

Synchronous hepatocellular carcinoma and lymphoepithelioma-like carcinoma arising from 2 different sites of the liver

A case report

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Abstract

Rationale: Most cases of primary liver cancer involve hepatocellular carcinoma (HCC). Lymphoepithelioma-like carcinoma (LELC) is defined as a tumor composed of undifferentiated epithelial cells with a prominent lymphoid infiltrate, which is rarely reported. Lymphoepithelioma-like HCC (LEL-HCC) is an uncommon variant of HCC, having an unclear process of development. Here, we report the first case involving simultaneous HCC and LEL-HCC.

Patient concerns: A 77-year-old female was accidentally found to have a hypoechoic hepatic nodule via an abdominal ultrasound during a health examination. Abdominal computed tomography scan revealed 2 hepatic nodules with arterial phase enhancement and washout in the late phase.

Diagnoses: We diagnosed the case with 2 distinct liver nodules, HCC and LEL-HCC.

Interventions: With suspicion of HCC, tumor resection (liver segments 4 and 5) was then performed. Histopathological examination of tumor 1 showed a moderately differentiated HCC and tumor 2 demonstrated a LEL-HCC. Immunohistochemically, the cells of tumor 2 were immunoreactive for cytokeratin (CK), CK7, and CK19. Epstein-Barr virus encoding small RNA (EBER) in situ hybridization results were negative.

Outcomes: Six months after resection, intrahepatic tumor recurrence was noted. Radiofrequency ablation was conducted.

Lessons: This is an interesting case providing circumstantial evidence of simultaneous development of HCC and LEL-HCC in distinct nodules of the liver with a background of chronic hepatitis B virus infection.

Abbreviations: AFP = alpha-fetoprotein, ARG1 = arginase-1, CK = cytokeratin, EBER = Epstein-Barr encoding region, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, Hep Par-1 = hepatocyte-specific antigen, ICC = intrahepatic cholangiocarcinoma, LELC = lymphoepithelioma-like carcinoma, LEL-CC = lymphoepithelioma-like cholangiocarcinoma, LEL-HCC = lymphoepithelioma-like hepatocellular carcinoma, TILs = tumor-infiltrating lymphocytes.

Keywords: chronic hepatitis B, hepatocellular carcinoma, lymphoepithelioma-like carcinoma, lymphoepithelioma-like hepatocellular carcinoma

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

The ethical approval from the Ethics Committee was not necessary to report this case because the case was reviewed retrospectively.

The authors of this study have nothing to disclose and no conflicts of interest.

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1. Introduction

Most cases of primary liver cancer involve hepatocellular carcinoma (HCC) followed by intrahepatic cholangiocarcinoma (ICC).^[1] Lymphoepithelioma-like HCC (LEL-HCC) is an uncommon variant of HCC with only 67 cases having been described since 1995.^[2] The histologic results, prognosis, and other features of LEL-HCC are quite different from the typical HCC, and the process of development of LEL-HCC remains unclear.^[3,4] We present the first reported case of a surgical patient who had synchronous HCC and LEL-HCC arising from 2 different sites of the liver.

2. Case presentation

A 77-year-old female with chronic hepatitis B virus infection was diagnosed as having liver tumors and was referred to our hospital for management. Hepatitis screening indicated chronic hepatitis B (HBsAg: 152.86 IU/mL, normal range: nonreactive, <0.05; HBV DNA: 2080 IU/mL, normal range: undetectable) without hepatitis C virus (HCV) infection. Physical examination displayed no abdominal tenderness or icteric sclera. Laboratory data showed elevated aspartate aminotransferase (90 U/L,

normal range: 0–40 U/L) and alanine aminotransferase (59 U/L, normal range: 5–45 U/L) levels. Serum alpha-fetoprotein (AFP) level was within normal limit (9.3 ng/mL, reference range: 0–20 ng/mL). No other abnormalities were found with regard to results of complete blood count, blood chemistry tests, and urinalysis. Abdominal contrast-enhanced computed tomography (CT) scan revealed a 2.2 cm liver nodule in segment 4, and a 1.5 cm nodule in segment 5 (Figs. 1 and 2). Both tumors presented enhancement in the arterial phase and washout in the venous phase (Figs. 1A, B and 2A, B). Under the impression of HCC, resection of both tumor nodules was conducted.

In the resected liver specimen, 2 masses, measuring 2.5 cm (Tumor 1, Fig. 3) and 1.7 cm (Tumor 2, Fig. 3) in the greatest dimension, were found. The 2 nodules were 1.2 cm away from

each other. Cut surface of tumor 1 revealed a yellowish-green nodule with ill-defined margin. Tumor 2 was a greyish-white nodule and had a relatively well-demarcated margin. Both nodules had no distinct capsular formation. Portal veins, hepatic veins, and bile ducts were unremarkable, with no evidence of tumor thrombus. Microscopically, tumor 1 showed a moderately differentiated HCC, consisting of polygonal tumor cells with eosinophilic or vacuolated cytoplasm arranged in a microtrabecular pattern (Fig. 4A, B). Histologic features of tumor 2 showed a lymphoepithelioma-like carcinoma (LELC), composed of poorly differentiated tumor cells admixed with intense lymphocytic infiltrates (Fig. 4C–E). By immunohistochemical staining, tumor 2 showed focally positive staining for cytokeratin (CK)7 (Fig. 4F) and CK19 (Fig. 4G), and was negative for arginase-1 (ARG1) and hepatocyte-specific antigen (Hep Par-1).

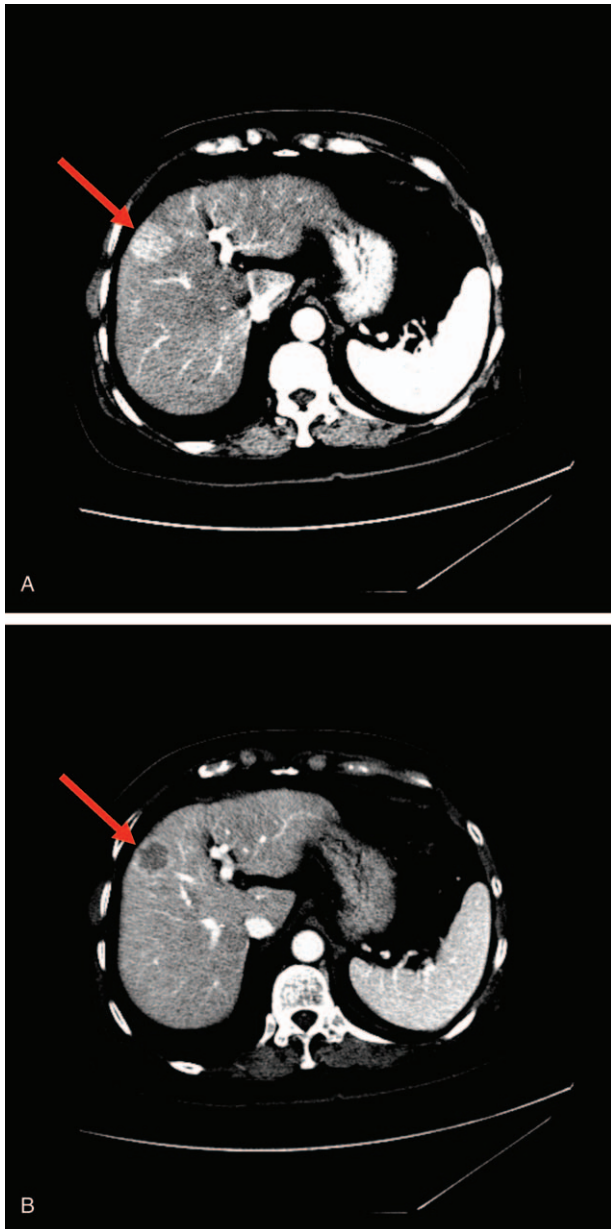


Figure 1. Computed tomography of the liver showing an enhanced nodule (A) with venous washout (B) (red arrow) over segment 4 (Tumor 1).

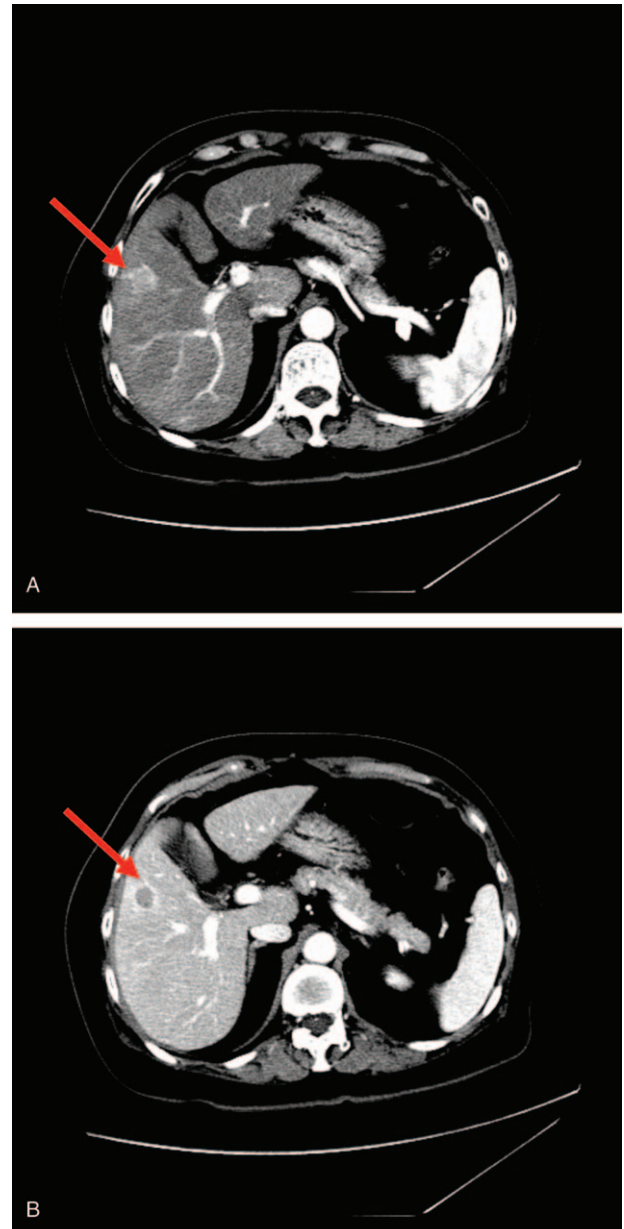


Figure 2. Computed tomography of the liver showing an enhanced nodule (A) with venous washout (B) (red arrow) over segment 5 (Tumor 2).

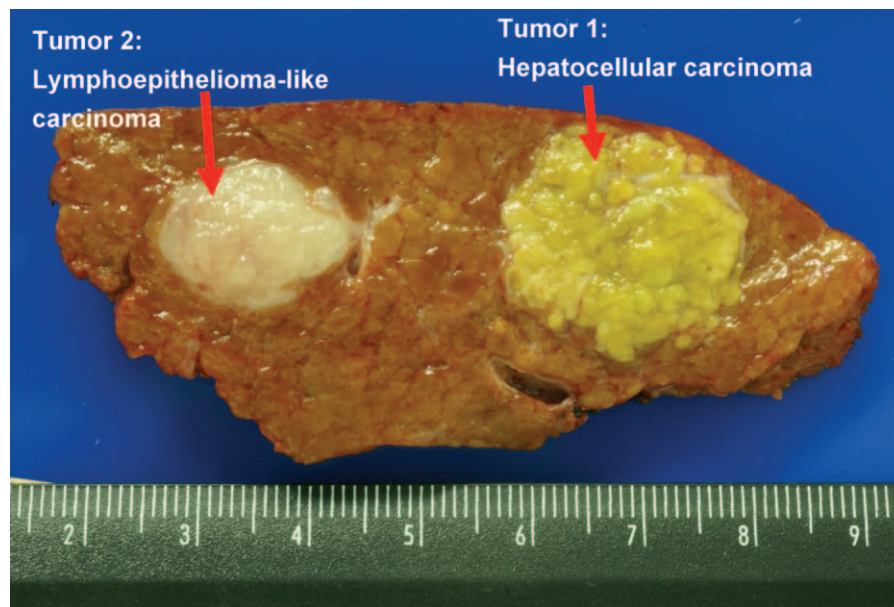


Figure 3. Cut surface of resected specimen. Tumor 1 is a yellowish-green nodule with an ill-defined margin. Tumor 2 is greyish-white and had a relatively well-demarcated margin.

Epstein–Barr encoding region (EBER) in situ hybridization was negative (Fig. 4H).

After the surgery, the patient received no adjuvant therapy and was followed up with an anti-HBV medication. Abdominal CT performed 6 months after liver resection revealed 2 arterial phase-enhancing nodules over segments 6 and 3 with sizes of 1.2 and 0.8 cm, respectively. Under the diagnosis of recurrent tumor, radiofrequency ablation was performed. The patient is alive till now, more than 28 months after the surgery with regular outpatient follow-up.

3. Discussion

Lymphoepithelioma is an uncommon carcinoma initially described in the nasopharynx in 1982.^[5] Since then, different cases have been reported in organs, such as salivary glands, stomach, lungs, colon, uterine, and ovaries,^[6] and were designated as LELCs. In 2010, the World Health Organization has characterized LELC as undifferentiated carcinoma cells with prominent infiltrating lymphocytes.^[7] LELCs arising from the head and neck region, thymus, lung, and stomach have variable associations with Epstein–Barr virus (EBV), whereas those occurring in the skin and urogenital tract have no known association with EBV. Primary hepatic LELC are rare and have been classified as LEL-HCC and lymphoepithelioma-like cholangiocarcinoma (LEL-CC). Until now, there are only about 67 cases of LEL-HCC, and more than 50% of the cases were reported after 2013.^[2] Because of the rarity of LEL-HCC, information regarding clinicopathologic features and clinical outcome is limited. Here, we present the first reported case of a patient who had synchronous HCC and LEL-HCC arising from 2 different sites of the liver.

The median age of patient with LEL-HCC is around 60 years. Compared with HCC, LEL-HCC has a higher incidence rate in female. The sex ratio of men to women in HCC and LEL-HCC tends to be 2:1 to 8:1 and 2:1, respectively.^[8,9] The rate of hepatitis B or C infection in LEL-HCC was 70.4%, indicating that HBV and HCV infections are not only risk factors for HCC

but also for LEL-HCC.^[2] In addition, there was no significant difference between LEL-HCC and HCC patients in the age at presentation, underlying chronic viral hepatitis, cirrhotic background, serum AFP level, tumor size, histologic grade, and frequencies of vascular invasion.^[10]

Clinical presentations and radiologic results of LEL-HCC are similar to HCC. In abdominal contrast CT, both LEL-HCC and HCC displayed early arterial enhancement and venous washout, similar to our case. An elevated tumor marker of AFP level was observed in half of the LEL-HCC cases.^[10] The serum AFP level of the current case was within normal range when the diagnosis of LEL-HCC was made.

In our case, histologic features of tumor 2 showed a LELC, composed of poorly differentiated tumor cells admixed with intense lymphocytic infiltrates. By immunohistochemical staining, tumor 2 showed focally positive staining for CK7 and CK19, and was negative for ARG1 and Hep Par-1. EBER in situ hybridization was negative. The LELC in our case is considered to be LEL-HCC. Immunohistochemically, Hep Par-1 and glypican-3 positive findings suggest a hepatocyte origin. However, in HCC cases, the sensitivity of Hep Par-1 was only 80%, and the poorer the differentiation of the tumors is, the lower the sensitivity of the Hep Par-1 staining it presents. Owing to the poor differentiation of our LELC tumor cells, the negative Hep Par-1 result is unable to confirm whether the tumor is LELC-HCC or LELC-CC. In addition, positive results of CK7 and CK19 represent bile duct origin, with positive findings of 17% and 31%, respectively, in LEL-HCC cases and both 100% in LEL-CC cases.^[3,8]

The first concern is that CK7 and CK19 were only focally positive in our case, and cases of CC preferred diffuse positive consequences. The second consideration is that the EBER in situ hybridization was negative. According to previous literature, EBV infection is highly associated with LELC when the tumors are located in specific regions, such as the salivary glands, stomach, lung, and thymus.^[11] Most of LEL-CC tumors were positive for EBV on an EBER in situ hybridization study, which is similar to that found in LELC in various other organ sites.^[2–4,6,10,11]

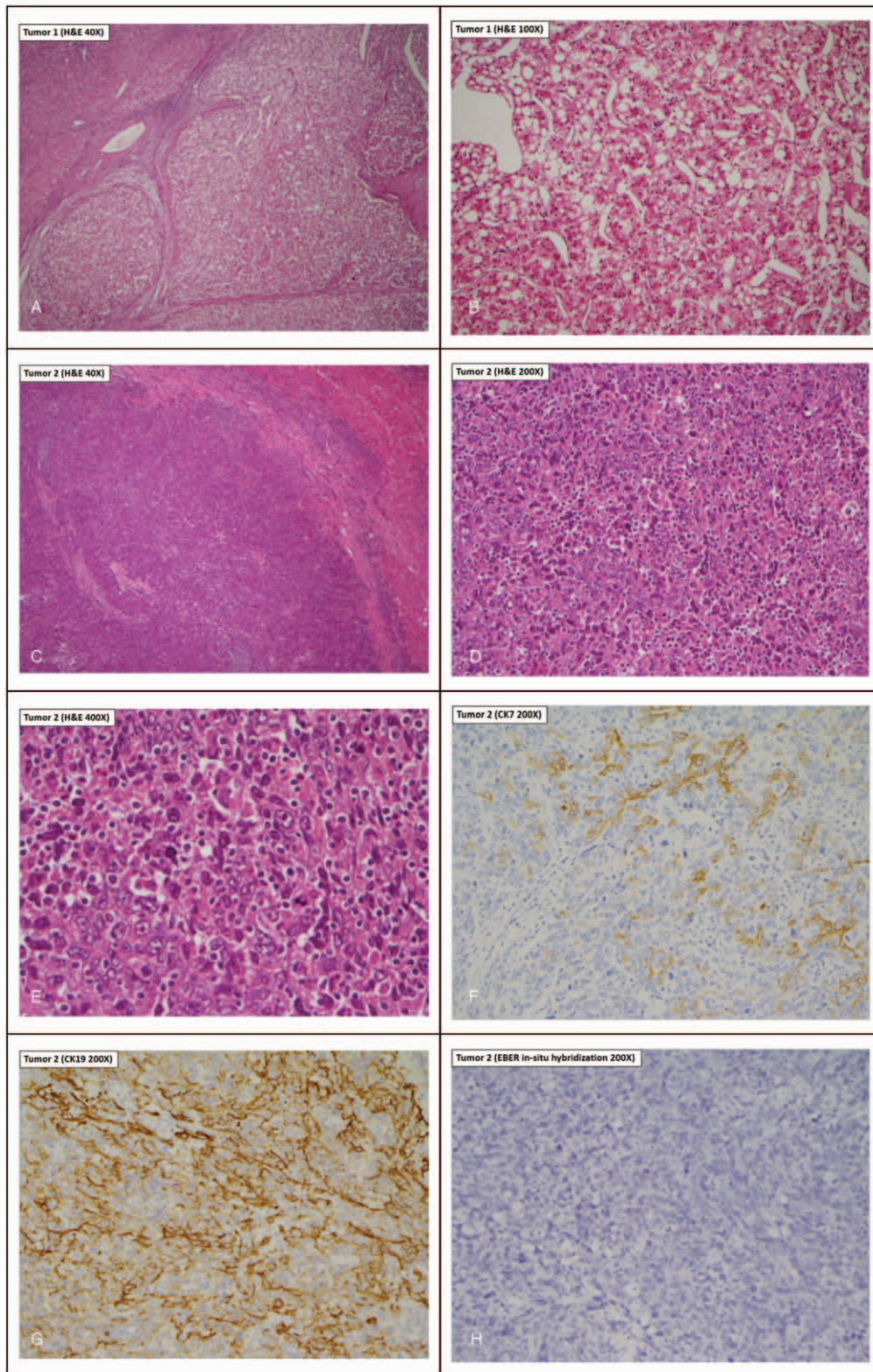


Figure 4. Microscopic features of tumors 1 and 2. Tumor 1 (A, B) moderately differentiated hepatocellular carcinoma. The tumor is composed of polygonal tumor cells with eosinophilic or vacuolated cytoplasm arranged in trabecular pattern. (H&E staining, original magnifications: 40 \times , 100 \times). Tumor 2 (C–H) LELC. The tumor is composed of poorly differentiated tumor cells admixed with intense lymphocytic infiltrates. (C–E: H&E staining, original magnifications: 40 \times , 200 \times , 400 \times). Immunohistochemically, the tumor cells are focally positive for CK7 (F, original magnification: 200 \times) and CK19 (G, original magnification: 200 \times). EBEB in situ hybridization is negative (H, original magnification: 200 \times). CK=cytokeratin, ERBR=Epstein–Barr encoding region, H&E=hematoxylin and eosin, HCC=hepatocellular carcinoma, LELC=lymphoepithelioma-like carcinoma.

Nevertheless, in the currently recorded LEL-HCC, only 1 case presented EBV positivity pathologically.^[8] EBV infection seems to be not a risk factor for LEL-HCC development.^[4,6,8] Thus, the present case with negative staining of EBER in situ hybridization supported the diagnosis of tumor 2 as LEL-HCC.

The majority of the LEL-HCC tumors were solitary (87.8%) and free of vascular invasion (84.7%).^[10] Compared with conventional HCC, LEL-HCC is usually diagnosed at an early stage with a lower recurrent rate (5-year progression free survival: 87.8% versus 46.6%) as well as a favorable prognosis (5-year overall survival rate: 94.1% versus 63.9%) even with lymph node invasion.^[3,4,6,8] It has been pointed out that the immune response against the tumor in LEL-HCC patients may be related to their survival benefit.^[2] Further studies are needed to clarify this point. First-line treatment of LEL-HCC includes liver resection and liver transplantation. Postoperative chemotherapy has been tried with 4 cases, but the effectiveness is unknown.^[4] Furthermore, researchers are studying PD1/PD-L1 targeting immunotherapy, lately.^[8]

The pathogenesis of LEL-HCC remains unknown. The mechanism of recruitment of TILs in LEL-HCC requires further studies. In the light of existing studies, 67 cases of LEL-HCC have been recorded since 1995.^[2] However, no synchronous development of HCC and LELC arising from different sites of the liver has been disclosed. This case represents the first reported case of synchronous small HCC and small LEL-HCC arising from the different liver nodules. Our case provides circumstantial evidence of simultaneous development of HCC and LEL-HCC in distinct nodules of the liver with a background of chronic hepatitis B virus infection.

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References

- [1] Ananthakrishnan A, Gogineni V, Saecian K. Epidemiology of primary and secondary liver cancers. *Semin Intervent Radiol* 2006;23:47–63.
- [2] Labгаа I, Stueck A, Ward SC. Lymphoepithelioma-like carcinoma in liver. *Am J Pathol* 2017;187:1438–44.
- [3] Wang JK, Jin YW, Hu HJ, et al. Lymphoepithelioma-like hepatocellular carcinoma: a case report and brief review of literature. *Medicine (Baltimore)* 2017;96:e9416.
- [4] Shinoda M, Kadota Y, Tsujikawa H, et al. Lymphoepithelioma-like hepatocellular carcinoma: a case report and a review of the literature. *World J Surg Oncol* 2013;11:97.
- [5] Applebaum EL, Mantravadi P, Haas R. Lymphoepithelioma of the nasopharynx. *Laryngoscope* 1982;92:510–4.
- [6] An SL, Liu LG, Zheng YL, et al. Primary lymphoepithelioma-like hepatocellular carcinoma: report of a locally advanced case and review of literature. *Int J Clin Exp Pathol* 2015;8:3282–7.
- [7] Bosman FT, Carneiro F, Hruban RH, Theise ND. Editors. WHO classification of tumours of the digestive system. 4th Edition, World Health Organization. 2010, pp. 417.
- [8] Putra J, Anderson TA, Roayaie S, et al. Metastatic lymphoepithelioma-like hepatocellular carcinoma: a potential diagnostic pitfall and demonstration of PD-L1 expression. *Ann Hepatol* 2017;16:157–9.
- [9] Buch SC, Kondragunta V, Branch RA, et al. Gender-based outcomes differences in unresectable hepatocellular carcinoma. *Hepatol Int* 2008;2:95–101.
- [10] Chan AW, Tong JH, Pan Y, et al. Lymphoepithelioma-like hepatocellular carcinoma: an uncommon variant of hepatocellular carcinoma with favorable outcome. *Am J Surg Pathol* 2015;39:304–12.
- [11] Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. *Am J Clin Pathol* 1995;103:308–15.