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Case Report

Lymphoepithelioma-Like Cholangiocarcinoma Associated With HCV: A Case Report and a Review of the Literature

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Lymphoepithelioma-like carcinoma is a particular form of undifferentiated carcinoma characterized by a prominent lymphoid stroma that was originally described in the nasopharynx. We present a case of hepatitis C virus (HCV)–associated lymphoepithelioma-like cholangiocarcinoma (LEL-CC), located at the liver, in a patient with history of malignancy. A 79-year-old man underwent partial hepatectomy with lymphadenectomy for a suspected metastasis of colon cancer 2.5 years after hemicolectomy for advanced colon cancer followed by adjuvant chemotherapy. The resected tumor was diagnosed as LEL-CC via a distinct histologic pattern with dense lymphoplasma cell infiltration. According to the available literature, our report describes a rare cases of HCV-associated LEL-CC that coexisted with other malignancy and that was associated with survival for more than 3 years after surgery, suggesting that surgical resection may be the recommended therapeutic option for LEL-CC to provide a definitive diagnosis as well as obtain a good prognosis, even in advanced stages of LEL-CC.

Key words: Lymphoepithelioma-like cholangiocarcinoma – Hepatitis C virus – Preoperative diagnosis – Prognosis – Treatment

Cholangiocarcinoma, a malignant tumor arising from the biliary epithelium, is characterized by sclerotic stroma with rare prominent lymphocytic infiltration. Although the etiology of cholangiocarcinoma remains poorly understood, previous studies illustrated that chronic hepatitis is associated with an increased oncogenic risk factor for cholangiocarcinoma.[1–3] Lymphoepithelioma-like cholangiocarcinoma (LEL-CC), occurring in the biliary system, is a tumor characterized by large undiffer-

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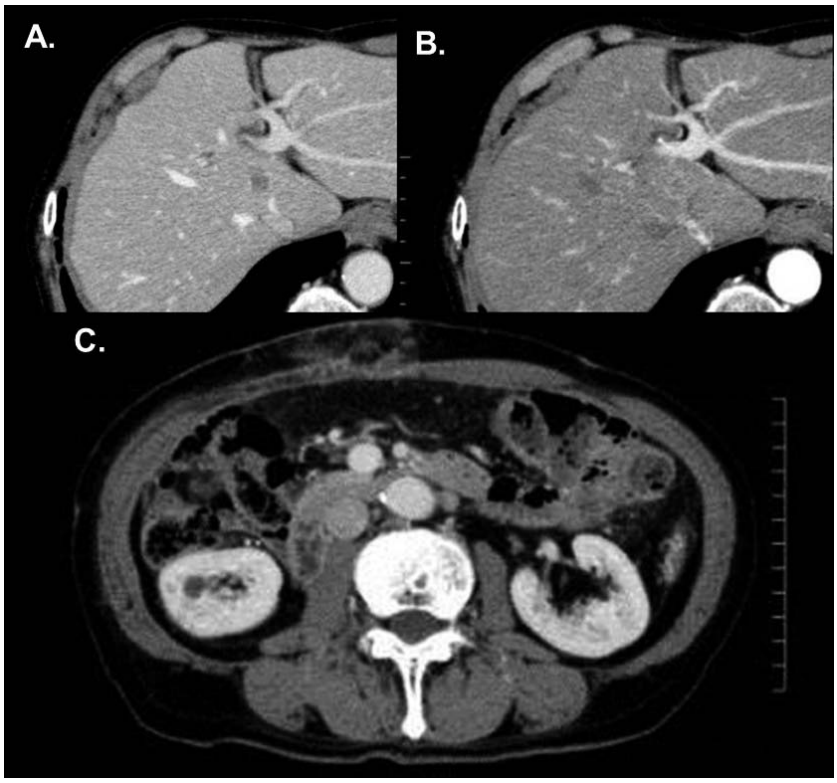

Fig. 1 Preoperative CT findings. (A) Contrast-enhanced CT revealed a relatively well-circumscribed mass (15 mm in diameter) in segment 1 of the liver. (B) The tumor displayed an enhancement in the late phase of contrast-enhanced CT. (C) A swollen lymph node around the abdominal aorta.

entiated epithelial cells with intense lymphoid stroma. LEL-CC, mostly developing in intrahepatic regions, is often related to Epstein-Barr virus (EBV) infection,[4] but it does not arise in patients with a history of chronic hepatitis or cancer. We previously reported a case of hepatitis C virus (HCV)–associated extrahepatic LEL-CC (LEL-ECC) arising in a patient treated for hepatocellular carcinoma (HCC).[16] In this study, we report 1 other case of HCV-associated intrahepatic LEL-CC (LEL-ICC) in a patient treated for advanced colon cancer and suggest that HCV infection may have an association with LEL-CC via a distinct mechanism from EBV.

Case Presentation

A 79-year-old man who underwent left hemicolectomy and postoperative adjuvant chemotherapy for pathologic stage IIIa colon carcinoma (T3N1bM0, Stage IIIB; 7th TNM classification) 2 years earlier was diagnosed with 2 hepatic tumors and multiple enlarged lymph nodes by CT in November 2012. Although he had an HCV infection, his liver function tests were normal and his serum tumor markers—including alpha-fetoprotein (2.8 ng/mL), carcinoembryonic antigen (4.7 ng/mL), and carbohydrate antigen 19-9 (8.0 U/mL)—were within the normal ranges. Contrast-enhanced multidetector computed tomography (CT) revealed 2 masses in segments 1 (1.5×1.2 cm) and 7 (1.0×1.0 cm) of the liver (Fig. 1A), and these masses displayed relative enhancement in the late phase (Fig. 1B). In addition, multiple enlarged lymph nodes were also detected in the porta hepatis and retropancreatic stations, as well as the para-aortic station (Fig. 1C). In January 2013, under the preoperative diagnosis of metastasis from colon cancer, we performed partial hepatectomy (segments 1 and 7) with lymphadenectomy in the hepatoduodenal ligament surrounding the common hepatic artery. The sectioned surface of the liver displayed a well-defined, nonencapsulated, solid tumor (Fig. 2A). Hematoxylin-eosin staining revealed the poorly differentiated component of solid sheets of tumor cells with dense lymphoplasmacytic infiltrate (Fig. 2B). Immunohistochemical examination demonstrated that the adenocarcinoma cells were diffusely positive for cytokeratin 19 (Fig. 2C), and negative for HepPar1 (Fig. 2D). In situ hybridization using EBV-encoded RNA 1 was negative in these cells (Fig. 2E). In the lymph node metastatic lesions, dense lymphoplasmacytic infiltration was observed within the tumor nests, similar to the primary lesion; but the portal area of the surrounding liver tissue of the tumor showed little

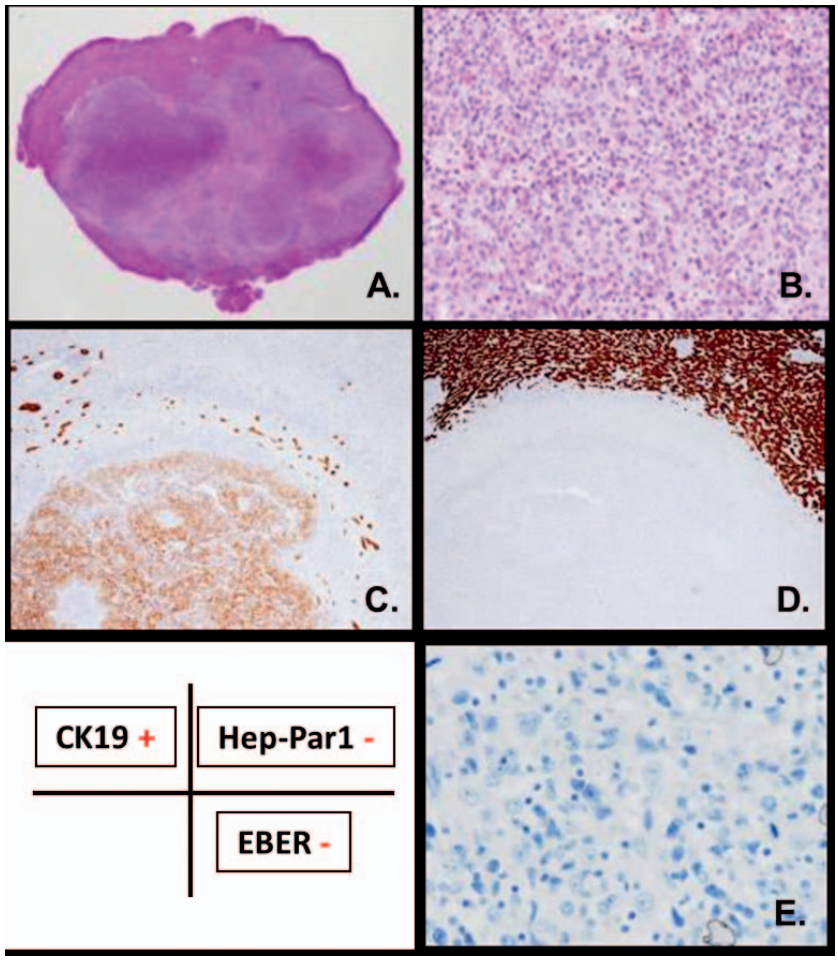

Fig. 2 Microscopic photographs of the resected liver specimen. (A) The sectioned surface displays a well-defined, nonencapsulated, solid tumor (HE stain, panoramic view). (B) The poorly differentiated component of solid sheets of tumor cells with dense lymphoplasmacytic infiltrate (HE stain, ×100). The adenocarcinoma cells are diffusely positive for cytokeratin 19 (C; immunohistochemistry, ×40) and negative for Hep-Par1 (D; ×40) and for in situ hybridization of EBV-encoded RNA (E; ×400).

lymphocytic infiltration, and fibrosis was not observed. The features suggesting chronic hepatitis and liver cirrhosis were not present. The patient was diagnosed with LEL-ICC concomitant with distant lymph node metastases, and he received additional postoperative chemoradiotherapy focused on the para-aortic enlarged lymph nodes. He has remained alive without additional recurrence for 43 months since hepatectomy.

Discussion

In the present report, we described a rare case of HCV-associated LEL-CC with some atypical clinical features. At present, 25 cases of LEL-CC have been described in the literature, but only pathologic findings were described for 7 cases.[4] Therefore, we summarized the clinical details of 19 cases, excluding the aforementioned 7 cases, in Table 1.

The mean age of presentation was 57.1 years (range, 19–79 years), with a male-to-female ratio of 9:10. All patients underwent surgical resection. The mean size of the tumor was 42 mm (range, 10–100 mm), and the median follow-up duration was 31.2 months (range, 2–84 months). The clinical outcome was good, with 70.6% of patients remaining alive without disease. The median survival time for surviving patients was 29.1 months (range, 2–84 months), and 11.8% of the patients died because of disease recurrence. Three patients had disease recurrence (cases 1, 3, and 7); the pattern of recurrence was local recurrence involving the lymph nodes (case 1) and other organs (cases 3 and 7). Two patients were reported to be treated with additional therapies (cases 1 and 7).

LEL-CC is frequently associated with EBV[4] but not chronic hepatitis. In fact, Table 1 demonstrates that LEL-CC was associated with EBV in 10 cases (52.6%); HBV in 6 cases (31.6 %), and HCV in 4 cases (21.1%). In addition, HCV and EBV were only noted positive for 1 patient with LEL-CC, and recent studies indicated that HCV is an important predis-

Table 1 Clinicopathologic features of cases of LEL-CC of the hepatobiliary tract reported in the literature

Case (ref.)	Age, y	Sex	Tumor size, cm	Hepatitis virus	EBV	LN metastasis	Surgery	Postoperative therapy	Clinical outcome	Duration of follow up
1 (5)	71	Female	5.0	–	+	–	Hepatectomy	Chemotherapy	Metastasis to regional lymph nodes and local recurrence, alive with tumor	3 y
2 (6)	64	Male	9.5	HCV	–	–	Hepatectomy	Unknown	Unknown	Unknown
3 (7)	19	Female	5.5	–	+	–	Hepatectomy	–	Metastasis to liver, died of tumor	44 mo
4 (8)	61	Male	6.0	–	–	–	Hepatectomy	–	Alive without tumor recurrence	11 mo
5 (9)	67	Female	5.0	HCV	+	+	Hepatectomy	–	Died of postoperative pancreatitis	Unknown
6	41	Male	3.0	HBV	–	–	Hepatectomy	–	Alive without tumor recurrence	8 mo
7 (10)	47	Female	10.0	–	+	–	Hepatectomy	–	Metastasis to multiple organs, died of tumor	4 y
8	42	Male	3.0	–	+	–	Hepatectomy	–	Alive without tumor recurrence	7 y
9	67	Female	3.0	–	+	–	Hepatectomy	–	Alive without tumor recurrence	7 mo
10	50	Male	4.0	HBV	+	–	Hepatectomy	–	Alive without tumor recurrence	16 mo
11	50	Female	4.0	HBV	+	–	Hepatectomy	–	Alive without tumor recurrence	2 mo
12 (11)	61	Female	3.5	HBV	+	–	Hepatectomy	–	Alive without tumor recurrence	2 y
13 (12)	64	Male	5.2	–	–	–	Hepatectomy	–	Alive without tumor recurrence	3 mo
14 (13)	63	Female	3.8	–	–	–	Hepatectomy	–	Alive without tumor recurrence	6 mo
15 (14)	79	Male	3.5	HBV	–	+	Hepatectomy/ lymphadenectomy	Radiation/transcatheter arterial embolization (TAE)	Alive without tumor recurrence	54 mo
16 (15)	57	Female	2.0	–	–	–	Hepatectomy	–	Alive without tumor recurrence	5 y
17 (16)	68	Male	3.0	HCV	–	–	PpPD	TAE	Alive without tumor recurrence	65 mo
18 (17)	35	Female	1.6	HBV	+	–	Hepatectomy	Unknown	Unknown	Unknown
19 (present case)	79	Male	1.5/1.0	HCV	–	+	Hepatectomy/ lymphadenectomy	Cardiac resynchronization therapy	Alive without tumor recurrence	43 mo

posing factor for the development of ICC,[18,19] suggesting that chronic hepatitis, particularly HCV infection, may play a role in carcinogenesis via a distinct mechanism from EBV infection. Further studies are needed to determine whether the association of EBV and/or chronic viral hepatitis with LEL-CC is oncogenically significant.

In our patients who had histories of malignancy—including a case previously reported (case 17)—a correct diagnosis could not be made preoperatively because of some unusual findings, such as the number and locations of the tumors. Table 1 illustrates that 18 of 19 patients presented with a single tumor, and these tumors developed in the liver as opposed to extrahepatic regions. Case 17 of LEL-ECC involved a preoperative clinical diagnosis of an inferior common bile duct cancer because there was no previous report about LEL-ECC. In addition, this case was the first case of LEL-CC in which multiple liver tumors were diagnosed as metastases from colon cancer preoperatively, as recurrence in the liver sometimes occurs at multiple sites after colorectal carcinoma resection.[20] Furthermore, it is an exceedingly rare case that liver tumors with distant lymph node metastases were developed for a short-term period (about 2 years) after the colon cancer surgery. These unusual clinical findings made it more difficult to make a correct preoperative diagnosis in our cases.

There is no consensus on standardized treatment strategies for LEL-CC. Only 3 patients had lymph node metastasis preoperatively. In case 5, metastasis was located in the regional (porta hepatis and retropancreatic) station, and in the other 2 cases (15 and 19), metastases were detected in both regional and distant (para-aortic) stations. Additional postoperative therapy was not administered to the patient with regional lymph node metastasis, who succumbed to postoperative pancreatitis. On the contrary, in patient 15, para-aortic lymph node dissection and postoperative radiation to the regional lymph nodes were completed, and the patient survived without recurrence for 54 months after tumor removal, although the patient recently developed metachronous HBV-associated HCC.[14] In this case, the second case of LEL-CC associated with distant lymph metastasis, the patient received postoperative palliative radiotherapy (30 Gy) delivered to the para-aortic lymph nodes, and the patient's lesion was diminished in size by more than 50%, 3 months after irradiation. The patient is still alive for 43 months without recurrence of LEL-CC (including lymph nodes metastatic spread), suggesting that postoperative radiotherapy is effective for treating LELC with distant lymph node metastasis. Additional regional radiotherapy after complete tumor resection might be recommended for curative treatment because there is no definitive chemotherapeutic regimen.

There is limited information regarding the prognosis of LEL-CC, although some previous papers reported that the prognosis of LEL-CC appears to be better than that of ordinary cholangiocarcinoma.[8,10] In general, lymph node metastasis and recurrent tumors appear to be associated with a poor outcome in patients with cholangiocarcinoma. Table 1 shows that 2 patients with LEL-CC (cases 3 and 7), both of whom died because of recurrence, survived approximately 4 years after surgery. In addition, metachronous lymph node metastases developed in only 1 patient with LEL-CC (case 1). The patient received additional chemotherapy and survived for 3 years after surgery, suggesting that patients with LEL-CC may become long-term survivors despite multiple relapses. Because LEL-CC is rare, careful long-term follow-up and the accumulation of cases are warranted to determine the disease course, and we need more data to support this proposal.

Conclusion

In summary, this report described a rare case of HCV-associated LEL-CC with some atypical features, including the tumor location and number, pattern of metastasis, and history of other cancer. We comprehensively reviewed all 19 cases together the current 1 case, and our results suggest a possible association between LEL-CC and HCV, which may play a role in carcinogenesis via a distinct mechanism from EBV infection. Although a definitive therapeutic regimen has not been established, complete resection of primary tumors with lymphadenectomy or additional radiation may be recommended for curative treatment and better prognoses of LEL-CC, even in patients with advanced disease. Reporting additional cases and further investigations into the biologic characteristics of LEL-CC are needed to develop appropriate therapeutic strategies and clarify the prognosis of this malignancy.

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