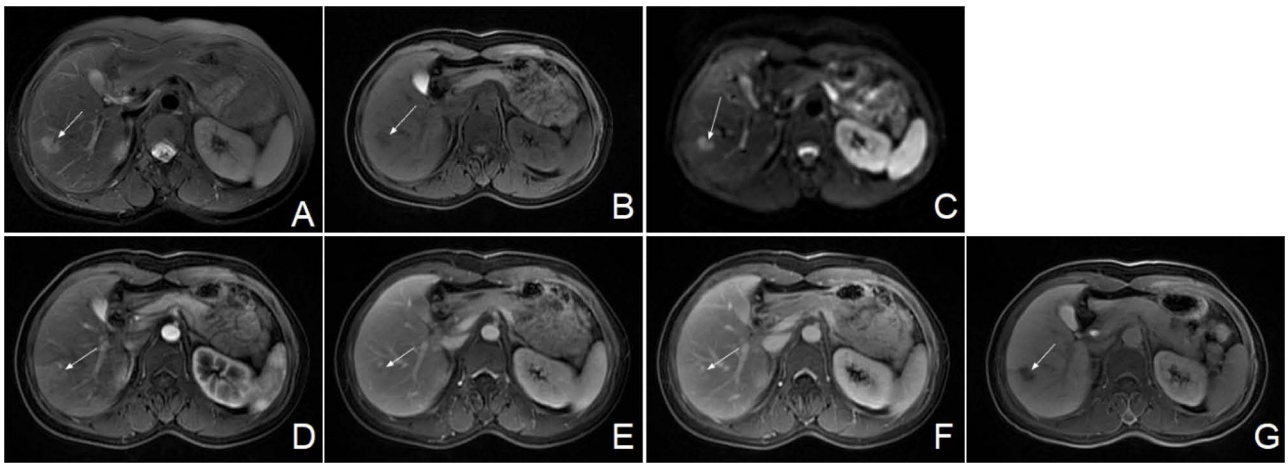


**Figure 3** Magnetic Resonance Imaging before surgery. MRI showed a lesion (white arrow) with high signal intensity on T2, low signal intensity on T1, and high signal intensity on DWI in segment 6 of the liver. The lesion showed enhancement on arterial phase and faded signal on portal and delayed phases. The hepatobiliary phase showed low signal intensity. (**A**) T2-weighted image; (**B**) T1-weighted image; (**C**) diffusion-weighted images; (**D**) arterial phase; (**E**) portal venous phase; (**F**) delayed phase; (**G**) hepatobiliary phase. MRI, magnetic resonance imaging.

operative recovery was uneventful, and the patient was discharged on postoperative day 8. During the routine follow-up 3 months after surgery, no evidence of recurrence was noted, and the liver function of the patient remained normal.

A 6.5cm×5cm×3 cm segment of the liver was resected. A 2cm×1cm×1cm gray, well-defined, non-encapsulated solid mass was grossly identified, 0.5 cm from the nearest resection margin (Figure 4).

Microscopically, the lesion is composed of a moderately differentiated adenocarcinoma and significant lymphocytic infiltration. Fibrous pseudocapsules were seen in some areas (Figure 5A). There was no microvascular invasion in the liver tissue near and far from the tumor (MVI grade M0), and no nerve invasion was found. Four satellite nodules were found in the liver tissue near the cancer. No cancer cells were found at the resection margin. The tumor cells have obvious atypia, the cells are round or oval, the nucleoli are obvious, and mitotic figures are easy to see (Figure 5B). Small focal steatosis can be seen in the surrounding liver tissue, a moderate amount of inflammatory cell infiltration can be seen in the liver lobules and portal areas, mild fibroplasia in the portal areas, and no cirrhosis changes: consistent with G3S1.

Immunohistochemical examination revealed positive in CK (pan), EMA, CK7, CK19, and negative in AFP, CEA, IDH1, Vimentin; P53(scattered positive), Ki67 (about 40%); The dense lymphocytic infiltrate consisted of T-lymphocytes (CD3 positive), B-lymphocytes (CD20 positive) and macrophages (CD68 positive); Hepatocyte specific markers: HepPar-1, Arginase-1 and CD10 were all negative; Hepatocellular carcinoma markers: CD34, GPC3 and GS were all negative while HSP70 was positive; Gastrointestinal stromal tumor markers: CD117 and CD34 were negative; EBV-

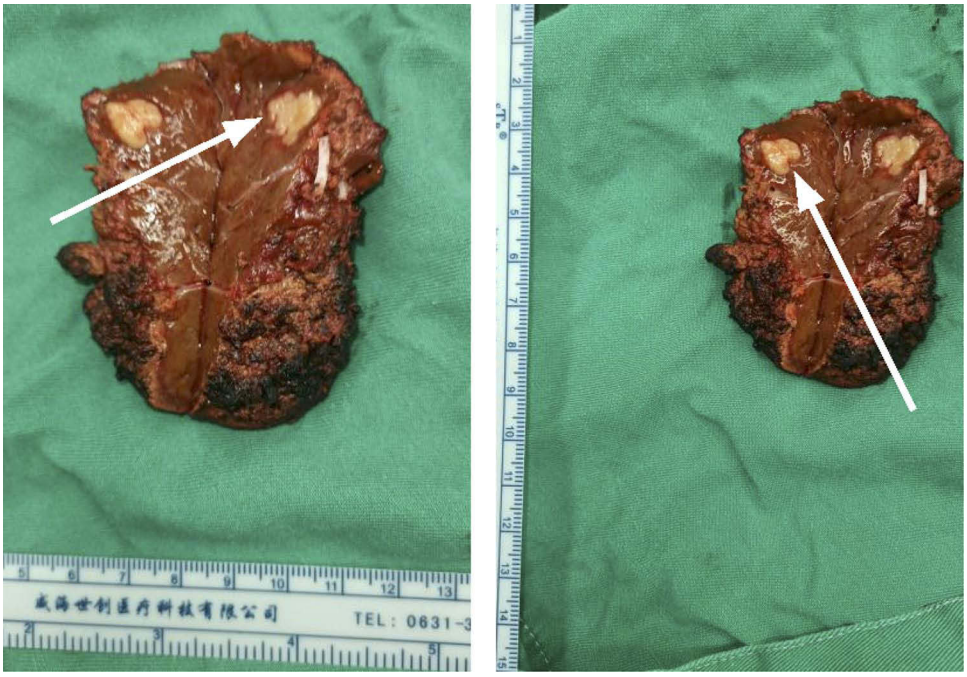

**Figure 4** Postoperative gross pathology. A grey foci (white arrow) measuring 2cm×1cm×1cm in the resected segment.

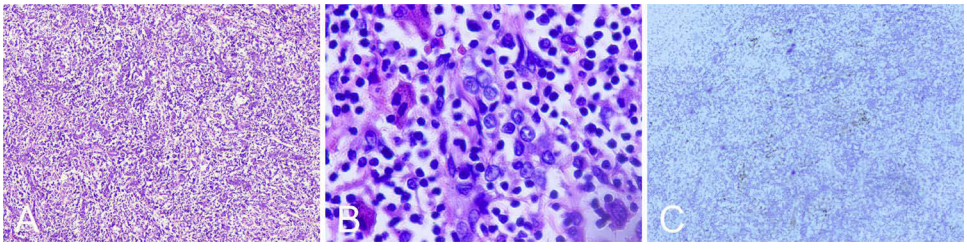


**Figure 5** Pathological and EBER in situ hybridization examinations after surgery. Microscopically, the Liver tumor tissue is composed of moderately differentiated adenocarcinoma cells and stromal infiltrating lymphocytes (**A**). The tumor cells have obvious atypia, the nucleoli are obvious, and mitotic figures are easy to see (**B**). EBER-encoded RNA was found positive in tumor tissues (**C**).

encoded RNA (EBER) in situ hybridization was performed and found positive in tumor tissues (Figure 5C). The non-neoplastic liver parenchyma with HBsAg positive did not show cirrhosis but fibrosis. All features fulfilled the diagnosis of lymphoepithelioma-like intrahepatic cholangiocarcinoma (LEL-ICC).

## Discussion

The incidence of ICC has been increasing worldwide over the past few decades, and its etiology is only beginning to be elucidated.[4,5] Recent epidemiologic evidence has now linked IHC to HBV infection, HCV infection, cirrhosis, nonalcoholic steatohepatitis, and diabetes.[5] The incidence of ICC is higher in Asia compared to Europe.[6,7] In recent years, most cases of lymphoepithelioma-like cholangiocarcinoma LEL-CC reported in various databases come from Asia.

Huang and Labgaa I's research showed that approximately 70.0% of LEL-CC is related to EBV infection, with most cases found in Eastern countries.[8,9] Tao Changcheng et al reviewed 34 cases of LEL-CC and found that it occurs more frequently in women aged ≤60 years old, and most of them are of yellow race. In terms of etiology, 76.5% had EBV infection, 38.2% had HBV infection, and only 2 cases had HCV infection.[10] Up to now, the roles of EBV and HBV in the occurrence and development of LEL-CC are still unclear. Adachiet S et al reported that there were no significant histopathological differences between EBV-negative and EBV-positive LEL-ICC.[11] Although most cases are associated with EBV, however, the specific role of EBV in the pathogenesis of LEL-ICC is unclear. In this case, pathology revealed a moderate amount of inflammatory cell infiltration in the liver lobules and portal areas. The pathogenesis of LEL-ICC may be related to the long-term stimulation of chronic inflammation.

The clinical manifestations of LEL-CC are non-specific, and AFP is mostly negative. There are currently no specific biomarkers for its diagnosis.

The contrast-enhanced ultrasound in this case showed high enhancement in the arterial phase, followed by rapid washout, low enhancement in the portal-venous and late phases, and normal blood vessel courses could be seen within the lesion. It needs to be differentiated from the following diseases. ①HCC: HCC in the noncirrhotic liver is typically hyperenhancing in the arterial phase with a chaotic vascular pattern, and hypoenhancing in the portal-venous and late phases. In this case, the lesion appeared to be enhanced at 11 seconds after the injection of the contrast agent, reaching the peak at 14 seconds and began to wash out from the center of the lesion at 22 seconds. Normal vascular course within the lesion and early (<60 seconds) washout is unusual for HCC. ②ICC: The typical CEUS pattern seen with intrahepatic cholangiocarcinomas is peripheral, rim-like contrast enhancement in the arterial phase and early hypoenhancement in the portal-venous and late phases. The vascular structure within the ICC lesion is disordered, and the contrast agent washout more slowly than in this case. In this case, the lesion appeared to be slight hyperenhancement at 11 seconds after the contrast agent was injected. It began to washout from the center of the lesion at 22 seconds, and wedge-shaped high hyperenhancement appeared around the lesion, with normal vascular pattern. The extremely rapid enhancement and washout process of the lesion, accompanied by normal blood vessel course, may be the characteristics of LEL-ICC. In addition, the wedge-shaped highly enhanced area around the lesion in the arterial phase appears to be inflammatory but looks malignant based on the extremely fast washout.

The MRI of this case showed a round shape in the S6 segment of the liver with a slightly lower T1WI, slightly higher T2WI, and high signal on DWI. In the arterial phase, heterogeneous enhancement within the lesion can be seen, and a wedge-shaped abnormal perfusion shadow can be seen behind the lesion. The portal venous phase and delayed phase showed heterogeneous enhancement, and the hepatobiliary phase showed low signal intensity. It needs to be differentiated from the following diseases.①FNH: Star-shaped fibrous scar hyperplasia is commonly seen in the center of typical FNH lesions. MRI shows iso- or slightly hypo-intensity in T1WI and slightly hyper-intensity in T2WI. Fibrous scars show hypo-intensity in T1WI and obvious hyper-intensity in T2WI. Most lesions on DWI show slightly hyper-intensity. Homogenous enhancement is seen during the arterial phase, then the lesion returns to precontrast density during the portal phase; Because there are still liver cells with normal functions in FNH that can take up contrast agents, they appear to be hyperintense or isointense in the hepatobiliary phase, and the central scar is hypointense. In this case, the above imaging findings are not consistent. ②Inflammatory pseudotumor: On T1WI, the lesion is iso- or slightly hypo-intense; on T2WI, if the lesion is dominated by coagulative necrosis and contains little free water, it will be hypo- or iso-intense; if there is inflammatory cell infiltration in the lesion, it will show slightly higher signal because it contains more

free water. Enhanced MRI usually shows no enhancement in the arterial phase, and mostly shows ring enhancement, edge enhancement, and uneven enhancement in the portal venous phase and delayed phase. It is difficult to distinguish this case from the MRI findings of inflammatory pseudotumor. Such imaging findings may be related to a large number of lymphocyte infiltration within the lesion.

It is worth noting that in both CEUS and MRI arterial phase, a wedge-shaped abnormal high-signal signal was seen around the lesion, and its specific clinical significance needs further study. It is still unclear whether the abnormal perfusion shadow on MRI is related to the lesion. In addition, whether the rapid washout and normal blood vessel course within the lesion demonstrated by CEUS are characteristics of early LEL-ICC remains to be studied.

At present, the gold standard for diagnosis of LEL-ICC is still pathology. In 1998, Wada et al defined LEL-HCC as the presence of more than 100 tumor-infiltrating lymphocytes in 10 high-power fields, but no conclusion has been reached yet.[12] The amount or density of lymphocyte infiltration required for diagnosis has not yet been determined. This case is a solitary lesion. Under the microscope, a large number of CD20 (B lymphocyte +) and CD3 (T lymphocyte +) can be seen infiltrating the tumor stroma. The cancer cells have obvious atypia and mitotic figures are easy to see. Immunohistochemistry was positive for CK7 and CK9, but negative for hepatocyte-specific markers and hepatocellular carcinoma markers. The patient was diagnosed as lymphoepithelioma-like intrahepatic cholangiocarcinoma. From the perspective of pathological characteristics, differential diagnosis mainly needs to be made with the following diseases: ①LEL-HCC: Tumor cells often express AFP. Hepatocyte-specific markers Hepar-1 and Arginase-1 and hepatocellular carcinoma markers GPC3, GS, and HSP70 were positively expressed. These markers were negative in this case, ruling out LEL-HCC. ② Cholangiocarcinoma: Most cancer cells in cholangiocarcinoma are arranged in a tubular manner, and lymphocyte infiltration is rare. In this case, abundant mature lymphocyte infiltration can be seen in the adenocarcinoma component, which can rule out cholangiocarcinoma. ③Malignant lymphoma: Immunohistochemistry is positive for LCA and can express a B or T lymphocyte marker. In this case, the tumor cells are of epithelial origin, and a number of lymphocytes around the epithelium are mature lymphocytes and plasma cells. The epithelial markers CK7 and CK19 are positive, which can rule out malignant lymphoma. ④Metastatic LELC: LELCs from different sites share similar morphological features. The tumor is characterized by poorly differentiated tumor cells with large vesicular nuclei and prominent nucleoli, accompanied by heavy lymphocytic infiltration. Therefore, when diagnosing LEL-ICC, it is essential to exclude metastases from LELCs originating from other sites, particularly the nasopharynx. Immunohistochemically, EBV-associated lymphoepithelioma-like nasopharyngeal carcinoma typically exhibits expression of broad-spectrum cytokeratin (CK pan), cytokeratin 5/6 (CK5/6), p63, and p40, while showing either no or low expression of CK7, CK8/18, CK8, and CKL. Lymphoepithelioma-like lung carcinomas typically demonstrate positivity for CK, CK5/6, epithelial membrane antigen (EMA), p63, and p40, suggesting squamous cell lineage. Given the similar microscopic morphology and immunohistochemical expression of these two diseases, imaging studies can aid in distinguishing their origins. Although rare, consideration should also be given to metastatic LELCs from other sites. Comprehensive physical examinations, laboratory tests, and imaging studies were conducted on our patient, revealing no lesions in organs other than the liver, including the nasopharynx.

Due to the limited number of reports, there is no report on standardized treatment strategies for LELC. Surgical resection remains the most effective treatment in almost all reported cases.[13,14] A small number of patients have also undergone radiofrequency ablation, immunotherapy combined with chemotherapy, and have achieved good results.[15,16] In this case, the patient underwent surgical resection and the operation was successful. So far, the patient has no signs of tumor metastasis or recurrence.

In addition, it is worth noting that literature shows that in LEL-CC, tumor cells and their interstitial immune cells (including lymphocytes, plasma cells, and neutrophils) all express PD-L1 to varying degrees, especially in Epstein-Barr virus-related cases. It is especially expressed in Epstein-Barr virus-related LEL-CC, suggesting that immunotherapy may be a potential treatment modality for LEL-CC.[17]

ICC is an aggressive malignant tumor, and the 5-year survival rate after surgical resection is only 15% to 40%.[18] The prognosis of LEL-ICC is better than that of traditional cholangiocarcinoma. Chan et al conducted a statistical analysis on 7 LEL-ICC patients and found that the 5-year overall survival rate was 100%, and some patients survived for 165 months without recurrence.[19] AlenSam Saji reported two patients who underwent surgery to remove tumors, followed by

adjuvant chemotherapy with the GS regimen, and combined immunotherapy including natural killer-cytokine-induced killing (NK-CIK) and nivolumab (PD-1 inhibitor), the prognosis is good, and the survival time is 100 months and 85 months respectively.[20] For some advanced patients with lymph node metastasis, the survival time after surgery and postoperative radiotherapy was 54 months without recurrence.[21] Although the number of reports on the prognosis of LEL-CC is limited, overall it is better than that of traditional cholangiocarcinoma. It may be that the infiltration of large numbers of lymphocytes reflects the host's anti-tumor immune response. Therefore, the prognosis of LEL-ICC is better than that of traditional hepatic cholangiocarcinoma. Compared with traditional intrahepatic cholangiocarcinoma, LEL-ICC has a lower postoperative recurrence rate and a longer survival period.

## Ethical Statement

No institutional approval was required for publishing the case details at our institution. Informed consent for clinical use of clinical data was obtained from the patient. Written informed consent for publication of their details was obtained from the patient.

## Informed Consent and Patient Perspective

The patient was satisfied with the medical procedure and the patient agreed with the publication of the article.

## Disclosure

The authors report no conflicts of interest in this work.

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