Primary Lymphoepithelioma-like Hepatocellular Carcinoma With Hepatic Cyst: a Case Report and Review of Literature

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Abstract

Background: Lymphoepithelioma-like hepatic carcinoma is a rare malignant tumor. It includes lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC) and lymphoepithelioma-like intrahepatic cholangiocarcinoma (LEL-ICC). We report the first case of hepatic cyst and LEL-HCC, which is extremely rare among hepatocellular carcinoma.

Case presentation: A 47-year-old female was admitted to our hospital with an unexpected health examination finding of liver nodules. Subsequently, the Computerized tomography (CT) revealed a tumor and a cyst. The Magnetic resonance imaging (MRI) found a 23×18 mm hepatic cyst in the right lobe of the liver and a 21×17 mm nodule in the left lateral lobe of the liver, and the nodule imaging was likely liver cancer. The patient underwent laparoscopic left lateral hepatectomy, and the histopathological examination revealed undifferentiated heterogeneous glandular epithelial cells with obvious lymphocyte infiltration. The Immunohistochemistry study CD3, CD20, Ki-67, CK, and CK19 results were positive, while CD10, P53, and CEA were negative in tumor tissues. Epstein-Barr virus (EBV) was negative in situ hybridization. For this patient, the LEL-HCC diagnostic was made according to the histopathological result. Surgical resection is the first choice for this kind of patients, but immunotherapy may be more promising for them in the future.

Conclusion: LEL-HCC is a rare variant of HCC, characterized by dense lymphocyte infiltration and a good prognosis. We report the first patient with hepatic cysts and LEL-HCC, which is distinctly uncommon in the HCC patients. Because the hepatic cyst and tumor are similar in certain imaging studies, our work can provide information for clinical diagnosis.

Background

Lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC) is a rare malignant tumor composed of undifferentiated epithelial cells with obvious lymphocyte infiltration.^[1] Lymphoepithelioma-like carcinomas (LELC) have also been found on the skin, stomach, bladder, vagina, ovary, uterus, and colon,^[2–8] and show similar pathological morphology features. There are far more patients with lymphoepithelioma-like intrahepatic cholangiocarcinoma (LEL-ICC) than that of LEL-HCC, suggesting that lymphoepithelioma-like liver carcinoma is more likely to occur in the bile duct glands around the intrahepatic bile duct. The accumulation of liver lymphocytes may be due to a unique immune response against liver tumors.^[9] Due to the lack of typical imaging graphics and laboratory examination results, LEL-HCC is easily misdiagnosed as hemangiomas or cirrhotic nodules before histopathology and immunohistochemistry. Although a few authors have previously reported LEL-HCC, no literature has reported a patient with LEL-HCC and liver cyst. We reported a 48-year-old Asian woman and analyzed the latest case review data until 2020 to provide more imaging and pathological information about this disease for clinical work.

Case Presentation

A 39-year-old woman was incidentally found to have two liver-occupying lesions during a routine medical examination in the tertiary hospital. The patient was referred to our hospital for better care the next day. The enhanced abdominal CT examination showed a lower density nodule in the upper part of the left lateral lobe of the liver. The enhanced scan was slightly strengthened, and the border was not clear. The size was about 23×16mm. The right lobe of the liver was scattered with a round and low-density shadow, without obvious enhancement, and the border was clear. The size of the largest one was about 24×28mm (Figure 1A, B). Further investigation of medical history revealed no specific symptoms, and physical examination revealed no abnormalities. Hepatitis virus markers were positive for HBsAg, HBeAg, and HBcAb. The patient's serum tumor marker carcinoembryonic antigen 724 (CEA724) was 9.67U/ml (normal range <6.9 U/ml). The other tumor markers, including alpha-fetoprotein (AFP), ferritin, abnormal tumor protein, CEA, CA125, and CA199, were negative. Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) were normal. The patient underwent an MRI in our hospital, and the results showed that the left lateral lobe liver had a slightly longer T1 and T2 nodule shadow, DWI diffusion was limited, and the size was about 21.2×17.7mm. The enhanced arterial phase was strengthened, and the portal vein phase and the delayed phase were mainly borderline enhancement. A long T1 and long T2 signal shadow existed in the right lobe of the liver, the size of which was about 23×18mm. The signal shadow boundary is clear and circular, and there is no enhancement in each phase of the enhanced scan (Figure 1C-H).

On being diagnosed with left lateral lobe liver cancer, the patient underwent laparoscopic left external lobe hepatectomy. Due to the small cyst on the left side of the liver and without any symptoms was not surgically removed. The surgeon saw no obvious liver cirrhosis during the operation, and a 20x20mm mass was seen on the surface of the left outer lobe. The operation time was 120 minutes, and the intraoperative blood loss was about 200 mL. Postoperative recovery was smooth, and she was discharged from the hospital on the 9th postoperative day. Visual inspection revealed that the resected mass was a gray-white lesion with no envelope and clear boundaries. Histopathological examination revealed that the lesion consisted of undifferentiated heterogeneous glandular epithelial cells with obvious lymphocyte infiltration (Figure 2). Immunohistochemistry showed CD3, CD20, Ki-67, CK, and CK19 were positive, while CD10, P53, and CEA were negative in tumor tissues. (Figure 3) Epstein-Barr virus (EBV) was negative in situ hybridization. All signs were consistent with the diagnosis of LEL-HCC. After 3 months of close follow-up, this patient did not have tumor recurrence or metastasis.

Discussion

Lymphoepithelioma-like carcinoma (LELC) is an undifferentiated carcinoma infiltrated by many lymphocytes and can appear in multiple tissues in the body. LEL-HCC is a rare tumor compared with LELC. In 2010, WHO (World Health Organization) confirmed the tumor as a "variant" of HCC, called lymphoepithelial-like hepatocellular carcinoma or inflammatory hepatocellular carcinoma.^[10] In the past, an article reported that a patient had LEL-HCC and HCC at different locations simultaneously.^[11] We reported the first patient with LEL-HCC and hepatic cyst. Due to the low invasiveness of LEL-HCC tissue, its imaging features were not as typical as traditional HCC.

To understand the characteristics of this rare disease, we reviewed 17 studies involving 57 cases of LEL-HCC patients.^[11–27] The clinical characteristics of the cases in these articles are summarized in Table 1. All patients included 34 males and 23 females; the average age was 59.5 years, ranging from 37 to 81 years. Most of the cases in the reviewed sample were single lesions, with tumor diameters ranging from 10–72 mm, with an average of 37 mm. Among 57 patients, 27 patients were diagnosed with cirrhosis (43.8%). Chronic hepatitis is closely related to liver cancer, 25 cases were hepatitis B, and 8 cases were hepatitis C in the retrospective cases. The AFP of HCC patients is often higher than 400ng/ml, but the AFP of LEL-HCC patients is usually negative. The rise of AFP levels is caused by the increase in AFP release from liver cells into the blood during tumor progression. The increase in AFP is not obvious due to the suppression of carcinogenesis and the immune response of tumors in patients with LEL-HCC. In addition, most patients with LEL-HCC have no specific symptoms and are diagnosed mainly by clinical examination. There was no significant difference in the incidence of tumors between the right and the left lobe of the liver. Six patients were diagnosed with LEL-HCC after liver transplantation, and 51 patients were diagnosed with partial hepatectomy. Only 4 patients with vascular invasion showed that the LEL-HCC is not as invasive as traditional hepatocellular carcinoma. The reason may be that infiltrating lymphocytes have an inhibitory effect on the malignant behavior of cancer cells.^[12]

Table 1

Clinicopathological characteristics of lymphoepithelioma-like HCC reported in the literature

Case (ref.)	Year	Age	Sex	No.of lesions	Site	Size[mm]	Cirrhosis	EBV	HBV	HCV	AFP (ng/ml)	Symptom	Treatment	Venous Invasion
1 [12]	1998	62*	10M/1F	NR	NR	22*	6/11	□	□	□	194.5	NR	LR	1/11
2 [13]	2000	54*	5M	2*	NR	34*	4/5	□	2/5	3/5	□	NR	LT	1/5
3 [14]	2004	39	F	1	NR	10	□	□	□	□	□	□	LT	□
4 [15]	2007	56	M	1	R	30	□	□	□	□	□	□	LR	□
5 [16]	2008	47	F	1	R	22	□	□	□	□	NR	□	LR	□
6 [17]	2009	57	M	2	R	27	□	□	□	□	17.5	□	LR	□
7 [18]	2013	79	M	1	L	50	□	□	□	□	43	□	LR	□
8 [19]	2014	68*	2M/6F	2:NR/6:1	NR	68*	□	□	□	□	6□/2□	NR	LR	NR
9 [20]	2015	50	M	1	R	30	□	□	□	□	31.9	□	LR	□
10 [21]	2015	81	F	1	L	72	□	□	□	□	80.5	□	LR	□
11 [22]	2015	57*	13M/7F	NR	NR	38*	8/20	□	17/20	□	7□/13□	NR	LR	2/20
12 [23]	2015	42	F	1	L	46	□	□	□	□	56.3	□	LR	□
13 [24]	2017	73	F	1	S7	12	□	NR	□	NR	2.4	□	LR	□
14 [25]	2017	58	F	1	S6	40	□	□	□	□	6852.0	NR	LR	□
15 [26]	2017	37	F	1	R	32	□	□	□	□	105.8	□	LR	□
16 [27]	2018	62	F	1	S6	50	□	NR	□	NR	394.9	□	LR	□
17 [11]	2018	77	F	2	S4.S5	22	□	□	□	□	9.3	□	LR	□
18	2020	47	F	1	L	23	□	□	□	□	2.8	□	LR	□

F, female; M, male; L, left liver; R, right liver; LR, liver resection; LT, liver transplantation; AWD, alive with disease; AWOD, alive without disease; DOD, died of disease; NR, not report; HBV, Hepatitis B virus; HCV, Hepatitis C virus; EBV, Epstein-Barr virus; AFP, Alpha-fetoprotein; * Indicated as mean value.

Epstein-Barr virus (EBV) is a member of the genus Lymphotropic Virus of the Herpesviridae family, and most adults have viral antibodies. Previous studies have shown that the EBV virus is closely related to nasopharyngeal carcinoma and Burkitt's lymphoma. In addition, lymphoid epithelioid carcinoma in most hollow organs is also associated with the EBV virus. However, there is no direct evidence of lymphoid epithelial cancer in the liver and breast related to EBV.^[28] Only one case of EBV-positive patients has been diagnosed with LEL-HCC.^[14] EBV is not limited to lymphoid epithelioma-like carcinoma^[29]. It plays a carcinogenic role in common epithelial carcinomas and may also play a carcinogenic role in precancerous hyperplasia and dysplasias. Almost all tissues and organs of LELC have a better prognosis than other subtypes of tumors at the same location.

The pathological features of LEL-HCC are poorly differentiated or undifferentiated, large, and atypical tumor cells; mitotic division is common. The tumor stroma is full of abundant inflammatory cells dominated by lymphocytes, similar to lymphoepithelial lesions.^[30] Lymphocytes can produce specific antibodies and then combine with immunoreactive substances, such as alexin to destroy cancer cells. Our immunohistochemical analysis showed that CD3(+), CD20(+), Ki-67(+), CK(+), and CK19(+) in tumor cells. Some articles have shown that T cells are more predominant than B cells in LEL-HCC, mainly composed of CD4 and CD8.^[16, 17, 26, 27] CD20+ (a B lymphocyte marker expressed on mature B cells but not on plasma cells) lymphocytes promote favorable outcomes in several human cancers, and the underlying mechanisms might include producing tumor-specific antibodies and secreting cytokines that enhance anti-tumor immunity in the local tumor environment.^[31] The expression of CK and CK19 is related to the poor differentiation of HCC. Intact CKs inhibit cell aggregation and promote cell movement by anchoring specific cell membrane receptors, closely related to tumor cells' invasion and metastasis mechanism.^[32] Ki67 is a nuclear antigen associated with proliferating cells. Its function is to participate in karyokinesis and is indispensable in cell proliferation. As an antigen that marks the cell proliferation state, Ki67 positive indicates that cancer cells are proliferating more actively, and the mechanism needs to be further researched. The first-line treatment of LEL-HCC is liver resection, which has been proven to achieve satisfactory results. Due to the massive infiltration of inflammatory cells in LEL-HCC, related to the body's supernormal immune response to tumors, PD1/PD-L1 targeted immunotherapy for LEL-HCC may have good prospects.^[24]

Conclusion

We report the first case of LEL-HCC with liver cyst, and the characteristic cytological feature of this rare tumor is the presence of many lymphocytes around the tumor cells. It is known that the prognosis of LEL HCC may be favorable by reviewing all cases reported as LEL-HCC in the English literature. Due to the lack of specificity of the clinical manifestations of the disease, pathological and cytological examinations can provide useful information for the diagnosis of LEL-HCC.

Abbreviations

LEL-HCC: Lymphoepithelioma-like hepatocellular carcinoma ; LELC: Lymphoepithelioma-like carcinomas ; LEL-ICC: Lymphoepithelioma-like intrahepatic cholangiocarcinoma ; CT: Computerized tomography ; MRI: Magnetic resonance imaging; EBV: Epstein-Barr virus.

Declarations

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Not applicable.

Authors' contributions

YZQ: Data collection, manuscript preparation, revising the manuscript. LFY: Data collection, Patient's surgery, WXL: manuscript preparation, final approval of the manuscript. MB: Study design, patient's coordinator, final approval of the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Written informed consent was obtained from the patient to participate in this case report.

Consent to publish

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1
(A, B) Abdominal CT showed a cyst (A) in the right liver and a tumor in the left lateral liver(B). (C-H) Preoperative MRI showing a 23×18 mm cyst in the right liver and a 21×17 mm tumor in the left lateral liver, (C) plain scan on T1WI; (D) plain scan on T2WI; (E) arterial phase; (F) portal venous phase; (G) delayed phase; (H) MRI with Gd-EOB-DTPA. CT, computed tomography. MRI, magnetic resonance imaging.

Figure 2
Microscopic features of tumors. Microscopically, the larger lesion composed of undifferentiated epithelial cells, prominent nucleoli and significant lymphocytic infiltration. (A) HE ×100; (B) HE ×400; HE, hematoxylin and eosin.

Figure 3

Immunohistochemical examinations after surgery. Microscopically, CD3, CD20, Ki-67, CK and CK19 were confirmed as positive, while CD10, P53, EBER and CEA were negative in tumor tissues. (A) CD3 $\times 200$; (B) CD20 $\times 200$; (C) Ki-67 $\times 200$; (D) CK $\times 200$; (E) CK19 $\times 200$; (F) CD10 $\times 200$; (G) P53 $\times 200$; (H) EBER $\times 200$; (I) CEA $\times 200$. EBER, EBV-encoded RNA; CK, cytokeratin; HE, hematoxylin and eosin.