Case Report

Epstein–Barr virus (EBV) associated lymphoepithelioma-like cholangiocarcinoma with elevated EBV DNA titer and treated with systemic chemotherapy

Chen-Yang Hua, Tse-Ching Chen, Shu-Wei Huang, Cheng-Lung Hsud, *

a Division of Hematology and Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan
b Department of Pathology, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan
c Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan
d Division of Hematology and Oncology, Department of Internal Medicine, Chang Gung Memorial Hospital at Linkou and Chang Gung University School of Medicine, Taoyuan, Taiwan

A R T I C L E  I N F O
Article history:
Received 7 May 2016
Accepted 9 August 2016
Available online xxx

Keywords:
Cholangiocarcinoma
Epstein–Barr virus
Lymphoepithelioma
Case report

A B S T R A C T
Lymphoepithelioma-like cholangiocarcinoma (LELCC) is a rare variant of intrahepatic cholangiocarcinoma. Epstein–Barr virus (EBV) was reported to be associated with LELCC in approximately 70% of cases by EBV-encoded small non-polyadenylated RNA (EBER) in situ hybridization. In reviewing literature, the treatment experience of advanced LELCC are lacking. In this study, we reported a young female patient diagnosed with locally advanced EBV-associated LELCC with elevated EBV DNA titer and treated with systemic chemotherapy.

Copyright © 2016, The Chinese Oncology Society. Production and hosting by Elsevier B.V. All rights reserved. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction
Lymphoepithelioma-like cholangiocarcinoma (LELCC) is a rare variant of intrahepatic cholangiocarcinoma. Epstein–Barr virus (EBV) was reported to be associated with LELCC in approximately 70% of cases by EBV-encoded small non-polyadenylated RNA (EBER) in situ hybridization. The outcome of early LELCC is reported to be superior to classic intrahepatic cholangiocarcinoma. However, experience with treatment for advanced LELCC is limited. In this study, we reported a young female patient diagnosed with locally advanced EBV-associated LELCC with elevated EBV DNA titer and treated with systemic chemotherapy.

2. Case report
2.1. Clinical features
A 32-year-old Chinese woman presented with abdominal pain for four weeks, accompanied by anorexia, relapsing fever, and general malaise. Her medical history was significant for latent hepatitis B infection. The patient’s pain was vaguely located in the upper abdomen, radiating to the back and progressing over time. Blood tests were prognostically significant for leukocytosis (WBC 30,700/μL), anemia (hemoglobin 8.3 g/dL), coagulopathy (prothrombin time 16.3 s), hyperbilirubinemia (total bilirubin 2.4 mg/dL), and elevated C-reactive protein (CRP, 228.9 mg/L).

A heterogenous liver hilar tumor was detected by abdominal sonography. Abdominal computed tomography (CT) showed a hepatic tumor with multiple enlarged lymph nodes at the para-aortic area as well as splenomegaly (Fig. 1). Dilatation of intra-hepatic bile duct was noted as well.

2.2. Pathologic findings
Upon microscopic examination of the patient’s core-needle biopsy specimen, the hepatic tumor cells had irregular large nuclei with syncytial growth pattern without glandular formation. The tumor stroma was significant with dense lymphoplasmacytic infiltration (Fig. 2A). Immunohistochemical staining was weakly positive for Hep Par 1 and negative for CK7, CK20 and TTF-1 (Fig. 2B). Epstein–Barr virus-encoded small non-polyadenylated RNA (EBER) signals were shown in the nuclei of lymphoepithelioma-like cholangiocarcinoma (Fig. 2C).
2.3. Treatment course

A percutaneously transhepatic cholangiographic drainage tube was inserted into the left intra-hepatic duct to relieve obstructive jaundice. Her serum hepatitis B DNA titer was undetected (less than 116 copies/mL), and EBV DNA titer was 598,000 copies/mL. Her serum tumor markers were within normal limits, including carbohydrate antigen 19-9 (CA19-9, 17.56 U/mL), carcinoembryonic antigen (CEA, 0.62 ng/mL) and alpha-fetoprotein (AFP, 3.4 ng/mL).

The patient underwent systemic chemotherapy of cisplatin and gemcitabine combination treatment. After one dose of cisplatin and one dose of gemcitabine, her serum EBV DNA titer decreased to 9090 copies/mL. However, the patient experienced esophageal variceal bleeding at day 17 of chemotherapy. Endoscopic variceal ligation was performed at the same time.

The patient received subsequent gemcitabine for one cycle after resolution of variceal bleeding. However, a subsequent CT scan showed progression of the hepatic tumor as well as regional lymphadenopathy. Following systemic chemotherapy of gemcitabine monotherapy, the patient’s serum EBV DNA titer had risen (Fig. 3). Thereafter, the patient died three months after she was diagnosed with disease.

3. Discussion

Lymphoepithelioma-like cholangiocarcinoma is histologically characterized by large undifferentiated cells with vesicular nuclei, prominent nucleoli, indistinct cell borders, and dense lymphoplasma cell infiltrations. In reviewing the English literature, only 27 cases of LELCC were reported. Clinical characteristics and pathologic features are summarized in Table 1. In reported cases of all 27 patients, a female-predominant (16/27) trend is observed. The median study participant age was 57, and about 70% (19/27) of the cases were positive with EBER in situ hybridization. Interestingly, the geographical distribution of reported cases was similar to nasopharyngeal carcinoma, with 69% (20/29) of the cases arising from east and southeast parts of Asia. How EBV infection contributes to carcinogenesis of LELCC needs further investigation.

Epstein–Barr virus DNA in serum/plasma has been reported as a prognostic marker for nasopharyngeal carcinoma. The presence of Epstein–Barr nuclear antigen 1 (EBNA-1) DNA in peripheral blood is a risk factor for patients with nasopharyngeal carcinoma developing distant metastasis as well as a lower survival rate. Furthermore, pretreatment plasma EBV DNA copy number and their clearance rates are also significant predictors for treatment outcome in patients with nasopharyngeal cancer. Whether EBV DNA in peripheral blood level can be used as a prognostic factor in patients with LELCC is not well-defined. To our knowledge, we were the first researchers to report elevated serum EBV DNA in patients...
with LELCC. In this case report, we demonstrated elevated EBV DNA level in a patient with advanced LELCC, and clearance after initial chemotherapy. The purpose of our study was to confirm whether peripheral blood EBV DNA level might correlate with disease progression in patients LELCC associated with EBV. Additionally, we further intended to assess EBV DNA titer in patients with LELCC associated with EBV.

The outcome of early LELCC is reported to be better than classical intra-hepatic cholangiocarcinoma (IHCC). Chan et al reported a seven-patient case series with surgically resected stage I LELCC, which demonstrated better overall survival and disease-free survival compared to randomly selected stage I IHCC. However, the clinical outcome and optimal treatment of advanced LELCC remains unknown. We reported the first Asian patient with advanced LELCC treated with systemic chemotherapy. Gemcitabine, a nucleoside analog, was reported to have an objective response rate of 0–30% as a single-agent, and 21–35% as combination therapy with cisplatin in treating bile duct cancer. In patients with nasopharyngeal carcinoma, gemcitabine also has an objective response rate of 28–48% as a single-agent, and 64–92% as combination therapy with cisplatin. In this case, we opted for combination therapy of cisplatin and gemcitabine for this patient based on the literature reports. However, the result was quite dismal despite initial EBV DNA response after one cycle of cisplatin and gemcitabine.

Programmed death ligand 1 (PD-L1) expression is a characteristic feature of EBV-associated malignancies. Research has shown that an increase of PD-1–expressing intratumoral CD8 T cells predicts a poor prognosis for nasopharyngeal carcinoma. Preliminary data from a phase Ib study, KEYNOTE-028, showed an overall response rate of 22.2% in 27 heavily pretreated patients with advanced nasopharyngeal carcinoma treated with pembrolizumab (anti-PD-1 antibody), with six partial responses. LELCC was characterized by dense lymphoplasmacytic infiltration in the tumor stroma as seen in nasopharyngeal carcinoma, and treatment strategy of immune checkpoint blockade appears reasonable. However, more clinical evidence and further effective systemic treatment should be investigated to more effectively optimize management of advanced LELCC.

**Conflict of interest**

All authors have no conflict of interest to be declared.

**References**


