

Lymphoepithelioma-Like Hepatocellular Carcinoma

Chih-Jung Chen¹, MD; Long-Bin Jeng², MD; Shiu-Feng Huang^{1,3,4,5}, MD, PhD

Lymphoepithelioma-like carcinomas (LELC) of the liver are rare. Only nine cases have been reported. All of them were considered to be cholangiocarcinoma and the majority were positive for Epstein-Barr virus (EBV) on EBER *in situ* hybridization. Here we report a case of hepatocellular carcinoma (HCC) mainly composed of LELC. The patient was a 56-year-old man with chronic hepatitis C virus (HCV) infection and cirrhosis. A right-side hepatectomy was performed to remove a 3-cm diameter tumor. Microscopically, the tumor was mainly composed of undifferentiated carcinoma with heavy lymphocytic infiltration, consistent with LELC. The tumor cells of the LELC component were focally positive for HePar 1, CK19 and CK7 and more diffusely positive (50% of tumor cells) for AE1/AE3 on immunohistochemical study. EBER *in situ* hybridization was negative. This is the first confirmed case of HCC with an LELC component. In the available literature, all three cases of LELC of the liver that were negative for EBV were associated with chronic viral hepatitis and cirrhosis, suggesting a different carcinogenesis of EBV-positive LELC of the liver. (*Chang Gung Med J* 2007;30:172-7)

Key words: hepatocellular carcinoma, lymphoepithelioma-like carcinoma, cholangiocarcinoma, chronic hepatitis C, cirrhosis

Lymphoepithelioma-like carcinoma (LELC) is a tumor composed of undifferentiated carcinoma with intense lymphoid stroma similar to nasopharyngeal carcinomas (undifferentiated type). LELC arising from the nasopharynx, salivary glands, stomach, lung and thymus are often related to Epstein-Barr virus (EBV) infection. On the other hand, EBV is not usually found in LELC of the skin, breast, urinary bladder and uterine cervix. Thus, it is suggested that fore-gut derived organs are more susceptible to EBV-associated LELC carcinogenesis.⁽¹⁾ LELC occurrence in the liver is very rare. All of the nine reported cases in the literature were considered to consist of cholangiocarcinoma.⁽²⁻⁶⁾ Most of these tumors were positive for EBV on EBER *in situ* hybridization study, which is similar to that found in LELC in various other organ sites. Lymphoepithelioma-like carcinoma as a

component of hepatocellular carcinoma (HCC) has not been reported previously. We present a case of HCC mainly composed of LELC and negative for EBV on EBER *in situ* hybridization.

CASE REPORT

A 56-year-old man with chronic hepatitis C infection was referred to Chang Gung Memorial Hospital (CGMH), Taiwan for excision of a 3-cm liver tumor in the right lobe. The serum level of alpha-fetoprotein was normal. No other tumor marker was examined. No image study was performed at CGMH. The patient received a right lobectomy of the liver under the impression of HCC. There was no local tumor recurrence during postoperative follow-up until metastatic lesions involving the peripancre-

From the ¹Department of Pathology, Taipei Municipal Wang-Fang Hospital, Taipei; ²Department of Surgery, China Medical University Hospital, Taichung; ³Department of Pathology, Chang Gung Memorial Hospital, Taipei, Chang Gung University College of Medicine; ⁴Department of Pathology, Taipei Medical University, Taipei; ⁵Division of Molecular and Genomic Medicine, National Health Research Institutes, Zhunan.

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Correspondence to: Dr. Shiu-Feng Huang, Division of Molecular and Genomic Medicine, National Health Research Institutes, 35, Keyan Rd., Zhunan Town, Miaoli County 350, Taiwan (R.O.C.) Tel.: 886-37-246166 ext. 35315; Fax: 886-37-586459; E-mail: sfhuang@nhri.org.tw

atic and para-aortic lymph nodes were noted on computed tomography scan 5 months postoperatively. He accepted 6 courses of chemotherapy with regimens of 5-fluorouracil, cisplatin, and mitoxantrone for 6 months and thalidomide therapy for 2 months. However, the para-aortic lesions persisted and hemoperitoneum occurred. The patient died 21 months after surgery. No nasopharyngeal tumors or neck lymph node enlargement was found during the whole clinical course.

Pathological findings

A 15.5 x 9.5 x 7 cm segment of the liver weighing 480 gm was resected. There was a 3.2 x 9.5 x 2.0 cm circumscribed soft tumor mass 0.5 cm from the nearest resection margin (Fig. 1A). Microscopically, the tumor was a confluent tumor composed of a large main mass 2 cm in diameter with three smaller attached nodules 0.8, 0.5 and 0.4 cm in diameter.

Each tumor nodule had its own fibrous capsule. There was no capsular invasion or microvascular invasion. The main tumor was composed of large undifferentiated epithelial cells with vesicular nuclei, prominent nucleoli, indistinct cell borders and heavy small lymphocytic infiltration, which are the characteristic features of LELC (Fig. 1B). Pseudoglandular structure formation was seen focally (Fig. 1C). The three smaller, well-encapsulated tumor nodules all showed the classic features of grade II, well differentiated HCC (Fig. 1D). No portal vein tumor thrombosis was seen. The adjacent liver was cirrhotic. Immunohistochemical studies with a panel of antibodies including HePar 1, CK7, CK19, AE1/AE3, CEA, CD3, and CD20 (Dako Corp., Carpinteria, California) were performed using an autostaining system (Ventana Medical System, Inc., Tucson, Arizona). The pretreatment methods consisted of microwave preheating in citrate buffer solution for

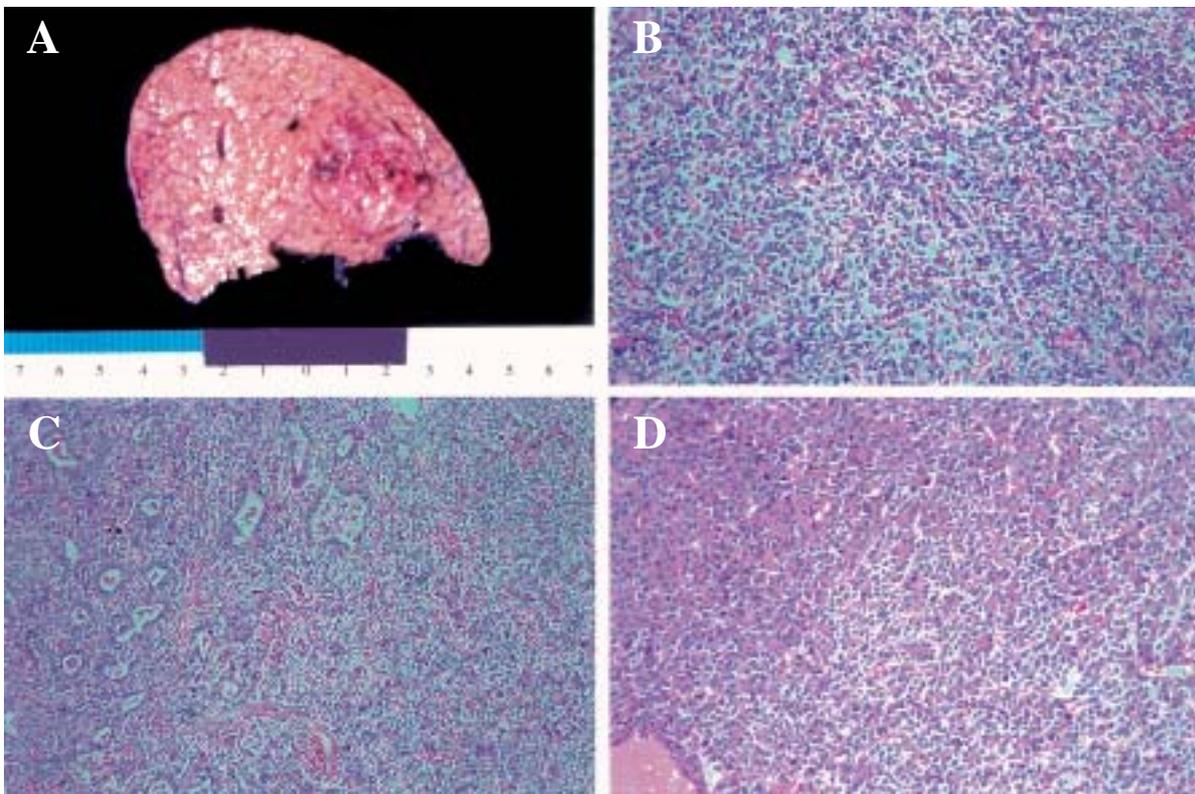


Fig. 1 (A) Surgical specimen showing a 3.2 x 2.7 x 2.0 circumscribed soft tumor mass in a cirrhotic liver. (B) Classical LELC with undifferentiated tumor cells in a dense lymphoid stroma (hematoxylin and eosin stain, original magnification x 100). (C) Pseudoglandular structures in a dense lymphoid stroma (x 200). (D) Well differentiated HCC arranged in a trabecular pattern (x 200).

15 minutes, and the dilution titers of each primary antibody were all 1:200. The LELC component was negative for CEA, and positive for HePar 1, CK19 and CK7 in a few focal areas (Fig. 2B and 3B). It was strongly positive for AE1/AE3 in approximately 50% of the tumor cells (Fig. 3A). The pseudoglandular structures in the tumor were also focally positive for HePar 1 (Fig. 2A) and AE1/AE3, but negative for CEA, CK7 and CK19. The smaller tumor nodules with the classical features of HCC were diffusely positive for HePar 1, and totally negative for CEA, CK7, CK19 and AE1/AE3 (Fig. 3A and 3B). The lymphocytic infiltrates were composed of a mixture of both T-cells and B-cells. The EBV was examined by RNA in situ hybridization using an EBER1-spe-

cific digoxigenin- labeled 30-base oligonucleotide antisense probe, as previously described.⁽²⁾ The result was negative.

DISCUSSION

We could find no reports of HCC with a lymphoepithelioma-like component in the English literature. In a report of HCC with lymphoid stroma by Emile et al,⁽⁷⁾ the tumor cells were similar to classical HCC with large hyperchromatic nuclei, abundant cytoplasm and trabecular patterns, which are not typical of LELC. The LELC component of this reported case was focally positive for HePar 1, which is direct evidence for the diagnosis of HCC, since HePar 1 is

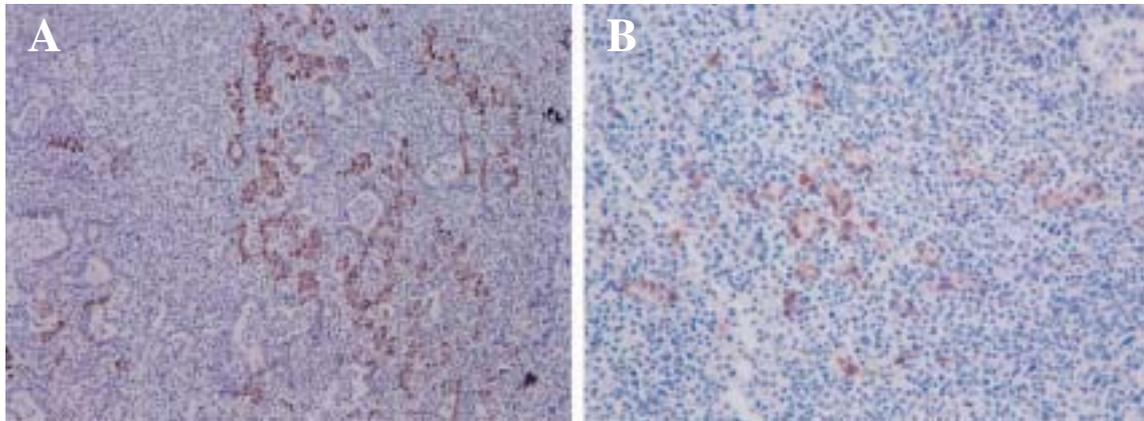


Fig. 2 Positive immunostaining for HePar 1 (A) tumor cells with pseudoglandular structures (x 200), (B) LELC component with undifferentiated tumor cells (x 200).

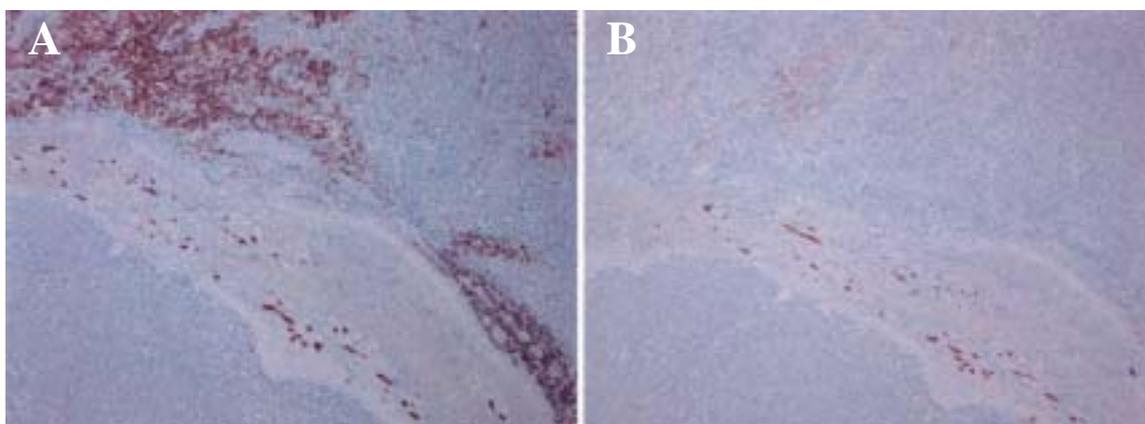


Fig. 3 (A) Strong immunostaining for AE1/AE3 in half of the tumor cells of the LELC component (right upper half region). The residual benign small bile ducts in the fibrous capsule separating the two tumor components are also strongly positive. The HCC component is totally negative (left lower half) (x 40). (B) Weak, focally positive immunostaining for CK7 in the LELC component and totally negative staining in the HCC component. The small bile ducts in the fibrous capsule are strongly positive (x 40).

a very specific marker for liver cells.⁽⁸⁾ Although the tumor cells were also frequently positive for AE1/AE3, they were totally negative for CEA, and only very focally positive for CK7 and CK19 including the pseudoglandular structures. The above staining patterns are not diagnostic for cholangiocarcinoma, which is usually diffusely and strongly positive for CK7 and CK19.⁽⁹⁾ All of the previously reported 9 cases of LELC of the liver were strongly positive for CK7 or CK19, which was the main reason why they were diagnosed as cholangiocarcinoma. On the other hand, focal positive staining for CK7, CK19 and AE1/AE3 is not uncommon in hepatocellular carcinoma.⁽¹⁰⁾ The presence of three concomitant smaller nodules of classic HCC directly connected with the main tumor mass in this study also supports the idea that the whole tumor was HCC with a main component of LELC.

Another unusual finding in the present case is that it was negative for EBV. We have summarized the clinico-pathological features of the ten reported cases including our case in the Table 1. There were only three cases that were negative for EBV (Case 3, 9 and 10). Interestingly, these three patients all suffered from cirrhosis related to chronic viral hepatitis. Two cases were associated with HCV and one with HBV. Three of the remaining seven patients also had

chronic viral hepatitis, but none of them had cirrhosis. Chronic viral hepatitis with cirrhosis is well known to be an important predisposing factor for the development of HCC.⁽¹¹⁾ Recent epidemiology evidence suggests that chronic viral hepatitis (both HBV and HCV) with cirrhosis is associated with cholangiocarcinoma.⁽¹²⁾ We speculate that these three cases of LELC that were negative for EBV are thus related to hepatitis virus associated carcinogenesis. Jeng et al, reported a liver tumor with features of LELC which was negative for EBV. That patient had chronic HCV infection with cirrhosis.⁽⁵⁾ They also suggested that the case reported by Kim et al, (also positive for HCV and negative for EBV) and their own case were more likely to be HCC in nature and related to HCV instead of EBV.

The prognosis of HCC for resectable cases is closely related to several clinicopathological features, such as functional status of the liver, presence of satellite tumors, and portal vein tumor thrombosis.⁽¹³⁻¹⁵⁾ Several histopathological features, including capsule formation, capsular invasion, microvascular invasion, histology grading and distance of resection margin have all been analyzed for their clinical significance in predicting the outcome.⁽¹⁴⁾ Among them, satellite lesion and microvascular invasion have been found to be the most signif-

Table 1. Summary of the Clinico-pathological Features of the 10 Reported Cases of Lymphoepithelioma-like Cholangiocarcinoma of the Liver

No.	Author (Reference No.)	Age(yr)/gender	Site	Size (cm)	HBV	HCV	Cirrhosis	EBV	Clinical outcome	Duration of follow up
1	Hsu HC, et al. ⁽²⁾	47/F	Left lobe	10	(-)	(-)	(-)	(+)	Metastasis to multiple organs 8 months after operation, died of tumor	4 years
2	Vortmeyer AO, et al. ⁽³⁾	71/F	Porta hepatis	5	(-)	(-)	(-)	(+)	Metastasis to regional lymph nodes and local recurrence in 2 years, alive with tumor	2 years
3	Kim YB, et al. ⁽⁴⁾	64/M	Right lobe	2	(-)	(+)	(+)	(-)	unknown	Unknown
4	Jeng YM, et al. ⁽⁵⁾	42/M	Right lobe	3	(-)	(-)	(-)	(+)	Alive without tumor recurrence	7 years
5	Jeng YM, et al. ⁽⁵⁾	67/F	Left lobe	3	(-)	(-)	(-)	(+)	Alive without tumor recurrence	7 months
6	Jeng YM, et al. ⁽⁵⁾	50/M	Right lobe	4	(+)	(-)	(-)	(+)	Alive without tumor recurrence	16 months
7	Jeng YM, et al. ⁽⁵⁾	50/F	Right lobe	4	(+)	(-)	(-)	(+)	Alive without tumor recurrence	2 months
8	Chen TC, et al. ⁽⁶⁾	67/F	Right lobe	5	(-)	(+)	(-)	(+)	Died of postoperative pancreatitis	unknown
9	Chen TC, et al. ⁽⁶⁾	41/M	Left lobe	3	(+)	(-)	(+)	(-)	Alive without tumor recurrence	8 months
10	Chen CJ, et al. (this report)	56/M	Right lobe	3	(-)	(+)	(+)	(-)	Metastasis to regional and para-aortic lymph nodes 5 months after operation, died of tumor	21 months

Abbreviations: yr: year; F: female; M: male; HBV: hepatitis B virus; HCV: hepatitis C virus; EBV: Epstein-Barr virus.

icant prognostic factors. This reported case did not have evidence of microvascular invasion, and the tumor was well-encapsulated with a free resection margin, but the patient still had a rather poor outcome, with early metastasis and a short survival. Emile et al, observed a better prognosis for their group of patients with HCC with lymphoid stroma.⁽⁷⁾ The clinical outcomes of the reported ten patients with LELC of the liver were quite variable (Table 1). The outcomes of five patients were uncertain since their follow up periods were quite short or because there was insufficient information. Only two patients had long disease-free survivals. Three patients, including the current reported case, had aggressive clinical courses with early metastasis and death. Thus, aggressive multimodality treatment for recurrent tumor or even adjuvant chemotherapy after tumor resection might be quite helpful in improving the survival.⁽¹⁵⁾ Since the case number of this entity is quite small, we need more data to support this proposal.

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類似淋巴上皮瘤之肝細胞癌

陳志榮¹ 鄭隆賓² 黃秀芬^{1,3,4,5}

本文報告一例肝臟之類似淋巴上皮瘤癌。此病人為一位46歲男性，過去有慢性C型肝炎及肝硬化之病史。大部分類似淋巴上皮瘤癌之EB病毒其原位雜交檢查皆為陽性。但回顧文獻上僅有之9例報告，再加上我們報告這1例。我們發現共有3例肝臟之類似淋巴上皮瘤癌，合併有慢性病毒性肝炎及肝硬化，而且EB病毒之原位雜交檢查為陰性。我們推測這些肝臟之類似淋巴上皮瘤癌之致癌成因和EB病毒之感染較無關，而和慢性肝炎病毒之感染較有關。(長庚醫誌2007;30:172-7)

關鍵詞：類似淋巴上皮瘤癌，肝細胞癌，膽管癌，慢性C型肝炎，肝硬化

¹台北市立萬芳醫院 病理科；²中國醫藥大學附設醫院 一般外科；³長庚紀念醫院 台北院區 病理科；⁴台北醫學大學 病理學科；⁵國家衛生研究院 分子與基因醫學研究組

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通訊作者：黃秀芬醫學博士，國家衛生研究院 分子與基因醫學研究組。苗栗縣350竹南鎮科研路35號。Tel.: (037)246166 ext. 35315; Fax: (037)586459; E-mail: sfhuang@nhri.org.tw