Clinical Case Report

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Lymphoepithelioma-like hepatocellular carcinoma

A case report and brief review of literature

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Abstract

Rational: Lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC) is a rare variant of hepatocellular carcinoma (HCC). To date, few cases have been reported in the literature, and almost no report in analyzing the different features of LEL-HCC.

Patient concerns: We describe a 37-year-old female patient with a 32 × 30 mm mass in the right liver.

Interventions: Complete surgical resection of the lesion was performed.

Diagnoses: Histopathological examination of the resected tumor revealed undifferentiated HCC cells with significant lymphocytes infiltration. Immunohistochemically, the tumor cells were positive for AFP (alpha fetoprotein), hepatocyte, CK8, and glypican-3. The patient was diagnosed with LEL-HCC.

Outcomes: The patient had a favorable clinical outcome, and was free from tumor recurrence after a 52-months follow-up.

Lessons: Our case was the youngest patient of all the reported cases, and the third case who was infected with both hepatitis B virus (HBV) and hepatitis C virus (HCV). LEL-HCC is a rare variant of HCC, with a relatively favorable prognosis. Further research recruiting more patients is required to determine the accurate causes and mechanism of LEL-HCC.

Abbreviations: AFP = alpha fetoprotein, CT = computed tomography, EBV = Epstein-Barr virus, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, LELC = lymphoepithelioma-like carcinoma, LEL-CC = lymphoepitheliomalike cholangiocarcinoma, LEL-HCC = lymphoepithelioma-like hepatocellular carcinoma.

Keywords: hepatocellular carcinoma, lymphoepithelioma-like carcinoma, variant

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent malignancies worldwide, especially in developing countries [1]; hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are the main recognized risk factors. Despite of the progress of diagnostic and therapeutic approaches in recent years, the prognosis of HCC is still poor. It was reported that the overall 5-year survival rate of HCC was approximately 5% to 6%.[2]

Lymphoepithelioma-like carcinoma (LELC) is one of the particular forms of undifferentiated epithelial carcinoma, characterized by massive lymphoid infiltration, and was first described in nasopharynx in 1982.[3] Subsequently, in various organs such as salivary glands,[4] stomach,[5] lungs,[6] colon,[7] thymus,[8] uterine,[9] and ovaries,[10] the particular tumor has been widely described. However, LELC is rarely reported in the liver. Hepatic LELC has 2 forms, lymphoepithelioma-like hepatocellular carcinoma (LEL-HCC) and lymphoepithelioma-like cholangiocarcinoma (LEL-CC). To date, at least 66 cases of LEL-HCC have been reported in the literature.[11]

Herein, we reported another unique case of LEL-HCC with infection of both HBV and HCV, to further understand the rare disease's characteristics. A brief literature review of reported cases of LEL-HCC (including the present case) was also presented, which were summarized in Table 1.[12–25]

2. Case presentation

A 37-year-old female patient with chronic HBV and HCV infection for decades was admitted to our hospital owing to a liver-occupying lesion during routine medical examination. Her past medical history was significant for diabetes mellitus and hypertension. Physical examination was unremarkable, except for mild abdominal tenderness. Abdominal contrast-enhanced computed tomography (CT) scan revealed a 32 mm × 30 mm slightly hypodense nodular lesion in the right liver with obscure boundary (Fig. 1A); arterial phase enhanced scan showed obvious enhancement (Fig. 1B) and portal phase with mild heterogeneous enhancement (Fig. 1C). Pertinent laboratory investigations showed positive for HBV and HCV. The tumor

Editor: Farid Azmoudeh-Ardalan.

J-KW and Y-WJ have equally contributed to the study and were the co-first authors.

The ethical approval from the Ethics Committee was not necessary to report this case because the case was reviewed retrospectively. Written informed consent was obtained from the patient for publication of this case report and all accompanying images.

This work was supported by National Nature Science of China (No. 30801111) and Science & Technology Support Project of Sichuan Province (No. 2014SZ0002-10).

The authors have no conflict of interest to disclose.

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Medicine (2017) 96:51(e9416)

Received: 20 April 2017 / Received in final form: 30 November 2017 / Accepted: 1 December 2017

http://dx.doi.org/10.1097/MD.0000000000009416

Table 1

Literature review of reported cases of LEL-HCC.

Reference	Age/sex	EBV	HBV	HCV	Liver cirrhosis	Tumor no.	Tumor size (cm)	Tumor location	Surgery type	Metastasis at operation	Postre-currence	Prechemoem-bolization	Postchemoem-bolization	Overall survival (mo)
Shirabe et al[12]	58/F	N	P	N	Y	1	2.2	R	LR	N	N	N	N	Alive without recurrence (83)
Wada et al[13]	62*/10M, 1F	N	N	P	6/11	U	2.2*	U	LR	N	U	U	U	5-y survival: 100%
Emile et al[14]	50/M	N	P	P	Y	1	4.0	U	LT	N	N	N	N	Alive without recurrence (120)
	54/M	N	N	N	N	2	2.0	U	LT	N	Y	Y	N	Died of disease (92)
	59/M	N	P	P	Y	4	5.0	U	LT	N	N	N	Y	Alive without recurrence (96)
	45/M	N	N	P	Y	1	2.0	U	LT	N	N	N	Y	Alive without recurrence (56)
	64/M	N	N	N	Y	2	4.0	U	LT	N	N	Y	Y	Alive without recurrence (36)
Si et al[15]	39/F	P	N	P	Y	1	1.0	U	LT	N	Y	N	N	Died of disease (5)
Chen et al[16]	56/M	N	N	P	Y	1	3.0	R	LR	N	Y	N	Y	Died of disease (21)
Nemolato et al[17]	47/F	N	N	N	N	1	2.2	R	LR	N	N	N	N	Alive without recurrence (15)
Park et al[18]	57/M	N	P	N	Y	1	2.7	R	LR	N	N	N	N	Alive without recurrence (60)
Shinoda et al[19]	79/M	N	N	N	N	1	5.0	L	LR	Y	Y	N	Y	Alive with recurrence (20)
Patel et al[20]	74/F	N	N	N	N	Multi	6.5	U	LR	N	Y	N	U	Died of disease (24)
	65/M	N	N	N	N	1	4.8	U	LR	N	N	N	U	Died of unrelated cause (60)
	65/F	N	N	N	N	1	1.3	U	LR	N	N	N	U	Alive without disease (108)
	70/F	N	N	N	N	1	2.7	U	LR	N	N	N	U	Alive without recurrence (72)
	61/F	N	N	N	N	Multi	9.5	U	LR	N	N	N	U	Died of unrelated cause (4)
	78/M	N	N	N	N	1	10.5	U	LR	N	Y	N	U	Alive with recurrence (48)
	78/F	N	N	N	N	1	6.0	U	LR	N	N	N	U	Alive without recurrence (24)
	57/F	N	N	N	N	1	13.0	U	LR	N	N	N	U	Died of unrelated cause (1)
An et al[21]	50/M	N	P	N	Y	1	3.0	R	LR	Y	Y	N	Y	Alive with recurrence (6)
Cacciato et al[22]	81/F	N	N	P	N	1	7.2	L	LR	N	N	N	N	Alive without recurrence (15)
Chan et al[23]	58*/13M, 7F	N	17/20	N	8/20	U	3.8*	U	LR	U	U	U	U	5-y survival: 88%
Wei et al[24]	42/F	N	N	N	N	1	4.6	L	LR	N	N	N	N	Alive without recurrence (8)
Present case	37/F	N	P	P	Y	1	3.2	R	LR	N	N	N	N	Alive without recurrence (52)

Calderaro et al[25] mentioned 13 cases of LEL-HCC who underwent liver resection for hepatocellular carcinoma in a literature, but no relevant information was provided.

F = female, L = left liver, LEL-HCC = lymphoepithelioma-like hepatocellular carcinoma, LR = liver resection, LT = liver transplantation, M = male, Multi = multiple, N = no or negative, No. = number, P = positive, Post = postoperative, Pre = preoperative, R = right liver, U = unknown, Y = yes.

* Indicated as mean value.

marker of alpha fetoprotein (AFP) was increased (105.90 ng/mL, normal <8). These findings were consistent with malignant nature of the liver tumor. Subsequently, a whole body positron emission tomography–computed tomography was performed, and there was no evidence of extrahepatic tumor. Based on above results, primary HCC was the initial diagnosis. The patient underwent surgery with complete tumor resection and the surgical margins were negative.

Macroscopically, the tumor was a yellowish solid mass, 32 mm in diameter. Histopathological examination of the resected specimen revealed that the tumor was consisted of undifferentiated HCC cells with significant lymphoid infiltration extending inside the tumor, which is the characteristic features of LELC (Fig. 2A). The epithelial tumor cells were featured by atypical, eosinophilic cytoplasm with large nuclei, prominent nucleoli (Fig. 2B). Immunohistochemically, the lymphoid infiltrate were composed of a mixture of CD8 and CD4 T-cells, with a predominance of CD8 cells. Meanwhile, the tumor cells were positive for AFP (Fig. 2C), hepatocyte (Fig. 2D), CK8 (Fig. 2E), and glypican-3 (Fig. 2F). No reactivity for CK7 or CK19 was observed. In situ hybridization for Epstein-Barr virus (EBV) was also negative. After discussion by several pathologists in our hospital, primary LEL-HCC was diagnosed. No postoperative chemotherapy or radiotherapy was performed for the patient. She had a favorable clinical outcome, and was free from tumor recurrence after a 52-months follow-up.

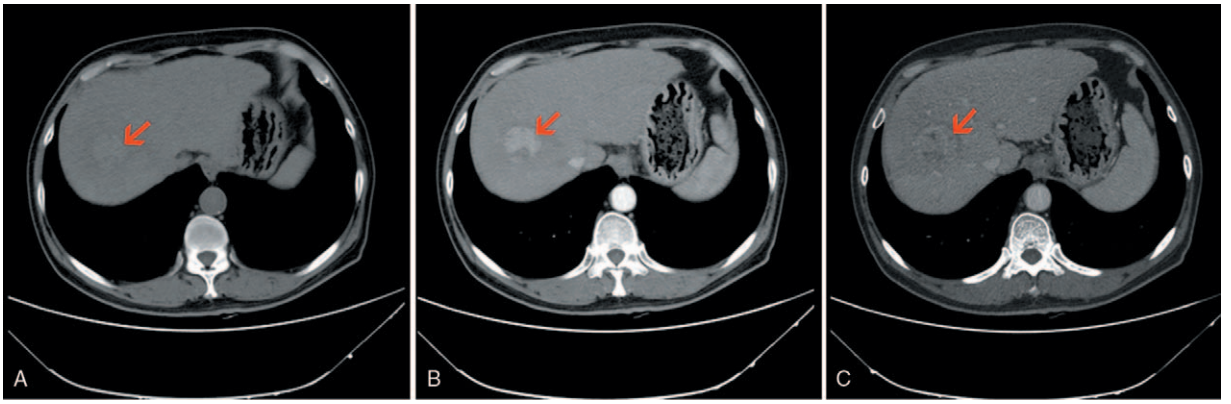

Figure 1. Abdominal CT showed a hypodense tumor (red arrow) in the right liver: (A) plain scan phase; (B) arterial phase; and (C) portal venous phase. CT = computed tomography.

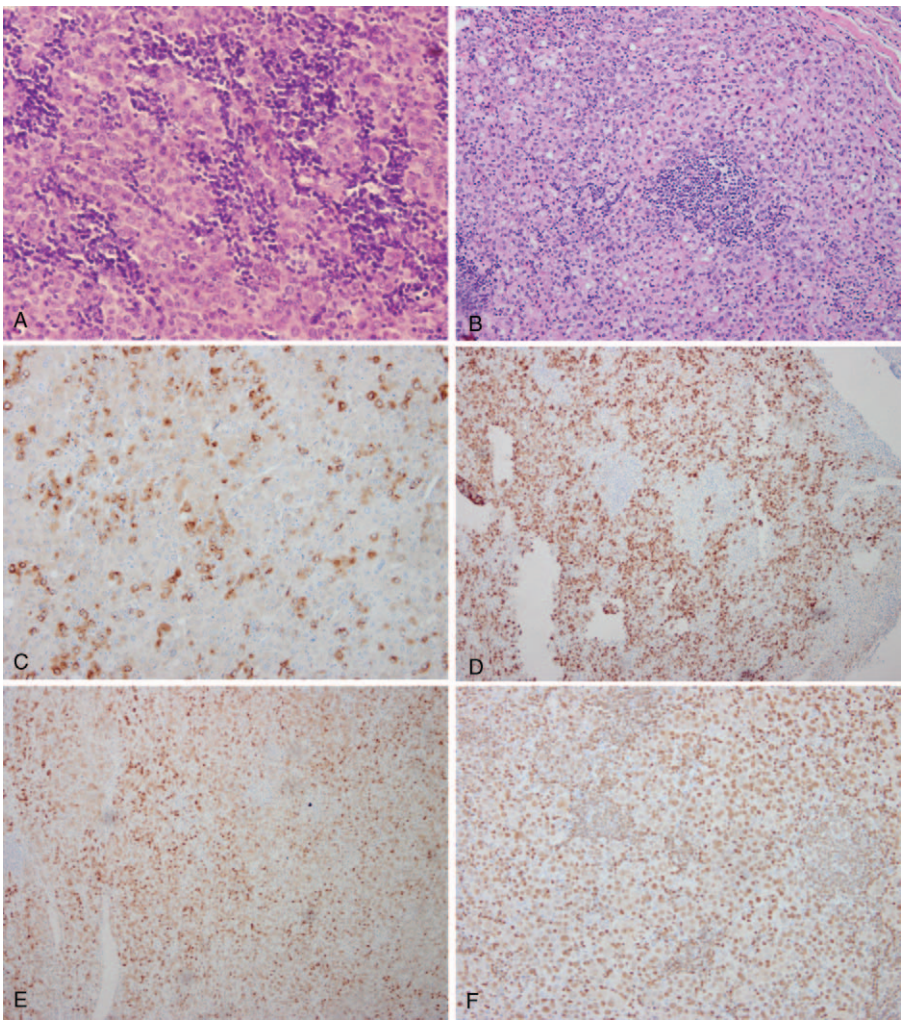

Figure 2. (A, B) The tumor was consisted of undifferentiated HCC cells with eosinophilic cytoplasm, and dense lymphoid stroma extending inside the tumor (HE × 200). Immunohistochemically, the tumor cells were positive for AFP (C), hepatocyte (D), CK8 (E), and glypican-3 (F). AFP = alpha fetoprotein, HCC = hepatocellular carcinoma, HE = hematoxylin and eosin.

3. Discussion

LELC is characterized by undifferentiated carcinoma cells with prominent infiltrating lymphocytes, originally described in nasopharynx. Subsequently, in various organs such as salivary glands, stomach, lungs, colon, thymus, uterine, and ovaries, the particular tumor has been widely described. In 2000, Emile et al retrospectively studied 162 cases of HCC who underwent orthotopic liver transplantation and found 5 cases who revealed abundant lymphoid stroma.[14] In the next year, Szekely proposed that "LELC" is defined as an undifferentiated epithelial tumor intermingled with a heavy lymphoid infiltrate.[26] In 2014, Patel et al reviewed all cases of HCC from 1988 in their institution and 8 cases of LEL-HCC were identified.[20] In 2015, Chan et al presented the largest series with 20 cases of LEL-HCC, from a 9-year retrospective cohort of patients who underwent surgical resection for HCC.[23] Recently, Labgaa et al reviewed the existing literature on LEL-HCC from epidemiological, clinicopathological, and research perspectives, and concluded that at least 66 cases of LEL-HCC have been reported till now.[11] The World Health Organization recognized this tumor as a variant of classical HCC.[27] The clinicopathological features of LEL-HCC are not clear now. To further understand this rare disease's characteristics, we reviewed previous cases reported in the literature. Clinicopathological data of all the cases including our case were summarized in Table 1. The male-to-female ratio was 1.7:1, and the mean age was 58 years (range, 37–81 years). Notably, our case was the youngest of all the patients.

The cause of LEL-HCC remains unclear at present. EBV has been demonstrated to be strongly associated with LELC when the tumor exists in salivary glands, stomach, lung, and thymus.[8] Also, the majority of LEL-CC are positive for EBV.[20] However, till now only one case of LEL-HCC was serology positive for EBV,[15] which may suggest that EBV infection is not a risk factor for LEL-HCC. In the only patient with EBV infection, he was dead of multiple recurrences 5 months after liver transplantation. Therefore, the biological implications of EBV in LEL-HCC need further discussion. HBV and HCV infection are widely recognized risk factors for HCC. The detail analysis of reported cases revealed that the rate of hepatitis virus infection in LEL-HCC was 70.4%, and the majority are HBV infection. Till now, only 3 patients were positive for both of HBV and HCV,[14] including the present case.

Clinical presentations of LEL-HCC are nonspecific. Most patients were asymptomatic, and liver-occupying lesions were found during health examination. Some patients have right upper abdominal pain or symptoms like chronic cholangitis.[17,19] Tumor marker of AFP was elevated in some cases,[18] which may provide a clue for the diagnosis of HCC. Table 1 showed that multiple nodular lesions were reported in 5 patients, whereas the others were single lesion. The mean tumor size was 3.8 cm, ranging from 1 to 13 cm. Notably, preoperative metastases were found in 2 cases with the presentation of enlarged lymph nodes next to the abdominal aorta,[19,21] and radical resection was performed.

Definitive diagnosis of LEL-HCC can only be based on pathological examination, which often presents with poorly differentiated or undifferentiated large epithelial tumor cells with abundant lymphocytes infiltration. The tumor cells commonly show large nuclei and prominent nucleoli with abundant eosinophilic cytoplasm. The biological implications of the lymphocytes are currently under debate, which may be related to an antitumor effect.[18] Immunohistochemically, epithelial tumor cells are usually positive for various cytokines, such as CK8. Positive hepatocyte and glypican-3 indicated a hepatocellular origin rather than a cholangiocellular origin. Meanwhile, negative CK19 and CK7 also do not support a bile duct origin because they are biliary-type cytokeratins. In our case, the tumor cells were positive for CK8, glypican-3, AFP, and hepatocyte, but negative for CK7 or CK19, supporting the diagnosis of LEL-HCC. All reported cases showed a predominance of T-cells rather than B cells, except one case in which the cell dominancy was not available in the literature.[20] The T-cell markers varied among the previous reports. Patel et al reviewed 8 cases of LEL-HCC, and an equal distribution of CD4 and CD8 positive cells was observed.[20] Chan et al reported that the mean ratio of CD8 and CD4 was 6:1.[23] Cacciato et al observed a high predominance of T cells, and the majority were CD4 positive cells, with only a few CD8 positive cells at the margin of the lesion.[22] The differential diagnosis included lymphoepithelioma-like cholangiocellular carcinoma and metastatic liver tumor. A whole body positron emission tomography–computed tomography excluding the possible existing extrahepatic disease supports the primary hepatic origin of the tumor.

The prognosis of LEL-HCC seems to be better than the conventional HCC in most cases,[19–21] with a 5-year survival of 67% from Table 1. However, the clinical outcomes were quite variable, ranging from aggressive clinical courses who died 5 months after surgery owing to recurrence,[15] to alive without recurrence for 10 years.[14] Interestingly, Park et al reported a case of regressing LEL-HCC, who was alive without recurrence for 50 months.[18] Postoperative recurrence was reported in 7 patients, and the shortest interval was 1 month after surgery.[21] In our case, 52 months have passed after surgery; the patient is still alive and free from tumor recurrence. Further accumulation and analyses recruiting more patients are needed to determine the prognosis of LEL-HCC.

There exists no consensus on standardized treatment strategy for LEL-HCC, and radical surgical resection or liver transplantation is still the most effective treatment currently. All of the patients with LEL-HCC, only 6, underwent liver transplantation, whereas the others underwent radical surgical resection. Some scholars have suggested that postoperative chemotherapy with sorafenib and cisplatin may benefit the patient[16,19]; however, due to the rarity of this disease, the effectiveness of these chemotherapeutic substances has not been determined. Six patients received postoperative chemotherapy, of which 3 suffered tumor recurrence. In addition, immunosuppressive therapy may trigger tumor malignant progression,[15] which limited its use.

4. Conclusions

LEL-HCC is a rare variant of HCC with a relatively favorable prognosis. We report a unique case of LEL-HCC with infection of both HBV and HCV. Further research recruiting more patients is needed to determine the accurate causes and mechanism of LEL-HCC.

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