



Case Report

Lymphoepithelioma-like Cholangiocarcinoma Mimicking Hepatocellular Carcinoma Imaging Features in a Young Patient with Hepatitis B Virus Infection: A Case Report and Literature Review

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Abstract

Lymphoepithelioma-like cholangiocarcinoma (LEL-CC) is a rare variant of intrahepatic cholangiocarcinoma. Only a few cases of LEL-CC have been reported, and the understanding of LEL-CC remains limited. Herein, we describe a case involving a 38-year-old Asian man with hepatitis B virus infection and LEL-CC. The patient's liver tumor was incidentally discovered during routine abdominal ultrasonography without obvious clinical signs or symptoms. Dynamic magnetic resonance imaging (MRI) revealed features of hepatocellular carcinoma and he underwent laparoscopic partial hepatectomy. Histologically, the liver tumor exhibited a lymphoepithelioma-like appearance and features of cholangiocarcinoma with Epstein-Barr virus infection.

Keywords: Epstein-Barr virus, hepatitis B virus, lymphoepithelioma-like cholangiocarcinoma

INTRODUCTION

Lymphoepithelioma-like carcinoma (LELC) is a rare malignancy characterized by tumors composed of undifferentiated epithelial cells with prominent lymphoid infiltration. Nasopharyngeal carcinoma is the most well-known type of LELC tumor. LELCs can also emerge at various

anatomical sites, including the lungs, gastrointestinal tract, thymus, and liver. In the liver, this type of tumor is

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extremely rare. Hepatic LELCs have been observed in both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHCC), which are further designated lymphoepithelioma-like HCC and lymphoepithelioma-like cholangiocarcinoma (LEL-CC), respectively. Only a few cases of LEL-CC have been described in reports which focused on radiologic and histologic analyses. LEL-CC has similar radiologic features to HCC and IHCC, so diagnosing LEL-CC by radiologic imaging remains a challenge for physicians. Herein, we describe a rare case of LEL-CC in a 38-year-old man with HCC-like image features.

CASE REPORT

A 38-year-old man with type 2 diabetes mellitus, hyperlipidemia, and hepatitis B virus infection underwent routine abdominal ultrasonography at our hospital, during which a lesion was found in the S3 segment of the liver, and the lesion increased in size from 1 cm to 2.7 cm over a 1-year period. On physical examination, there was no abdominal pain, vomiting, or weight loss. The results of a liver function test panel were within normal limits. Serum levels of tumor markers, including alpha-fetoprotein, carcinoembryonic antigen, and cancer antigen 199, were not elevated. Hepatitis virus markers revealed positive hepatitis B surface antigen (854.79 IU/mL) and negative hepatitis C antibody. Magnetic resonance imaging (MRI) revealed an abnormal signal intensity of approximately 1.9 cm × 1.7 cm in the S2/3 segment of the liver, with hypersignal intensity on T2-weighted imaging (T2WI) [Figure 1c] and heavy-T2WI with fat suppression. Dynamic gadolinium-enhanced MRI showed hyposignal intensity on precontrast T1WI, early enhancement in the arterial phase [Figure 1a], and washout in the portal venous and delayed phase [Figure 1b]. These were typical imaging characteristics of HCC. Accordingly, under the assumption of HCC diagnosis, the patient underwent laparoscopic partial hepatectomy.

Grossly, a solitary tumor measure 1.7 cm in size was present in the resected liver tissue [Figure 1d]. Histopathological analysis revealed carcinoma cells in solid nests, cord, or tubule growth patterns with an indistinct intercellular border in a dense lymphoplasmacytic stroma. Immunohistochemically, the tumor cells were positive for cytokeratin (CK [AE1/AE3]) [Figure 1e], CK7, and CK19 and negative for CK5/6, P63, HepPar-1, arginase-1, and glutamine synthetase. Epstein-Barr virus (EBV)-encoded RNA *in situ* hybridization was positive in the tumor cell nuclei [Figure 1f]. Collectively, these features fulfilled the criteria for the diagnosis of LEL-CC. Nasopharyngolaryngoscopy revealed no evidence of nasopharyngeal tumors, and no evidence of recurrence was found 2 years postoperatively.

DISCUSSION

In this case report, we present a patient diagnosed with LEL-CC with similar radiologic features to HCC. In general,

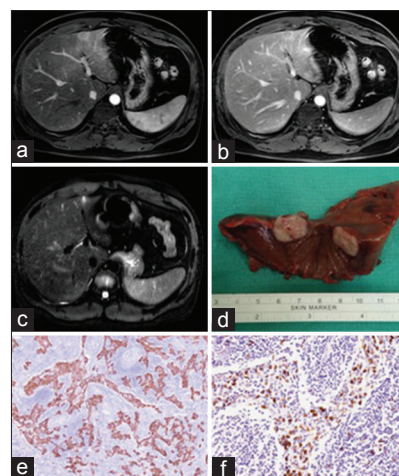


Figure 1: Magnetic resonance imaging revealing a solitary tumor, measuring 1.9 cm × 1.7 cm, in the S2/3 segment of the liver with iso-hyper signal intensity in the arterial phase (a), hyposignal intensity in the delayed phase (b), and hypersignal intensity on T2-weighted imaging (c). Macroscopic analysis of the resected specimen revealed a grayish white, firm, solitary tumor with a rough, inked green surface (d). Histopathology revealed highlighted lymphoepithelioma-like cholangiocarcinoma tumor cells with cytokeratin immunostaining (e) and positive for Epstein-Barr-encoded RNA *in situ* hybridization in the tumor cell nuclei (f). (×20 in [e] and ×100 in [f])

cholangiocarcinoma is difficult to diagnose by radiologic imaging because of its wide spectrum of radiologic appearances. Typically, mass-forming cholangiocarcinomas are hypo-to-isointense on T1WI with variable hyperintensity on T2WI depending on the proportion of fibrosis, necrosis, and mucin. Contrast-enhanced T1WI shows minimal-to-moderate thin peripheral enhancement on early images, with centripetal progression on delayed images.^[1] Lymphoepithelioma-like cholangiocarcinoma (LEL-CC) is a rare variant of IHCC, which may have an atypical radiologic pattern of mass-forming cholangiocarcinoma. According to a previous study,^[2] LEL-CC is hypointense on T1WI and hyperintense on T2WI and diffusion-weighted imaging, which is similar to mass-forming cholangiocarcinoma. Different from mass-forming cholangiocarcinoma, LEL-CC often displays early enhancement in the arterial phase and washout in the portal venous phase and delayed phase, which are typical imaging characteristics of HCC. Due to the similarity in radiologic findings between mass-forming cholangiocarcinoma, LEL-CC, and HCC, histopathology is considered mandatory to confirm the diagnosis.

With regard to the pathology, LEL-CC is composed of variable glandular differentiation with moderate amounts of syncytial, amphophilic cytoplasm, and prominent lymphoplasmacytic infiltration.^[3] In contrast to the dense lymphoplasmacytic infiltration found in LEL-CC, conventional-type cholangiocarcinoma shows little-to-scattered lymphoplasmacytic infiltration.^[4] In addition, in cholangiocarcinoma, poorly formed glands composed of cells with moderate atypia and high nuclear/cytoplasmic

Table 1: Demographic information, manifestations, treatment, and prognosis of reported cases of lymphoepithelioma-like cholangiocarcinoma

Reference	Year	Age	Sex	Race	Symptom	Number of lesion	Size (mm)	Site	HBV	HCV	EBV	Cirrhosis	Treatment	Follow-up (months) ^b	Outcome
Hsu <i>et al.</i> ^{[5]a}	1996	47	Female	Asian	Abdominal fullness	2	120	Left lobe	-	-	+	-	Left lobectomy	48	DOD
Vortmeyer <i>et al.</i> ^[6]	1998	71	Female	White	Incidental finding	2	50	Central of porta hepatitis	-	-	+	-	Liver resection	36	AWD
Kim <i>et al.</i> ^[7]	1999	64	Male	Asian	Incidental finding	1	20	S6	-	+	-	+	Liver resection	NA	NA
Ortiz <i>et al.</i> ^[8]	2000	19	Female	White	Abdominal fullness	1	55	Left lobe	-	-	+	-	Left lobectomy	44	DOD
Jeng <i>et al.</i> ^{[9]a}	2001	42	Male	Asian	Incidental finding	1	30	S6	-	-	+	-	Segmentectomy	84	AWOD
	2001	67	Female	Asian	Incidental finding	1	30	Lateral segment	-	-	+	-	Left lobectomy	7	AWOD
	2001	50	Male	Asian	Vague epigastric pain	1	40	Left lobe	-	-	+	-	Left lobectomy	16	AWOD
	2001	50	Female	Asian	Incidental finding	1	40	Right lobe	-	-	+	-	Atypical hepatectomy	2	AWOD
Chen <i>et al.</i> ^{[10]a}	2001	67	Female	Asian	Abdominal pain	1	50	S8	-	+	+	-	Hepatectomy	<1	POD
	2001	41	Male	Asian	Abdominal pain	1	30	S2	+	-	-	+	Liver resection	8	AWOD
Szekely ^[11]	2001	61	Male	NA	Incidental finding	1	60	NA	-	-	-	-	Liver resection	11	AWOD
Huang <i>et al.</i> ^{[12]a}	2004	60	Female	Asian	Incidental finding	1	35	S5	-	-	+	-	Liver resection	24	AWOD
Min <i>et al.</i> ^[13]	2007	46	Male	Asian	NA	1	27	NA	+	-	+	-	Liver resection	84	AWD
Adachi <i>et al.</i> ^[14]	2008	64	Male	Asian	Fever	1	52	Left lobe	-	-	-	-	Lateral segmentectomy	3	AWOD
Henderson-Jackson <i>et al.</i> ^{[15]a}	2010	63	Female	Asian	Right-sided flank and back pain	1	40	Medial segment	-	-	+	-	Liver resection	6	AWOD
Hur <i>et al.</i> ^[16]	2011	57	Female	Asian	Incidental finding	1	20	S6	-	-	-	-	Segmentectomy	60	AWOD
Lee ^{[17]a}	2011	79	Male	Asian	Incidental finding	2	35	Lateral segment	+	-	-	+	Left lobectomy	54	AWOD
Chan <i>et al.</i> ^[18]	2014	53	Female	Asian	Incidental finding	1	16	Right lobe	+	-	+	+	Liver resection	165	AWOD
	2014	40	Female	Asian	Incidental finding	1	75	Right lobe	+	-	+	-	Liver resection	56	AWD
	2014	57	Female	Asian	Non-painful vague and abdominal mass	1	71	Left lobe	-	-	+	-	Liver resection	128	AWOD
	2014	56	Female	Asian	Dyspepsia and reflux symptoms	1	60	Left lobe	-	-	+	-	Liver resection	69	DOD
	2014	59	Female	Asian	Incidental finding	1	60	Left lobe	+	-	+	-	Liver resection	72	AWOD
	2014	45	Female	Asian	Biliary colic	1	30	Left lobe	-	-	+	-	Liver resection	71	AWD
	2014	57	Female	Asian	Incidental finding	1	30	Right lobe	-	-	+	-	Liver resection	58	AWOD
Liao <i>et al.</i> ^{[19]a}	2015	35	Female	NA	Incidental finding	1	17	Medial segment	+	-	+	+	Left lobectomy	NA	NA
Aosasa <i>et al.</i> ^[20]	2015	65	Female	NA	Incidental finding	1	64	Caudate lobe	-	+	-	-	Liver resection	20	AWOD
Chang <i>et al.</i> ^{[21]a}	2015	70	Female	Asian	Incidental finding	1	10	Right lobe	-	+	-	-	Liver segmentectomy	36	AWOD
Labgaa <i>et al.</i> ^[22]	2016	58	Male	Asian	Incidental finding	1	22	Left lobe	+	-	+	-	Liver resection	61	AWOD
Ding <i>et al.</i> ^[2]	2019	75	Female	Asian	Incidental finding	1	15	Left lobe	-	-	+	NA	Left lateral hepatectomy	3	AWOD

Contd...

Table 1: Contd...															
Reference	Year	Age	Sex	Race	Symptom	Number of lesion	Size (mm)	Site	HBV	HCV	EBV	Cirrhosis	Treatment	Follow-up (months) ^b	Outcome
Lin <i>et al.</i> ^[23]	2020	61	Female	Africa-American	Incidental finding	1	23	Right hepatic lobe	–	–	+	+	No operation	NA	Death
	2020	23	Male	Africa-American	Abdominal pain	Multiple	NA	Bilateral lobes	–	–	+	NA	No operation	NA	NA
Current case ^a	2019	38	Male	Asian	Incidental finding	1	17	S3	+	–	+	–	Partial hepatectomy	12	AWOD
^a Case was reported in Taiwan, ^b The month of follow-up was claimed in the case report, AWD: Alive with disease, AWOD: Alive without disease, DOD: Died of disease, EBV: Epstein-Barr virus, HBV: Hepatitis B virus, HCV: Hepatitis C virus, NA: Not available, POD: Postoperative dead, +: positive, -: negative															

ratio are surrounded by dense, desmoplastic stroma. Most importantly, the conventional type of cholangiocarcinoma is negative for EBER-ISH stain.

To the best of our knowledge, 31 cases of LEL-CC^[2,5-23] have been reported in the English literature. In these cases, the mean age of the patients was 53 years (range, 19–79 years), with female predominance (65.6% [21/32]), and most cases were reported in Asia (78.1% [25/32]). The LEL-CC lesions were usually solitary (87.5% [28/32]) with a tumor diameter ranging from 15 mm to 120 mm. Patients with larger tumors tended to present with abdominal discomfort or pain (31.3% [10/32]), whereas most of the smaller tumors were discovered incidentally (62.5% [20/32]). Most (93.8% [30/32]) patients underwent surgical resection. Two patients did not undergo surgical treatment due to decompensated cirrhosis and left portal vein metastasis, respectively.

Similar to nasopharyngeal carcinoma, most LELCs are strongly associated with EBV infection, as are LELCs in the digestive tract, lung, and thymus. We found a high percentage (75.0% [24/32]) of EBV-positive LEL-CC in our literature review [Table 1]. This implies that EBV may be directly involved in the carcinogenesis of LEL-CC, which may result from the immune response elicited by EBV infection. According to our review, overall survival for EBV-positive LEL-CC was not significantly different from that for EBV-negative LEL-CC ($P = 0.41$) [Figure 2]. We assume that the lack of statistical significance was due to the small sample size.

Our case had the typical characteristics of HCC in radiologic imaging, including early enhancement in the arterial phase and washout in the portal venous and delayed phase. Furthermore, our case had chronic hepatitis B, which is a known risk factor for HCC. Accordingly, HCC was first impressed according to the clinical presentation and imaging. After discussion with the patient, he chose surgical intervention other than liver mass biopsy.

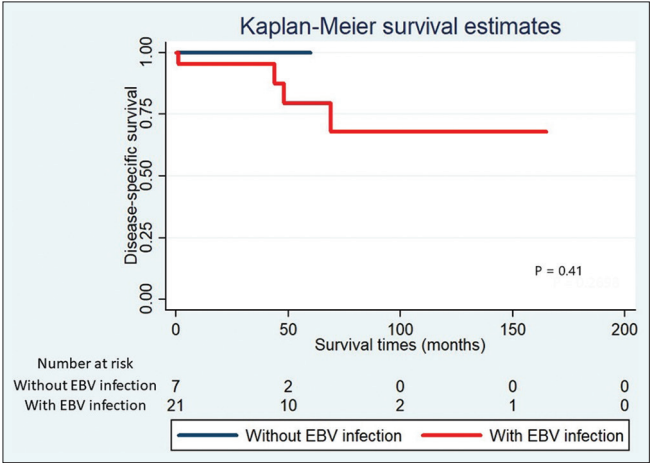


Figure 2: Kaplan–Meier disease-specific survival curves for patients with and without EBV infection. EBV: Epstein–Barr virus

In summary, LEL-CC is a rare variant of IHCC, which has both similar and different radiologic features to HCC and mass-forming cholangiocarcinoma. Diagnosing LEL-CC remains a challenge for physicians and radiologists, and so a pathological diagnosis is crucial for these cases.

Ethical approval

This case report was approved by the Institutional Review Board of the MacKay Memorial Hospital (IRB number 22MMHIS220e).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understood that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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