Lymphoepithelioma-like hepatic carcinoma: A report of 3 cases and review of the literature

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Case report

Keywords: Liver Cancer, Lymphoepithelioma-like carcinoma, Hepatocellular carcinoma, Cholangiocarcinoma

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Abstract

Background: Lymphoepithelioma-like hepatic carcinoma is a rare distinctive variant of liver cancer with unique epidemiological and pathological characteristics, characterized by dense lymphocyte infiltration. It can be divided into lymphoepithelioma-like hepatocellular carcinoma and lymphoepithelioma-like intrahepatic cholangiocarcinoma. Existing research shows that its prognosis is good. Up to now, only 101 cases have been reported. More rarely, combined lymphoepithelioma-like hepatocellular carcinoma and cholangiocarcinoma has been found.

Case presentation: The first patient was a 62 years old Chinese man with hepatitis B virus infection presented with a single lesion in the liver. The patient underwent surgical treatment and was discharged on the 4th day. The patient was diagnosed as combined lymphoepithelioma-like hepatocellular carcinoma and cholangiocarcinoma and has been alive for 15 months. The second patient was a 63 years old Chinese woman with right upper abdominal pain and hepatitis B virus infection. The imaging examination a single lesion in the liver. The patient underwent surgical treatment and was discharged one week later. The patient was diagnosed as lymphoepithelioma-like hepatocellular carcinoma and was considered to be the recurrence of lymph nodes about 2 years after operation. The patient underwent local radiotherapy and has been alive for 60 months. The third patient was a 50 years old Chinese man with hepatitis B virus infection presented with a single lesion in the liver and two enlarged lymph nodes. The patient received liver puncture before operation to indicate lymph node metastasis and had local recurrence after liver resection. The patient underwent chemotherapy and radiotherapy. The patient was diagnosed as lymphoepithelioma-like hepatocellular carcinoma. Finally, the patient died at 24 months follow-up.

Conclusions: This article reports 3 cases of LELC and reviews the current research discovery, which suggests that even the locally advanced patients of LELC with postoperative recurrence and preoperative lymph node metastasis should be actively treated and intervened for a longer survival period.

Keywords: Liver Cancer, Lymphoepithelioma-like carcinoma, Hepatocellular carcinoma, Cholangiocarcinoma

Background

At present, liver cancer is now the second cause of cancer-related death in the world[1].Primary liver cancer is one of the most common malignant tumors in China. The incidence rate is third, and the mortality rate is fourth[2].Primary liver cancer is composed of hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC). Because most patients are in advanced stage, the treatment options available are very limited. Research shows that its 5-year survival rate is only 16% in the United States, making it the most aggressive malignancy after pancreatic cancer[3].

LELC is a kind of tumor composed of undifferentiated epithelial cells, which has obvious lymphoid infiltration and was originally used to describe nasopharynx. Subsequently, other organs, including the lung, breast, prostate, bladder, uterus and liver, were also reported[4–9]. Similar to primary liver cancer, LELC can be divided into lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC) and lymphoepithelioma-like intrahepatic cholangiocarcinoma (LEL-CC).[10]In 1998, Wada et al[11] defined LELC as the presence of more than 100 tumor infiltrating lymphocytes in 10 high power fields, but no unified definition has been formed. Only a few cases have been reported during this period. LELC was subsequently acknowledged by the World Health Organization as a distinctive variant of liver cancer in 2010[12], and its diagnosis needs to observe lymphocyte infiltration, but the density of lymphocyte infiltration required for further diagnosis is not clear. Therefore, the definition and pathological classification of LELC are still under study. LELC is a relatively rare finding with a significant increase in the number of reported cases over the past few years (Fig. 1). Up to now, from 1998 to 2020, 41 literatures have been searched, 67 cases of LEL-HCC and 34 cases of LEL-CC have been reported.

At present, it is believed that LELC has unique epidemiological and pathological characteristics. Compared with the typical HCC and ICC, the prognosis of LELC is good. It may be related to a large number of lymphocyte infiltration[10]. In a word, LELC is a distinctive variant of liver cancer. Its lymphocytic infiltration may be related to immune response and good prognosis. Its pathogenesis and factors affecting prognosis deserve further study.

This article reports 3 cases of LELC and reviews the current research discovery on LELC in terms of epidemiology, clinical treatment, pathology and research prospects.

Case Presentation

First case

The first patient was a 62 years old Chinese man who was hospitalized on September 5, 2018 due to the high AFP found during the routine physical examination and the liver tumor indicated by abdominal ultrasound. Laboratory examination showed that AFP: 19.5 ng/ml (0–7 ng/ml), CEA: 5.31 ng/ml (0–5 ng/ml), CA199: 17.26u/ml (0-37u/ml). Hepatitis B examination showed that HBsAb(+), HBeAb(+), HBcAb(+). No abnormality in blood routine test. Blood biochemical test showed that DBIL was 5.9umol/l (0-5.1umol/L), IBIL was 13.70umol/l (0-11.97umol/L). Coagulation test showed that the plasma D-dimer was 0.61 mg/l FEU (0-0.55 mg/L FEU). PET-CT showed that there was a slightly low density nodular shadow under the capsule of the left outer lobe of the liver, the boundary was unclear, about 2.8 × 2.4 cm. The radiation uptake was increased and the maximum SUV was 4.0. It was regarded as malignant lesions and the radiation uptake of the remaining liver parenchyma was no clear difference. Multiple lymph nodes was found in the abdominal and part of the radioactivity uptake increased. The maximum SUV is 4.6 and a large diameter lymph node is about 0.9 cm. No other extrahepatic tumor was found in imaging examinations.

After discussion by multidisciplinary team (MDT), we decided to perform surgical treatment for the patients and the way of operation is laparoscopic left lateral lobectomy of the liver. Intraoperative findings: no ascites was found, no nodule was found in abdominal and pelvic peritoneum, no abnormality was found in spleen, stomach, small intestine and large intestine, no obvious expansion of gallbladder and common bile duct. The appearance of gallbladder is

normal, no stones or masses are found in it. Enlarged lymph nodes not detected around hepatoduodenal ligament. The liver is soft without obvious cirrhosis. The tumor is located in the left lateral lobe of the liver. It is tough and protrudes on the surface of the liver. The rest of the liver is normal. Macroscopically, a 16 × 8 × 4 cm segment of the liver was resected. There was a 2.8 × 2.5 × 2.5 cm grey-white hard tumor mass in the section. Pathologic diagnosis: lymphoepithelioma-like hepatic carcinoma (LELC). It is mainly hepatocellular carcinoma with differentiation of scattered cholangiocarcinoma, which is mainly solid nest like. Edmondson-Steiner stage: III(Poorly differentiated). The tumor belongs to small liver cancer, involving the liver capsule, without clear necrosis or microvascular invasion(MVI:0). There is no satellite nodule in the surrounding liver tissue and no cancer at the cutting edge of the liver. TNM stage: T1N0M0. BCLC stage: A. Immunochemistry analysis shows AFP(-), Arg-1(-), CA199(-), CK18(3+), CK19(1+), CK7(1+), GPC3(3+),Hepatocyte(+) and EBER ISH(+). This case can be diagnosed as LELC. The operation was successful and the patient was discharged on the 4th day after the operation. After discussion by MDT, We decided to do regular observation rather than postoperative adjuvant treatment according to pathologic diagnosis. The patient has been alive for 15 months since performance of surgery and the patient's living condition is good.

Second Case

The second patient was a 63 years old Chinese woman who was hospitalized on on January 22, 2015 due to paroxysmal right upper abdominal pain for one year. Hepatitis B examination showed that HBsAb(+), HBeAb(+), HBcAb(+). Laboratory examination showed that AFP: 1.49 ng/ml (0–7 ng/ml), CEA: 0.545 ng/ml (0–5 ng/ml), CA199: 9.02 u/ml (0-37u/ml). The patient were treated with aspirin after coronary stent implantation for coronary heart disease 3 years ago. The patient's previous history of hypertension is under good control at present. The patient underwent hysterectomy 15 years ago for endometriosis. Abdominal MRI suggested that liver S7 was a space occupying lesion, considering the possibility of malignant tumor, cholangiocarcinoma or metastatic cancer, with liver lymph node metastasis and slightly larger spleen. On January 27, 2015, the patient underwent irregular resection of the right liver plus hilar lymphadenectomy. Macroscopically, a 7 × 7 × 3.5 cm segment of the liver was resected. There was a 3.2 × 2 × 2.2 cm grey-white hard tumor mass in the section. The tumor boundary was not clear, involving the hepatic capsule, and the closest distance from the base margin was 1.1 cm. There was no obvious nodular change in the surrounding liver. Pathological diagnosis is LELC. It is mainly hepatocellular carcinoma. The tumor involved the hepatic capsule, and no cancer was found at the cutting edge of the liver base. Lymphocytes infiltrated the peripheral hepatic portal area and no metastatic cancer was found in the lymph nodes removed. TNM stage: T1N0M0. BCLC stage: A. Immunochemistry analysis shows CK18(2+), CK7(-), CK19(-), CEA(-), Hepatocyte(-), AFP(-), EBER(-), CD20(-), CD4(1+) and CD8(-). This case can be diagnosed as LELC.

The patient recovered well and was discharged one week later. There is no obvious abnormality in regular reexamination for more than one year. The patient received PET-CT for whole body on December 26, 2016, which revealed multiple lymph nodes in the portal space, with high uptake. The largest SUV is 11.0. The short diameter is about 2.5 cm, which is considered to be the recurrence of lymph nodes after liver cancer operation. After discussion by MDT, because of the close relationship of tumor between blood vessels and duodenum, it is difficult to operate. It is suggested that local radiotherapy should be performed. From February 6, 2017 to March 10, 2017, IMRT was performed in our hospital after completing the examination. Prescription dose of first course: 95% pGTV 6.72 Gy/3.36 Gy/2f,95% PTV 3.6 Gy/1.8 Gy/2f; Prescription dose of second course: pGTV 55.2 Gy/2.4 Gy/23f95% PTV 41.4 Gy/1.8 Gy/23 f., 25 radiotherapy completed. Simultaneous Xeloda chemotherapy taken orally twice was used on radiotherapy day, which prescription dose was 1650 mg/m^2/d. Then the patient carried out auxiliary acid suppression, mucosal protection, liver protection and blood promotion treatment and was discharged smoothly after treatment. After 60 months of follow-up, the patient is in good condition. Disease free survival (DFS) is 23 months.

Third Case

The third patient was a 50 years old Chinese man who was hospitalized on April 29, 2014 due to the liver tumor found during the routine physical examination. Hepatitis B examination showed HBsAg(+), HBeAb(+), HBcAb(+), HCV-Ab(+) and HBV-DNA(-). Laboratory examination showed that AFP: 31.93 ng/ml (0–7 ng/ml), CA199: 10.51u/ml (0-37u/ml). The patient had type II diabetes mellitus, and the blood sugar was well controlled at present. Abdominal MRI showed 2.7 × 2.2 cm right anterior segment tumor with cirrhosis.(Fig. 2A). Multiple enlarged lymph nodes can be seen in the retroperitoneum, with a maximum of about 5.2 × 3.4 cm (Fig. 2B). An enlarged lymph node can be seen behind duodenal ligament, next to the portal vein (Fig. 2C). Abdominal ultrasound showed a hypoechoic nodule at liver dome, about 1.9 × 2 cm. A hypoechoic lymph node, about 4.2 × 2.9 cm, can be seen 5 cm behind the peritoneum, without obvious blood flow signal. After discussion by MDT, the patient underwent endoscopy and colonoscopy, and malignant lesion in stomach or colorectum was excluded. Percutaneous ultrasound guided biopsy was performed for the tumor and enlarged lymph node. The pathology showed no cancer in the liver tumor but existing cancer cells in the lymph node. To assure the result, the patient received PET-CT for whole body, which was considered as primary liver cancer. PET-CT showed increasing radioactive uptake lesion in the VIII segment of liver and increasing radioactive uptake lymph nodes in portal, retropancreatic, and retroperitoneal regions. After second discussion by MDT, tumor and enlarged lymph nodes resection was recommended. On May 23, 2014, the patient underwent hepatectomy of VIII segment and two enlarged lymph nodes resection. The liver was dark red in slightly decreased size with diffuse micronodular sclerosis in intraoperative findings. The tumor was in the segment VIII of right lobe, about 3.5 × 3 cm (Fig. 3A). One enlarged lymph node was next to the portal vein, behind duodenal ligament, about 4.5 × 3 cm(Fig. 3B). Another was on the upper margin of pancreas, next to abdominal aorta and common hepatic artery, about 5.5 × 4 cm (Fig. 3C). Macroscopically, segment of the liver resected was about 10 × 8.5 × 7 cm. There was a 3.5 × 3.5 × 3 cm circumscribed grey-white soft tumor from the nearest liver resection margin. Adjacent liver tissue was micronodular cirrhosis. Microscopically, the tumor was composed of poorly differentiated hepatocellular carcinoma with lymphoid infiltration. There was no liver capsular invasion and microvascular invasion. And the margin of liver incision was negative (Fig. 4A). The two resected lymph nodes were infiltrated with hepatocellular cancer cells in center (Fig. 4B). Immunochemistry analysis shows AE1/AE3 (2+), AFP (1+), CK18 (2+), CK19(2+), CK20 (1+), CK7 (-), and EBER (-) (Fig. 4C/4D). Pathological diagnosis is LELC. TNM stage:T1N1M0. BCLC stage: C.

One month after the operation, pre-chemotherapy abdominal CT showed retroperitoneal enlarged lymph nodes, considered as local recurrence. From August 4, 2014 to September 2, 2014, the patients received 3 cycles chemotherapy of oxaliplatin and tegio; from October 5, 2014, the patients received 1 cycle chemotherapy of paclitaxel / cisplatin ; from October 21, 2014 to November 14, 2014, the patients received 2 cycles chemotherapy of paclitaxel ; from November 28, 2014 to December 28, 2014, the patients received 3 cycles chemotherapy of cisplatin. Reexamination of CT after nine cycles of chemotherapy indicated that the retroperitoneal multiple enlarged lymph nodes had little change compared with the anterior lymph nodes. Later, patients were treated with radiotherapy. Locating and delineating the target area: GTV: Retroperitoneal lymph nodes can be seen on imaging. PGTV: GTV expands outward by 0.5 cm. CTV: GTV, hilar and retroperitoneal lymphatic drainage area. PTV: CTV plus 0.5 cm (front, back, left and right) plus 1 cm (up and down). Prescription dose: 95% PGTV 60.2 Gy/ 2.15 Gy/ 28F, 95% PTV 50.4 Gy/1.8 Gy/28F. On March 5, 2015, the radiotherapy was completed and the patient was discharged smoothly.

The patient died at 24 months follow-up. The DFS is 1 month. Overall survival (OS) is 24 months. This patient was previously reported by us and we updated and integrated the information. The detailed clinical data and pathological characteristics of the above three patients are shown in Table 1 and Table 2.

Table 1
The demographic and oncological characteristics of 3 patients

Case	Sex	Age, years	Region	HBV	HCV	Cirrhosis	AFP, > 7 μg/L	BCLC stage	No. Of lesions	Size,mm	Treatment	Recurrence	FU, mo.	Outcome	D m
First	M	62	Asian	+	-	-	+	A	1	28	LR	N	15	AWOD	/
Second	F	63	Asian	+	-	-	-	A	1	32	LR + RT	Y	60	AWOD	2
Third	M	50	Asian	+	-	+	+	C	1	35	LR + CT + RT	Y	24	DOD	1

F, female; M, male; +, positive; -, negative; AFP, a-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; N, NO; Y, Yes; LR, liver resection; CT, Chemotherapy; R Radiotherapy; AWOD, alive without disease; DOD, died of disease; FU, follow-up; mo., months; DFS, Disease-free survival.

Table 2
Pathological classification and immunohistochemical markers of 3 patients

Case	Diagnosis	Classification	Lymph node	TNM stage	AFP	Hepatocyte	CK7	CK19	CK18	EBER ISH
First	LELC	Hepatocellular&Cholangio-carcinoma differentiation	/	T1N0M0	-	+	+	+	+	-
Second	LELC	Hepatocellular	N	T1N0M0	-	-	-	-	+	-
Third	LELC	Hepatocellular	P	T1N1M0	1+	-	-	+	+	-

LELC, lymphoepithelioma-like hepatic carcinoma; -, negative; +, positive; AFP, a-fetoprotein; EBER, EBV-encoded RNA; ISH, in situ hybridization.

Literature review

LELC is a distinctive variant of liver cancer and can be divided into LEL-HCC and LEL-CC. LELC is a relatively rare finding. Up to now, from 1998 to 2020, 41 literatures have been searched, 67 cases of LEL-HCC and 34 cases of LEL-CC have been reported.

1. Lymphoepithelioma-like Hepatocellular Carcinoma (lel-hcc)

LEL-HCC is one of the pathological classification of LELC. To date, 67 cases of LEL-HCC have been reported and are detailed in Table 3. Available demographics of the patients and features of the tumors are displayed in Table 4. Calderaro et al[13] mentioned 13 cases of LEL-HCC who underwent liver resection for hepatocellular carcinoma in a literature, but no relevant information was provided. According to the current literature analysis, the majority of patients with LEL-HCC are male White, 63% of them are male patients, and the median age is 58 years old (37–81). 22 patients were complicated with HBV infection, accounting for 41%; 19 patients with HCV infection, accounting for 35%; 24 patients with cirrhosis, accounting for 45%; 21 patients with AFP increased, and higher than 20 ug/L, accounting for 51%; most patients with BCLC stage of 0/A; 25% of patients showed vascular invasion; only one patient with EBV infection. Most of the patients received surgical treatment, accounting for 91%, and 6 patients received liver transplantation.

Macroscopically, the tumor has good limitations and encapsulation, which is gray-white, soft to touch[9]. The median size of the tumor is 38 mm (10–130); histologically, the cancer cells are poorly differentiated, composed of atypical cells, with prominent nuclei and nucleoli. A large number of lymphocytic infiltrates are characteristic and common in LEL-HCC, which can be distinguished from typical HCC and compared with LEL-CC[11, 14]; most of infiltrating lymphocytes are T cells, mainly CD8 + T cells, and focal CD20 + B cells are also found[14].

The diagnosis of LEL-HCC mainly depends on pathological methods. There is no specificity in the clinical manifestations and imaging examination of patients. Most of the patients are confirmed by pathological diagnosis and immunohistochemistry after surgical treatment.

In terms of survival and prognosis, the prognosis of LELC is better than that of typical liver cancer. According to Chan et al[15], compared with HCC, LEL-HCC has better overall survival (5-year survival 94.1%: 63.9%; P = 0.007) and progression free survival (5-year survival 87.8%: 46.6%, P = 0.002). Multivariate

analysis suggested that LEL-HCC was an independent prognostic factor for overall progression free survival.

Table 3
Reported Cases of LEL-HCC

Reference	Age/Sex	Race	HBV	HCV	EBV	Liver cirrhosis	AFP, > 20 μg/L	Tumor location	BCLC (0/A)	Tumor no.	Tumor size(mm)	Vascular invasion	Treatment
An et al[9]	50/M	Asian	+	-	-	+	+	R	-	1	35	-	LR
Wang et al[16]	37/F	NA	+	+	-	+	+	R	+	1	32	NA	LR
Chen et al[17]	56/M	Asian	-	+	-	+	+	R	+	1	32	-	LR
Cacciato Insilla et al[18]	81/F	NA	-	+	-	-	+	L	+	1	72	NA	LR
Shinoda et al[19]	79/M	Asian	-	-	-	-	+	L	+	1	42	-	LR
Wei et al[20]	42/F	Asian	-	-	-		+	L	+	1	46	NA	LR
Park et al[14]	57/M	Asian	+	-	-	+	-	R	+	1	27	NA	LR
Emil et al[21]	50/M	White	+	+	-	+	-	NA	+	1	40	-	OLT
	54/M	White	-	-	-	-	-	NA	+	2	20	-	OLT
	59/M	White	+	+	-	+	-	NA	-	4	50	-	OLT
	45/M	White	-	+	-	+	-	NA	+	1	20	-	OLT
	64/M	White	-	-	-	+	-	NA	-	2	40	+	OLT
Si et al[22]	39/F	Latino	-	+	+	+	NA	NA	+	1	10	+	OLT
Nemolato et al[23]	47/F	NA	-	-	-	-	NA	R	+	1	22	NA	LR
Shirabe et al[24]	58/F	Asian	+	-	NA	+	+	R	+	1	22	NA	LR
Patel et al[25]	74/F	White	-	-	-	-	-	NA	-	Multi	65	+	LR
	65/M	White	-	-	-	-	-	NA	+	1	48	-	LR
	65/F	White	-	-	-	-	+	NA	+	1	13	-	LR
	70/F	White	-	-	-	-	+	NA	+	1	27	-	LR
	61/F	White	-	-	-	-	-	NA	-	Multi	95	+	LR
	78/M	White	-	-	-	-	-	NA	+	1	105	+	LR
	78/F	White	-	-	-	-	-	NA	+	1	60	-	LR
	57/F	White	-	-	-	-	-	NA	-	1	130	+	LR
Chan et al[15]	58*/13M, 7F	NA	17/20	0	0	8+/20	13/20	NA	20+/20	1	38	NA	LR
Wada et al[11]	62*/10M, 1F	NA	0/11	11/11	/	6/11	NA	NA	NA	NA	22	1+/11	LR
Calderaro et al mentioned 13 cases of LEL-HCC who underwent liver resection for hepatocellular carcinoma in a literature, but no relevant information was pr													
F, female; M, male; +, positive; -, negative; AFP, a-fetoprotein; NA, not available; HBV, hepatitis B virus; HCV, hepatitis C virus; EBV, Epstein-Barr virus; no., numbe resection; CT, Chemotherapy; OLT, orthotopic liver transplant; N, NO; Y, Yes; FU, follow-up; mo., months; *Indicated as mean value.													

Table 4
Population and tumor characteristics of patients with LEL-HCC and LEL-CC

Classification	Male	Medianage, years (range)	Race		HBV+	HCV+	Cirrhosis	AFP, > 20 μg/L	BCLC stage,0/A	Single lesion	Median size, mm (range)	Vascular invasion	EBV+
			White	Asian									
LEL-HCC (n = 67)	34/54	58 (37–81)	13/20	6/20	23/54	18/54	24/53	21/41	37/43	38/43	38(10–130)	7/28	1/41
LEL-CC (n = 34)	12/34	57 (19–77)	2/27	25/27	13/34	2/34	5/34	0/4	NA	29/34	35(15–120)	NA	26/34

Data are given as number/total. AFP, a-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; EBV, Epstein-Barr virus; NA, not available.

2. Lymphoepithelioma-like cholangiocarcinoma(LEL-CC)

LEL-CC is one of the pathological classification of LELC. To date, 34 cases of LEL-CC have been reported and are detailed in Table 5. Available demographics of the patients and features of the tumors are displayed in Table 4. Compared with lel-hcc, it has fewer cases. According to the current literature analysis, the patients with LEL-CC are mainly Asian women, with 92% Asian patients, median age of 57 years (46–64); 13 patients with HBV infection, accounting for 39%; 2 patients with HCV infection, accounting for 6%; 5 patients with cirrhosis, accounting for 15%; AFP is normal; 24 patients with EBV infection, accounting for 76%. 28 patients received surgical treatment, accounting for 93%.

Macroscopically,, the tumor tissue was white-brown, firm and without capsule and similar to the typical ICC[10]. The median size of the tumor is 35 mm (15–120); histologically, there are two different components in LEL-CC: LEL-CC and typical cholangiocarcinoma exist at the same time, or they are only composed of LEL-CC, and the histological differences are in sharp contrast with LEL-HCC[26, 27]. In infiltrating lymphocytes, there are mainly CD3 + T cells, focal CD20 + B cells and CD138 + plasma cells[10, 28].

Similar to LEL-HCC, the diagnosis of LEL-CC mainly depends on pathological methods. The clinical manifestations and imaging examination of patients are not specific. The vast majority of patients need to rely on surgical treatment and later pathological diagnosis.

In terms of prognosis and survival, LEL-CC related data are limited. A retrospective study[29] compared 7 cases of LEL-CC with 11 cases of stage matched ICC, indicating that there was no significant difference in DFS (5-year survival was 57.1%; 11.7%; P = 0.1), and the total survival was significantly higher than that of ICC (5-year survival was 100%; 13.2%; P = 0.003).

Table 5
Reported Cases of LEL-CC

Reference	Age/Sex	Race	HBV	HCV	EBV	Liver Cirrhosis	Tumor no.	Tumor size(mm)	Treatment	FU, months	Outcomes
Gearty et al[30]	28/F	Asian	+	-	+	NA	1	40	CT	9	Died
Ding et al[31]	75/F	Asian	-	-	+	-	1	15	LR	3	Alive
Ling et al[32]	64/M	Asian	+	-	+	-	1	20	LR	11	Alive
	40/M	Asian	+	-	+	-	1	35	LR	32	Alive
Zhang et al[33]	38/F	Asian	+	-	+	-	1	28	LR	6	Alive
Shih et al[34]	77/F	White	+	-	-	+	2	17	LR	28	Alive
Tan et al[35]	22/M	White	NA	NA	+	NA	Multi	NA	CT	NA	Died
Adachi et al[36]	64/M	Asian	-	-	-	-	1	52	LR	3	Alive
Chen et al[37]	67/F	Asian	-	-	+	-	1	50	LR	1	Died
	41/M	Asian	+	-	-	+	1	30	LR	8	Alive
Henderson-Jackson et al[38]	63/F	Asian	-	-	+	-	1	40	LR	6	Alive
Hsu et al[39]	47/F	Asian	-	-	+	-	2	120	LR	48	Died
Huang et al[40]	60/F	Asian	-	-	+	-	1	35	NA	24	Alive
Hur et al[41]	57/F	Asian	-	-	-	-	1	20	LR	60	Alive
Jeng et al[42]	42/M	Asian	-	-	+	-	1	30	LR	84	Alive
	67/F	Asian	-	-	+	-	1	30	LR	7	Alive
	50/M	Asian	-	-	+	-	1	40	LR	16	Alive
	50/F	Asian	-	-	+	-	1	40	LR	2	Alive
Kim et al[43]	64/M	Asian	-	+	-	+	1	20	LR	NA	NA
Labgaa et al[26]	58/M	Asian	+	-	+	-	1	22	LR	61	Alive
Lee[44]	79/M	Asian	+	-	-	+	2	35	LR	54	Alive
Liao et al[27]	35/F	NA	+	-	+	+	1	16	LR	NA	NA
Ortiz et al[45]	19/F	White	-	-	+	-	1	55	LR	44	Died
Szekely[46]	61/M	NA	-	-	-	-	1	60	NA	11	Alive
Vortmeyer et al[47]	71/F	White	-	-	+	-	2	50	NA	36	Alive
Chan et al[29]	53/F	Asian	+	-	+	+	1	16	LR	165	Alive
	40/F	Asian	+	-	+	-	1	75	LR	56	Alive
	57/F	Asian	-	-	+	-	1	71	LR	128	Alive
	56F	Asian	-	-	+	-	1	60	LR	69	Died
	59/F	Asian	+	-	+	-	1	60	LR	72	Alive
	45/F	Asian	-	-	+	-	1	30	LR	71	Alive
	57/F	Asian	-	-	+	-	1	30	LR	58	Alive
Aosasa et al[48]	65/F	NA	-	+	-	-	1	64	LR	20	Alive
Min et al[49]	46/M	Asian	+	-	+	-	1	27	LR	84	Alive

F, female; M, male; +, positive; -, negative; NA, not available; HBV, hepatitis B virus; HCV, hepatitis C virus; EBV, Epstein-Barr virus; no., number; LR, liver resection; CT, Chemotherapy; OLT, orthotopic liver transplant; FU, follow-up; mo., months; *Indicated as mean value.

Discussion

It is worth noting that two cases of LELC with both hepatocellular carcinoma and cholangiocarcinoma are found in the literature. We call it “combined lymphoepithelioma-like hepatocellular carcinoma and cholangiocarcinoma” (cLEL-HCC-CC).

The first literature[50] reported a 62 years old woman who was admitted to the hospital because of the right upper abdominal drop pain with hepatitis B.Laboratory examination showed that AFP: 394.90 ng/ml (0–7 ng/ml). The imaging examination showed that the tumor in the VI segment of the liver was about 50 mm. The patient received surgical treatment. The postoperative pathological and immunohistochemical markers showed that there were two epithelial cell groups in the tumor, one of which expressed CKS AE1 / AE3, hepatecyte, TTF1, AFP, CD10, the other part expressed CK7 and CK19. The former indicates the source of hepatocytes and the latter indicates the source of bile ducts. This is the first report about cLEL-HCC-CC in English literature.

The second literature[51] reported a 40 years old man who was admitted to the hospital because of finding liver tumor by physical examination with hepatitis B. Laboratory examination showed that AFP: 4539.2 ng/ml. CT showed irregular low-density shadow, uneven internal density and unclear boundary, about 21 × 21 mm, in the lower border area of segment V and VI of the liver. After enhancement, the lesions showed irregular enhancement in the arterial phase without obvious lymphadenopathy and we considered that it was liver cancer. After the operation, the tumor cells were found to be heteromorphic, with a large number of mature lymphocytic infiltrates. Immunohistochemistry showed that CK7, CK19, CK8/18, hepatecyte were positive, and in situ hybridization EBER was negative. Immunohistochemistry suggested the origin of hepatocyte and bile duct. After operation, the patients were given 2 times of hepatic artery intubation chemotherapy, and no tumor recurrence or metastasis was found after close follow-up for 30 months. The patients were in good condition.

The first case we reported was pathologically diagnosed as LELC after surgical treatment. Under the microscope, it was mainly hepatocellular carcinoma with differentiation of scattered cholangiocarcinoma. The markers of immunochemistry were CK18 (3+), CK19 (1+), CK7 (1+), GPC3 (3+) and hepatecyte (2+). Combined with the reports of the above two cases, we believe that this case can also be diagnosed as cLEL-HCC-CC.

We compared the clinical data and pathological immunohistochemical factors of three patients with cLEL-HCC-CC. The results are shown in Table 6. It can be found that 2 patients were male Asian patients, 3 patients had HBV infection and AFP increased. All the patients were single tumor, less than or equal to 50 mm. All patients received operation. The results of immunohistochemistry showed that they all originated from hepatocytes and bile ducts, of which 3 cases were positive for hepatecyte, CK7 and CK19. The longest follow-up period is 30 months. The survival of the patients is good. Compared with mixed liver cancer, this cLEL-HCC-CC is very rare. It is almost difficult to retrieve the relevant information in the literature. In the future, more research and reports are needed to improve this special pathological type.

Table 6
Clinical and pathological data of cLEL-HCC-CC

Reference	Sex	Age, years	Region	HBV	HCV	AFP, > 7 μg/L	No.Of lesions	Size, mm	Treatment	FU, mo.	Outcome	Immunohistochemical Markers				
												AFP	Hepatocyte	CK7	CK19	
First case	M	62	Asian	+	-	+	1	28	LR	13	AWOD	-	+	+	+	
Filotico et al[50]	F	62	NA	+	-	+	1	50	LR	NA	NA	+	+	+	+	
Wei et al[51]	M	40	Asian	+	-	+	1	21	LR	30	AWOD	-	+	+	+	

F, female; M, male; +, positive; -, negative; HBV, hepatitis B virus; HCV, hepatitis C virus; NA, not available; No., number; AFP, a-fetoprotein; AWOD, alive without d follow-up; mo., months; LR, liver resection; EBER, EBV-encoded RNA.

LELC has been defined as a distinctive variant of liver cancer by the World Health Organization. The diagnosis requires pathological observation of a large number of lymphocyte infiltration, but the density of lymphocyte infiltration needed for diagnosis has not been determined. Therefore, the diagnosis is mainly based on pathological methods. Under the microscope, there are atypical tumor cells with low differentiation or undifferentiation, characterized by a large number of lymphocytic infiltrates. According to the above pathological characteristics, it can be distinguished from typical liver cancer. At the same time, according to the microscopic observation and the expression of immunohistochemistry factors, it can be divided into two types: LEL-HCC and LEL-CC. LELC can be diagnosed by pathological methods, but this is limited to patients who have received hepatectomy, liver puncture or liver transplantation. At present, some researches have explored and perfected the diagnosis of LELC in the aspects of new immunohistochemical factors and gene detection.

The clinical manifestations of LELC patients are not special. Most of the patients have physical examination findings, some of them have right upper abdominal pain or chronic cholecystitis symptoms[19, 23, 50]. Because of its nonspecific clinical manifestations, it is difficult to diagnose LELC before operation. EBV infection is an important cause of Nasopharyngeal carcinoma (NPC)[52]. Whether or not there is EBV infection in LELC is a more concerned aspect at present. According to our statistical data (Table 2), only one patient with LEL-HCC has EBV infection, while 25 patients with LEL-CC have EBV infection, accounting for 76%. This indicates that the occurrence and development of LEL-CC may be closely related to EBV infection. This finding is worthy of further study to understand whether EBV is directly involved in the development of LEL-CC, or whether it provides protection by causing special immune response, so as to improve its prognosis.

The prognosis of patients with LELC is better than that of typical liver cancer, which may be related to a large number of lymphocyte infiltration, which is based on a few case reports and small retrospective studies. The second patient reported was admitted to hospital for one year because of abdominal pain,

and recurred after operation. The patient received radiotherapy later. At present, the follow-up period is 61 months. The patient has a good survival, no metastasis and recurrence. The DFS is 23 months. The third patient, who received liver puncture before operation to indicate lymph node metastasis, had local recurrence after operation. The patient received nine cycles of chemotherapy and one cycle of radiotherapy. Finally, the patient died at 24 months follow-up. These two patients suggest that even the locally advanced patients of LELC with postoperative recurrence and preoperative lymph node metastasis should be actively treated and intervened, and the patients may still have a longer survival period. However, a more convincing prospective experimental study is needed to explore the prognosis of LELC.

We summarize the diagnosis and treatment strategy of LELC: first, because LELC is a relatively rare and low incidence rate of liver cancer variant, it is necessary to consider the possibility of LELC in the process of diagnosis and treatment of liver cancer. Meanwhile, it is suggested that the treatment strategy should be formulated under MDT; second, preoperative EBV can be perfected, if it is positive, it will more support the diagnosis of LELC; third, in the case of the advanced liver tumor, it is suggested to perform liver biopsy, perfect the relevant pathological diagnosis, if it is LELC, it should be treated more actively; fourth, according to the postoperative pathological results, if it is LELC, because it may have a better prognosis, even if the local recurrence and metastasis, it is still recommended to actively intervene and treat, to strive for the possibility of long-term survival.

Conclusion

At present, the study of LELC is still in progress, but the preliminary study shows that it is a distinctive variant of liver cancer, characterized by large lymphocyte infiltration, which is divided into LEL-HCC, LEL-CC and cLEL-HCC-CC with unique epidemiological and pathological characteristics. Its diagnosis mainly depends on pathological methods, and the treatment mainly depends on surgery.

Up to now, 41 literatures have been searched from 1998 to 2020. 67 cases of LEL-HCC and 34 cases of LEL-CC have been reported. According to the existing research, LELC has a better prognosis, even the patients with local recurrence and distant metastasis may still have a long-term survival. Whether EBV affects the development and prognosis of LELC is not clear yet. Prospective study is needed to explore the prognosis of LELC.

Abbreviations

LELC: Lymphoepithelioma-like hepatic carcinoma; HBV: hepatitis B virus; HCV: hepatitis C virus；EBV: Epstein-Barr virus; LEL-HCC: Lymphoepithelioma-like hepatocellular carcinoma; LEL-CC: Lymphoepithelioma-like cholangio-carcinoma; cLEL-HCC-CC: combined lymphoepithelio-ma-like hepatocellular carcinoma and cholangiocarci-noma; HCC: Hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; MDT: multidisciplinary team; MRI: Magnetic resonance imaging; F: female; M: male; AFP: a-fetoprotein; NA: not available; FU: follow-up; mo.: months; No., number; DFS: Disease-free survival; LR: liver resection; CT: Chemotherapy; RT: Radiotherapy.

Declarations

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None.

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Authors' contributions

CT and KZ contributed equally as first authors. CT and KZ collected data and wrote the paper. JW and WR performed the operation as chief surgeon. WR and FW supervised the writing of the paper especially in the Discussion section. SA participated in the operation as an assistant and participated in the writing of the paper. JW represents Department of Hepatobiliary Surgery and supervised the writing of the paper. All authors significantly contributed to this study and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed are included in this published article.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of the case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interest.

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Figures

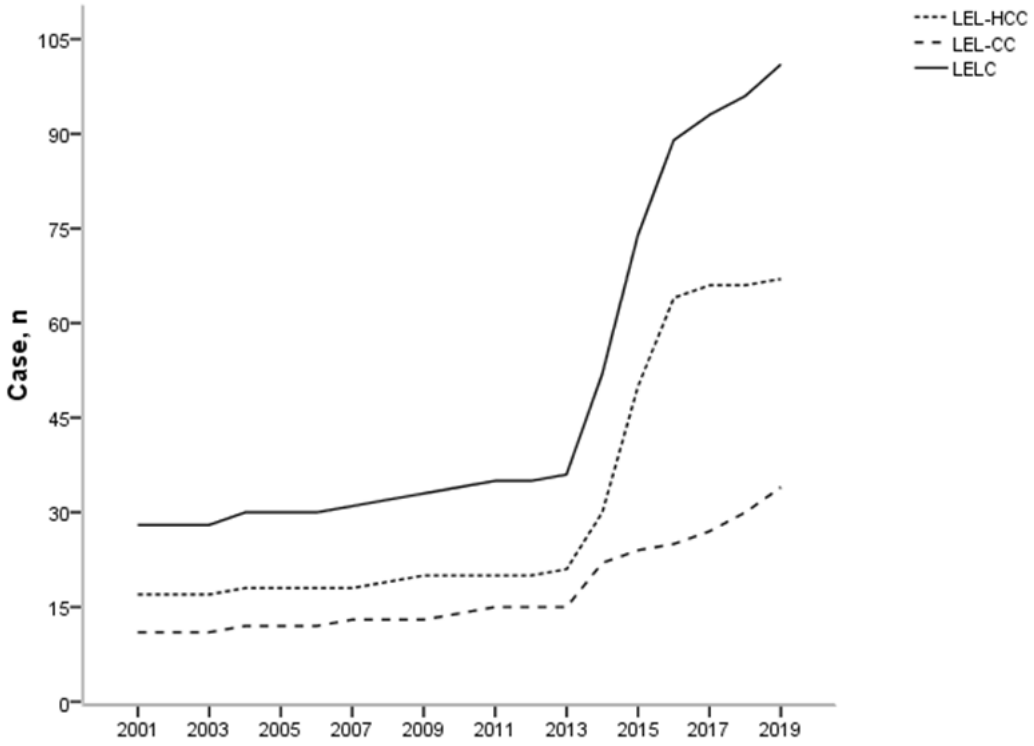

Figure 1

Number of reported cases of lymphoepithelioma-like hepatic carcinoma (LELC). Number of cases reported in the English literature since 2001, for lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC), lymphoepithelioma-like cholangiocarcinoma (LEL-CC), and both types.

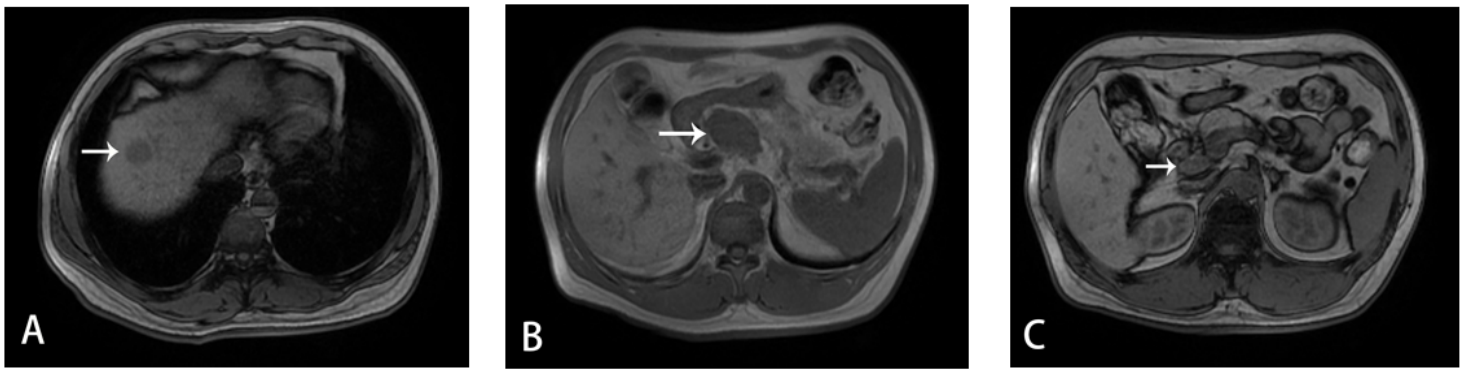

Figure 4

Preoperative MRI findings. MRI showing a 2.7x2.2cm tumor in segment VIII, hypointense on T1-weighted images (A). An enlarged lymph node was on the upper margin of pancreas, next to common hepatic artery and abdominal aorta, about 5.2×3.4cm (B). An enlarged lymph node behind duodenal ligament, next to the portal vein (C).

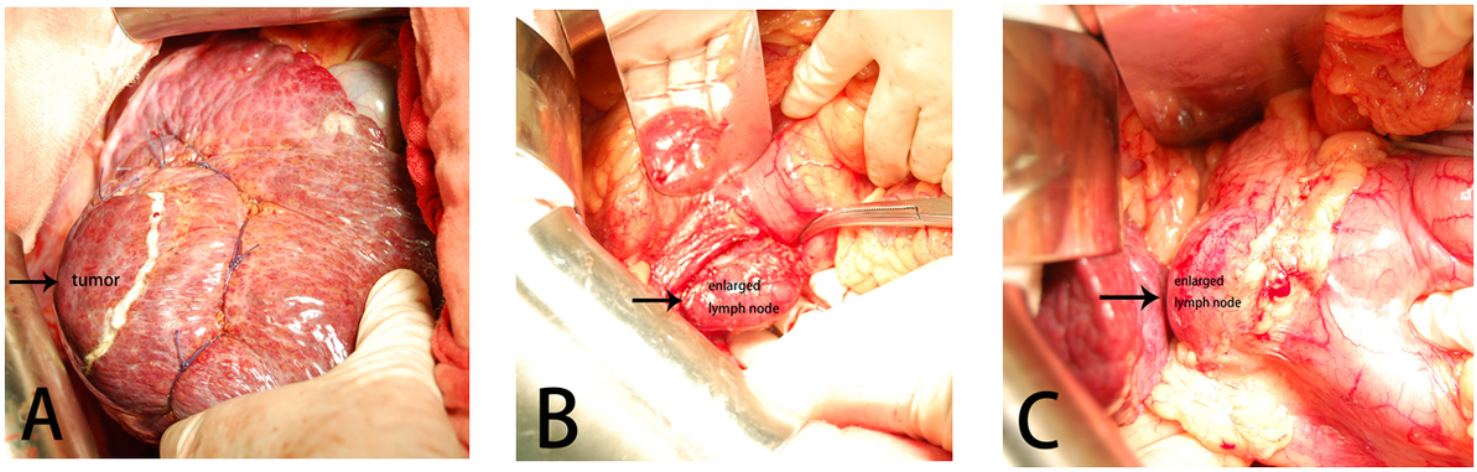

Figure 6

Intraoperative findings. The tumor was in the segment VIII, in the size about 3.5×3cm (A). An enlarged lymph node was behind duodenal ligament, next to the portal vein, about 4.5×3cm (B). Another enlarged lymph node was on the upper margin of pancreas, next to common hepatic artery and abdominal aorta, about 5.5×4cm (C).

Figure 8

Microscopic findings of the resected specimen. Proliferation of atypical large cells, characterized by an eosinophilic cytoplasm, with large nuclei and prominent nucleoli. Epithelial cells were surrounded by a dense lymphoid stroma, extending inside the tumor (HE, ×400) (A). Metastatic lymph node with poorly differentiated hepatocellular carcinoma in center (HE,×200)(B). Immunohistochemical staining for AE1/AE3 is (2+) positive in hepatocellular LELC (IHC, ×100)(C) . Immunohistochemical staining for EBER is negative in epithelial cells of hepatocellular LELC (IHC, ×100) (D).