

# Contrast-enhanced Ultrasound Features of Lymphoepithelioma-Like Cholangiocarcinoma with Multiple Metastases: A Case Report

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**Abstract:** Lymphoepithelioma-like cholangiocarcinoma (LEL-CC) is an intrahepatic cholangiocarcinoma with a prominent lymphoid infiltrate. According to previous reports, most LEL-CCs are a single lesion with a notably better prognosis compared to typical liver cancers. However, most literature reported pathological features and lacked imaging features, especially that of ultrasound. We report on a 74-year-old female with LEL-CC presented with headache and malaise for six months. We performed superficial ultrasonography, abdominal ultrasonography, hepatic contrast-enhanced ultrasound, positron emission tomography-computed tomography, and ultrasound-guided biopsy. We definitively diagnosed LEL-CC with multiple metastases in the liver, skeleton, and lymph nodes.

**Key words:** Ultrasonography; Contrast-enhanced imaging; Cholangiocarcinoma; Liver; Metastasis

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Lymphoepithelioma-like intrahepatic cholangiocarcinoma (LEL-CC) is a rare distinctive variant of liver cancer characterized by a large number of lymphocytic infiltrates exceeding tumor cells, which has a favorable outcome [1]. However, only a few case reports have been involving imaging; most imagings of them are insufficient, particularly ultrasound [2]. Here, we report a case of LEL-CC with multiple metastases characterized by not only conventional ultrasound and contrast-enhanced ultrasound (CEUS), but also confirmed by positron emission tomography-computed tomography (PET-CT) and pathological examination.

## Case Report

A 74-year-old female with a 6-month history of headache and malaise presented to the hospital for treatment. She had a history of hypertension and diabetes, which were well controlled for 10 years with

metformin, pyrrolidone, gliclazide, and telmisartan. The gallbladder was resected 6 years previously due to cholecystolithiasis.

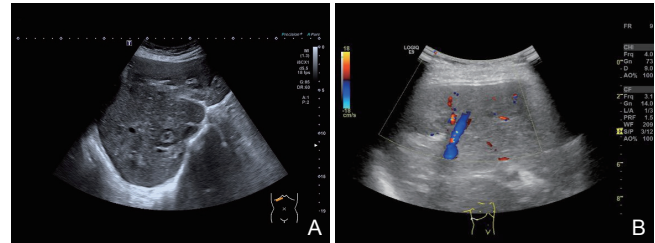
On physical examination after admission, multiple enlarged lymph nodes (approximately 30 × 30 mm) were palpated in the left neck that were hard, well defined, movable, and smooth. Laboratory examinations showed lactate dehydrogenase (LDH) 663.3 U/L, carbohydrate antigen (CA) 125 108.0 U/mL, CA153 12.5 U/mL, CA199 11.6 U/mL, carcinoembryonic antigen (CEA) 1.36 ng/mL, and alpha-fetoprotein (AFP) 2.44 ng/mL. Assays for hepatitis B virus and hepatitis C virus were HBsAg-negative, HBsAb-positive, HBeAg-negative, HBeAb-positive, HBcAb-positive, and HCV-negative.

Superficial ultrasonography revealed multiple hypoechoic nodules in the left neck. One of the largest nodules (32 × 16 mm) was located in level III of the left neck. On gray-scale ultrasound images, the nodules were well defined, indistinguishable between the cortex

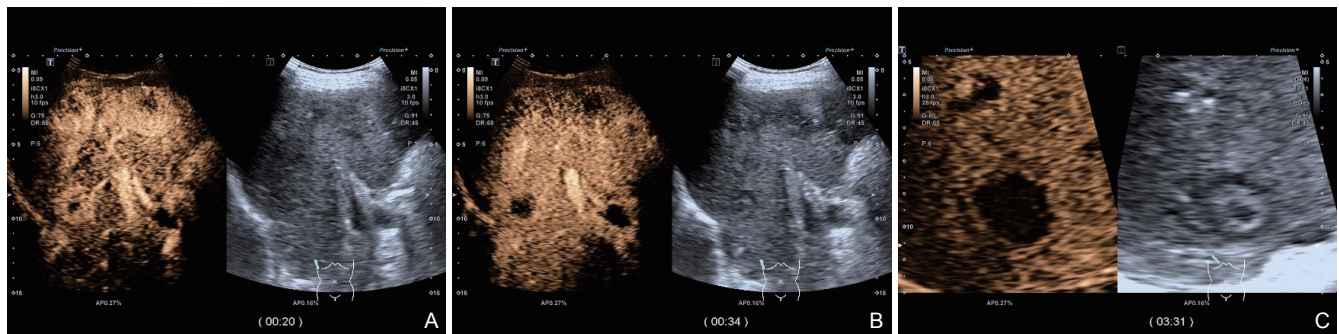
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and medulla, and disappeared at the lymphatic hilum. Color Doppler flow imaging (CDFI) showed the vascular pattern of nodules was aberrant and subcapsular. Ultrasound-guided biopsy of the nodules in the left neck was performed. Pathological examination suggested that the nodules were lymphoepithelioma-like carcinoma, and further examination should be performed on the nasopharynx and lung in particular. Molecular pathology was Epstein-Barr-encoded RNA (EBER)-positive. Immunohistochemical staining findings were CK-positive, P40-positive, eGFR-positive, VEGF-positive, CK5-positive, CK6-positive, Vim-negative, LCA-negative, S-100-negative, and Ki-67 approximately 90% positive. Routine abdominal ultrasound examinations were performed and multiple hypoechoic metastases were found in the liver. One of the largest liver masses (measuring of  $43 \times 28$  mm) was located in segment VII, which was uniform on internal echogenicity and showed a halo on peripheral echotexture. Overall, these masses had a bull's-eye appearance (Fig. 1A). CDFI

showed aberrant subcapsular vascular patterns (Fig. 1B). Thus, hepatic CEUS was conducted to obtain confirmatory information on the masses. The masses had rapid peripheral centripetal enhancement during the early arterial phase (Fig. 2A) and began to fade during the arterial phase (Fig. 2B). In the portal venous and the delayed phases, the masses were without enhancement. Finally, the tumor margins were clearer on CEUS (Fig. 2C).



**Figure 1** Routine abdominal ultrasonography. (A) Multiple hypoechoic masses spreading in the liver had an overall bull's-eye appearance; (B) Vascular patterns were aberrant and subcapsular.



**Figure 2** Hepatic contrast-enhanced ultrasound. (A) Masses showed rapid peripheral centripetal enhancement during the early arterial phase (20 seconds); (B) Masses began to fade during the arterial phase (34 seconds); (C) Masses were washed out during portal venous and delayed phases (211 seconds).

Concurrently, chest computed tomography (CT) showed that the lung was near normal except for some inflammation. Magnetic resonance imaging (MRI) of the nasopharynx showed the mucosa was only slightly thickened. Hence, PET-CT examinations were undertaken to explore the origin of the masses and determine the tumor stage. Multiple masses were detected in the liver, while the nasopharynx and lung were normal. Metastases were also visualized in the lymphatic and skeletal systems (Fig. 3).

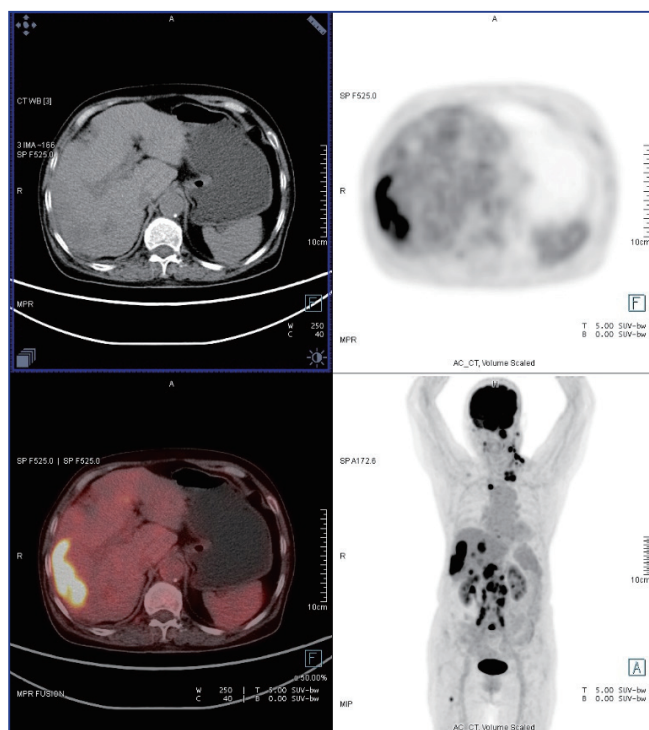
Ultimately, an ultrasound-guided biopsy of the intrahepatic masses was performed. Pathological examination confirmed LEL-CC. Molecular pathology was EBER-positive. Immunohistochemical staining results were CK7-positive, CK19-positive, CK8/18-positive, hepatocyte-negative, AFP-negative, P40-positive, LCA-negative, S-100, negative, and Ki-67 approximately 80% positive. The patient underwent

chemotherapy with sintilimab plus cisplatin and gemcitabine; the patient was alive at the 7-months postoperative follow-up.

## Discussion

Lymphoepithelioma-like carcinoma is a tumor composed of undifferentiated epithelial cells with a prominent lymphoid infiltrate. This entity was originally reported in the nasopharynx and subsequently has been observed in the lung, breast, prostate, bladder, uterus, liver, etc [3]. Notably, lymphoepithelioma-like carcinomas of the liver, including hepatocellular carcinoma (LEL-HCC) and intrahepatic LEL-CC are relatively significant findings because of their markedly better outcome compared to typical liver cancers [4]. This may be related to immunohistochemistry, such as Ki-67. Based on the World Health Organization (WHO)

2019 classification of tumors, in lymphocyte-rich hepatocellular carcinoma which is also called LEL-HCC, lymphocytes outnumber tumor cells in most fields on hematoxylin and eosin staining [1]. As a rare subtype of intrahepatic cholangiocarcinoma, the information about LEL-CC is few. Most studies had included pathology reports but lacked ultrasound features, especially CEUS.



**Figure 3** PET-CT. Multiple masses were detected in the liver, while the nasopharynx and lung were normal. Lymphatic Metastases were found in left cheek, left pharynx, bilateral neck, left supraclavicular area, right cardiodiaphragmatic angle, first hepatic hilum, abdominal periaorta, and bilateral common iliac periaorta. Skeletal metastases were also found in the right acromion, third thoracic vertebra, fifth lumbar vertebra, and right femur.

In our case, the patient had a history of headache and malaise with lymphadenectasis in the left neck. The combination of increased CA125 and EBER-positive status implied epithelial carcinoma with lymph node metastases. Conventional and CEUS examinations were then performed on this patient. Gray-scale ultrasound showed the tumors were multiple, hypoechoic, well defined, and normally shaped, with a blurry hypoechoic halo. To our knowledge, most LEL-CCs consist of a single lesion without metastasis; only a few cases of multiple lesions with metastases have been reported [5]. In this patient, CDFI showed an aberrant, subcapsular vascular pattern. CEUS showed rapidly peripheral centripetal enhancement and early washout during the

arterial phase without enhancement in the portal venous or delayed phases. However, these ultrasound features of LEL-CC had never been considered as specific for a differential diagnosis of hepatic metastasis, possibly due to its rarity [6], with diagnosis confirmed by the pathology.

Regarding CT and MRI, the imaging patterns have been described in some reports. In our patient, some imaging patterns showed marked peripheral arterial enhancement in the arterial phase and gradual centripetal enhancement in the delayed phase, while others showed homogeneous, moderate to marked enhancement in the arterial phase and gradual washout with a central scar or patchy enhancement in the delayed phase [7], which were the same appearance with those on CEUS.

## Conclusion

In summary, further exploration of the ultrasound features of LEL-CC is warranted, because they help assess the disease before treatment. Although it is deficient in specificity for the diagnosis of the disease, this case provides additional information of ultrasound and CEUS features of LEL-CC. However, the evidence is still limited to characterize sonographic findings based on a few cases in literature.

## Conflict of Interest

The authors have no conflict of interest to declare.

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