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Case Report

Intrahepatic Cholangiocarcinoma With Lymphoepithelioma-like Carcinoma Components Not Associated With Epstein-Barr Virus: Report of a Case

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A carcinoma displaying undifferentiated features with dense lymphoplasmacytic infiltration is defined as lymphoepithelioma-like carcinoma (LELC). Intrahepatic cholangiocarcinoma (ICC) with LELC components is rare, and most LELCs are associated with Epstein-Barr virus (EBV). We report here on a case of ICC with LELC components not associated with EBV. A 65-year-old woman was incidentally found to have a hepatic tumor in the caudate lobe. An extended right hepatectomy with lymphadenectomy was performed. Histologically, the tumor was mainly 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. Immunohistochemical studies revealed that the tumor cells were positive for cytokeratin 19 but were negative for glypican 3. *In situ* hybridization using EBV-encoded RNA was negative. Therefore, a diagnosis of ICC with LELC components not associated with EBV was made. Because there is limited information available regarding the prognosis and treatment of ICC with LELC components because of the limited number of reported cases, additional studies will be needed to clarify the clinicopathologic features of this disease.

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Lymphoepithelioma-like carcinomas (LELCs) are tumors that are composed of undifferentiated carcinoma with an intense lymphocytic infiltrate, and they have histomorphologic features identical to those of undifferentiated nasopharyngeal carcinomas. These tumors have been reported in various anatomic sites, such as the stomach, salivary gland, and thymus.[1] The occurrence of LELC in the hepatobiliary tract is rare. Most LELCs have been reported to be associated with the Epstein-Barr virus (EBV).[1–4] To the best of our knowledge, only 6 cases of intrahepatic cholangiocarcinoma (ICC) with LELC components not associated with EBV infection have been reported,[5–10] and only 2 cases with lymph node metastases at the time of surgery have been reported.[5,9] In this paper, we report on an unusual case of an ICC with LELC components accompanied by lymph node metastases not associated with EBV infection.

Case Report

A 65-year-old woman was incidentally found to have a hepatic tumor by abdominal ultrasonography at a local hospital. Enhanced computed tomography (CT) revealed a heterogeneous liver tumor measuring 5 cm in diameter in the caudate lobe adjacent to the right portal branch and the inferior vena cava. CT revealed a low-attenuation mass measuring 5 cm in diameter in the right hepatic anterior lobe and caudate lobe adjacent to the right portal branch and the inferior vena cava. Dynamic contrast-enhanced CT showed a slightly enhanced mass in the arterial phase, which washed out in the portal and delayed phases (Fig. 1). Magnetic resonance imaging showed that the hepatic mass appeared to be hypointense on T1-weighted images and hyperintense on both T2-weighted images and diffusion-weighted images (Fig. 2). The laboratory findings were as follows: hematocrit, 36.0%; platelets, $208 \times 10^3/\mu L$; aspartate aminotransferase, 25 U/L (normal <35 U/L); alanine aminotransferase, 20 U (normal <28 U); bilirubin, 0.4 mg/dL (normal <1.0 mg/dL); albumin, 4.4 g/dL; and prothrombin time, 88.9%. The indocyanine green retention rate after 15 minutes was 7.1%. The findings for the serum hepatitis B virus (HBV) surface antigen were negative, whereas the patient tested positive for hepatitis C virus (HCV) antibodies. Her serum carcinoembryonic antigen level was elevated, at 10.7 ng/mL (normal <5 ng/mL), but the levels of other tumor markers, including alpha-fetoprotein (6.0 ng/mL; normal <10 mg/mL), des-gamma-carboxy prothrombin (PIVKA-II; 31 mAU/mL; normal <40 mAU/mL), and CA19-9 (11.3 U/mL; normal <37 U/mL), were within the normal ranges. An extended right hepatectomy was performed, and enlarged lymph nodes that were noted in the porta hepatica were removed. The length of the operation was 7 hours and 25 minutes, and the total amount of blood loss was 499 mL.

A 14.7 × 14.3 × 8.0 cm segment of the liver weighing 660 g, and the enlarged lymph nodes in the porta hepatica were resected. Macroscopically, there was a 6.4 × 4.9 × 4.7 cm circumscribed, round, yellowish white, soft tumor found in the resected segment (Fig. 3). The background liver was not cirrhotic. Microscopically, the neoplasm was mainly composed of large undifferentiated epithelial cells with vesicular nuclei, prominent nucleoli, indistinct cell borders, and heavy small lymphocytic infiltration, which are characteristic features of LELC. No carcinoma cells invaded the bile duct, and the surgical margin was free. Alcian blue staining was positive in the epithelial lining. Immunohistochemically, the tumor cells were positive for cytokeratin 19, but they were negative for glypican 3 (Fig. 4). *In situ* hybridization using EBV-encoded RNA was negative. Based on these analyses of the resected liver mass, the patient was diagnosed with ICC with LELC components not associated with EBV. A total of 2 of the 10 resected lymph nodes revealed metastasis, which exclusively consisted of LELC components.

The patient's postoperative course was uneventful, and the patient has been free from tumor recurrence for 20 months since the surgery.

Discussion

Neoplasms with features of undifferentiated carcinoma with intense lymphoid stroma are classified as LELCs, and it has been reported that LELCs can occur in various organs, including the salivary gland,[11] thymus,[12] trachea,[13] lung,[14] esophagus,[15] stomach,[16] urinary bladder,[17] uterine cervix,[18] and vagina.[19] To the best of our knowledge, 8 cases of lymphoepithelioma-like hepatocellular carcinoma,[20–23] 1 case of LELC of the inferior common bile duct,[24] and 16 cases of ICC with LELC component

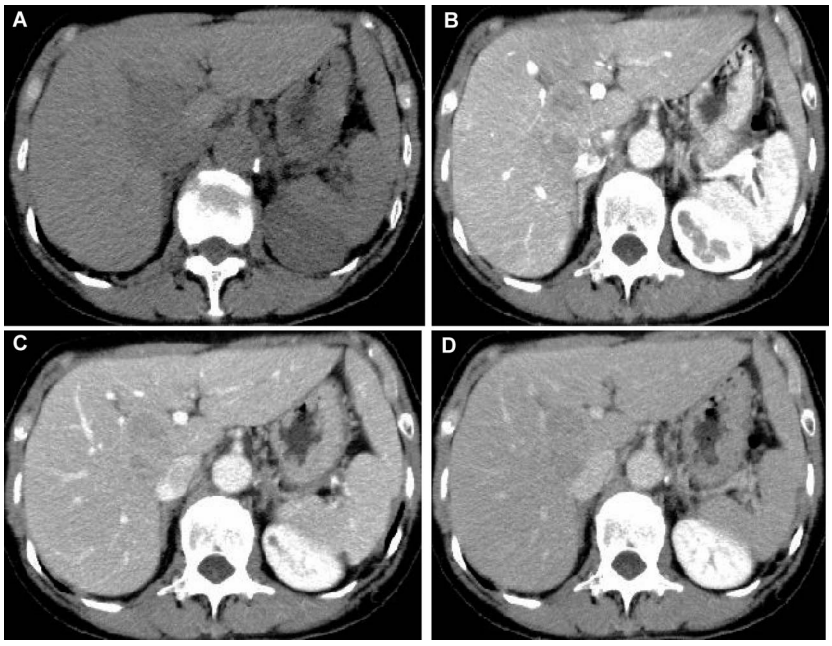

Fig. 1 CT images. (A) CT revealed a low-attenuation mass in the right hepatic anterior lobe and caudate lobe in the simple phase. Dynamic contrast-enhanced CT showed a slightly enhanced mass (B) in the arterial phase, which washed out in the (C) portal phase and in the (D) delayed phase.

have been reported in the English literature.[2–10,25–27] In this case, the tumor cells showed positive immunoreactivity for cytokeratin 19 but no immunoreactivity for glypican 3, a useful marker of hepatocellular carcinoma. This immunohistochemical phenotype was considered to be an indicator for the diagnosis of cholangiocarcinoma. A summary of the previously reported cases of ICC with LELC components is shown in Table 1.

Like nasopharyngeal carcinomas, most LELCs are strongly associated with EBV,[1] as are LELCs of the salivary gland,[11] thymus,[12] lung,[14] and stomach.[16] In contrast, EBV was not associated with LELCs observed in the oral cavity,[28] urinary bladder,[17] uterine cervix,[29] and vagina.[19] In lymphoepithelioma-like hepatocellular carcinoma, 87% (7 of 8) of cases were EBV negative,[20,21,23] and 1 case of LELC of the inferior common bile duct was also EBV

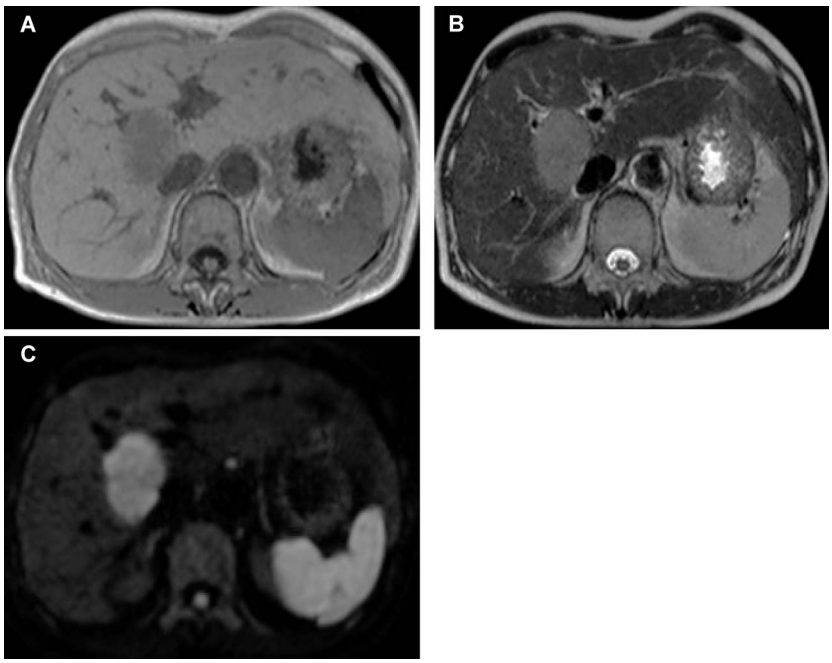

Fig. 2 Magnetic resonance imaging showed that the hepatic mass appeared to be hypointense (A) on T1-weighted image and hyperintense on both (B) T2-weighted image and (C) diffusion-weighted image.

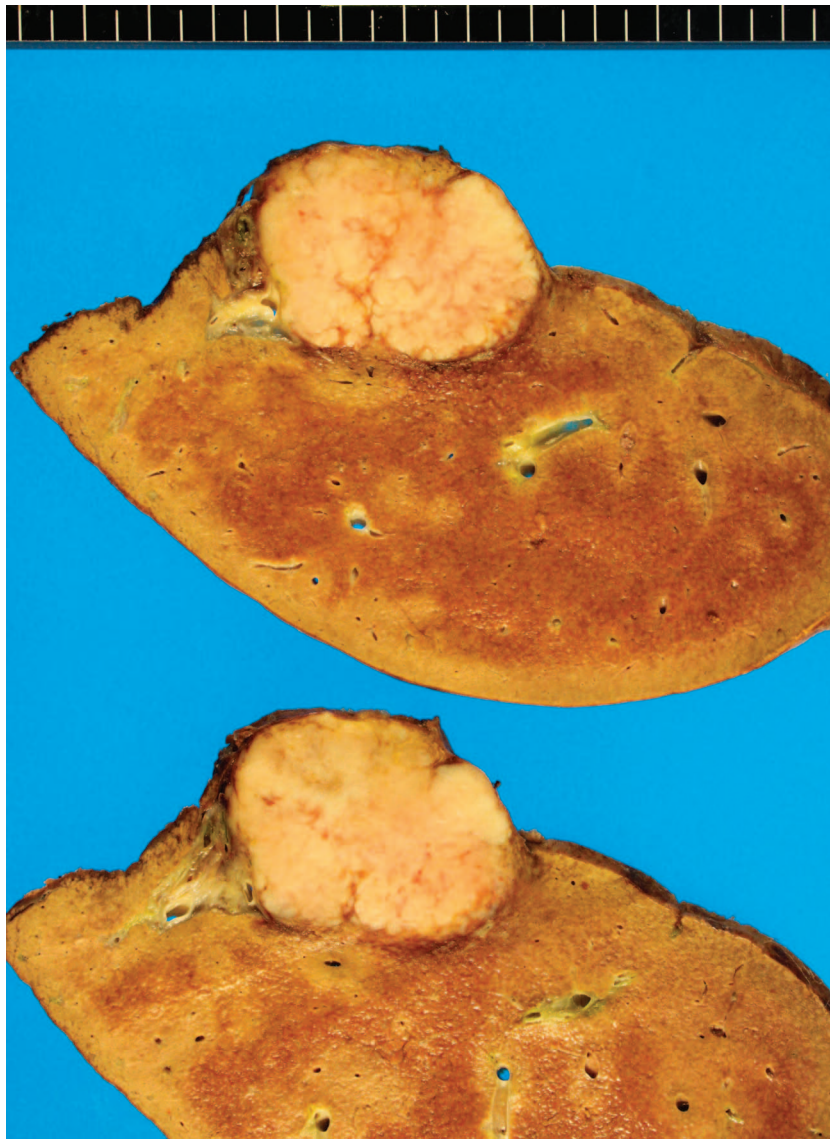

Fig. 3 Macroscopic findings of the resected specimen. Image shows circumscribed, round, yellowish white, soft tumor.

negative.[24] On the other hand, in ICC with LELC components, 38% (6 of 16) of cases were EBV negative. These results suggest that the involvement of EBV genome integration in LELC depends on the origin of the LELC. Furthermore, Adachi *et al*[7] reported that there are no obvious histopathologic differences between EBV-positive and EBV-negative ICC with LELC components. Therefore, the role of EBV in the tumorigenesis of LELC remains poorly understood and controversial, and lymphoepithelioma-like morphologic changes in cholangiocarcinoma can occur in both the presence and absence of EBV genome integration.

The present case was HCV positive, and several previous studies[30,31] have reported that HCV infection plays an etiologic role in ICC; Lee *et al*[32] indicated that there is a close relationship between the development of ICC and HBV infection. However, previous reports showed that only 31% (5 of 16) of patients were HBV positive and 13% (2 of 16) of patients were HCV positive. These findings suggest that the roles of HBV and HCV in the pathogenesis of ICC with LELC components are unclear and the further accumulation of studies is needed.

It has been reported that LELC of the stomach and lung has a better prognosis than other neoplasms of these sites.[33,34] Similarly, the prognosis of ICC with LELC components seems to be better than that of the conventional type of cholangiocarcino-

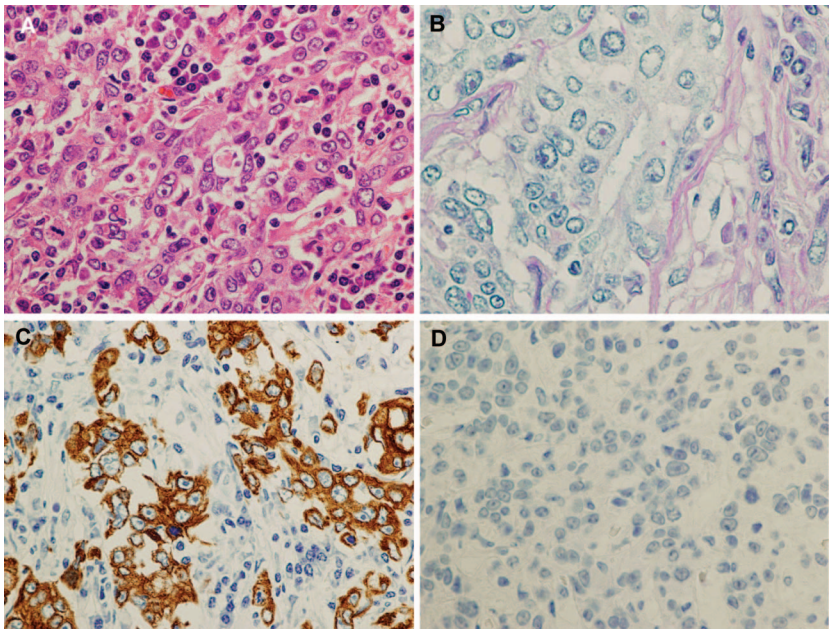

Fig. 4 Histologic specimen of liver tumor. (A) The neoplasm was mainly composed of large undifferentiated epithelial cells with vesicular nuclei, prominent nucleoli, indistinct cell borders, and heavy small lymphocytic infiltration. (B) Alcian blue staining was positive in epithelial lining. (C) Immunohistochemical staining demonstrated positivity for cytokeratin 19. (D) Immunohistochemical staining demonstrated negativity for glypican 3.

ma.[8,25,35] There is no consensus on a standardized treatment strategy for LELC. In the previously reported cases, the patients all underwent surgical resection of their tumors. Lee[5] reported that a case with metastasis to a para-aortic lymph node at the time of surgery underwent postoperative radiation and was still alive without recurrence 54 months after the surgery. The present patient also had lymph node metastases, but the metastatic lymph nodes were resected completely at the time of surgery, and the patient is alive without recurrence 20 months after the surgery. Cases of ICC with LELC components accompanied by lymph node metastases are extremely rare. Because there is limited information available regarding the prognosis and treatment of ICC with LELC components because of the limited number of reported cases, additional studies will be needed to clarify the clinicopathologic features of this disease.

Table 1 A summary of clinicopathologic features of intrahepatic cholangiocarcinoma with lymphoepithelioma-like carcinoma components

Case no.	Source	Age, y/sex	Site	Size, cm	EBV	HBV	HCV	LN	Outcome	Follow-up, mo
1	Hsu *et al*[27]	47/F	Left lobe	10	+	−−	−	Unknown	Died of disease	48
2	Vortmeyer *et al*[26]	71/F	Portal hepatis	5	+	−	−	−	Alive with disease	24
3	Kim *et al*[10]	64/M	Right lobe	2	−	−	+	−	Unknown	Unknown
4	Ortiz *et al*[4]	19/F	Left lobe	5.5	+	−	−	−	Died of disease	44
5	Chen *et al*[9]	67/F	Right lobe	5	+	−	+	+	Died, postoperative pancreatitis	Unknown
6	Chen *et al*[9]	41/M	Left lobe	3	−	+	−	−	No recurrence	8
7	Jeng *et al*[25]	42/M	Right lobe	3	+	−	−	−	No recurrence	96
8	Jeng *et al*[25]	67/F	Left lobe	3	+	−	−	−	No recurrence	7
9	Jeng *et al*[25]	50/M	Right lobe	4	+	+	−	−	No recurrence	16
10	Jeng *et al*[25]	50/F	Right lobe	4	+	+	−	−	No recurrence	2
11	Szekely[8]	61/M	Unknown	6	−	−	−	−	No recurrence	11
12	Huang *et al*[3]	60/F	Caudate lobe	3.5	+	+	−	−	No recurrence	24
13	Adachi *et al*[7]	64/M	Left lobe	5.2	−	−	−	−	No recurrence	3
14	Henderson-Jackson *et al*[2]	63/F	Left lobe	4	+	−	−	−	No recurrence	6
15	Lee[5]	79/M	Left lobe	3.7	−	+	−	+	No recurrence	54
16	Hur *et al*[6]	57/F	Right lobe	2	−	−	−	−	No recurrence	60
17	Our case	65/F	Caudate lobe	6.4	−	−	+	+	No recurrence	20

LN, lymph node metastasis.

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