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Intrahepatic Lymphoepithelioma-Like Cholangiocarcinoma Not Associated with Epstein-Barr Virus: A Case Report

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Key Words

Lymphoepithelioma-like carcinoma · Cholangiocarcinoma · Liver · Epstein-Barr virus

Abstract

Lymphoepithelioma-like cholangiocarcinomas are rare tumors and most of them are related with Epstein-Barr virus (EBV) infection. Here, a case of a patient with lymphoepithelioma-like cholangiocarcinoma not associated with EBV infection is presented. In a 79-year-old man with hepatitis B virus-associated cirrhosis, a liver mass was detected on abdominal CT. Macroscopically, the resected tumor was pale gray, rubbery and well defined. Histologically, the tumor was composed of two components: an adenocarcinoma that formed irregular small glands and a lymphoepithelioma-like carcinoma that exhibited sheets of undifferentiated epithelial cells with lymphoid stroma. Lymphoplasmacytic infiltrates were more predominant in the lymphoepithelioma-like carcinoma than in the adenocarcinoma. Both components were roughly divided, but they gradually merged. Immunohistochemically, the adenocarcinoma component was diffusely positive for AE1/AE3, cytokeratin 7, cytokeratin 19 and epithelial membrane antigen, while the lymphoepithelioma-like carcinoma component was focally positive for them. However, both components were diffusely positive for p53 protein, and in situ hybridization using EBV-encoded RNA 1 was negative in both components as well. Examination of a resected para-aortic lymph node revealed metastasis exclusively of the lymphoepithelioma-like carcinoma component.

Introduction

Lymphoepithelioma-like carcinomas have a histomorphology identical to that of undifferentiated nasopharyngeal carcinomas and have been described in various organs.

Lymphoepithelioma-like carcinomas of the liver, however, have rarely been reported, and the majority of them are considered to be lymphoepithelioma-like cholangiocarcinoma. Histologically, lymphoepithelioma-like cholangiocarcinomas are composed of two components: an adenocarcinoma and a lymphoepithelioma-like carcinoma. To the best of my knowledge, only 16 cases of lymphoepithelioma-like cholangiocarcinoma have been reported in the medical literature [1–11], and 11 of these cases were related to Epstein-Barr virus (EBV) infection [1–3, 5–7, 9]. Here, a case of lymphoepithelioma-like cholangiocarcinoma that was not associated with EBV infection is presented.

Case Report

A 79-year-old man underwent abdominal computed tomography (CT) because of hepatitis B virus (HBV)-associated cirrhosis. The abdominal CT revealed a $3.7 \times 2.5 \times 2.5$ cm hypervascular mass near the dome of the left lateral lobe of the liver. Multiple enlarged lymph nodes were noted in the porta hepatis and retropancreatic areas. The serum HBV surface antigen was positive and the anti-hepatitis C virus (HCV) antibody was negative. The liver function tests were normal, and the serum tumor markers, including alpha-fetoprotein, carcinoembryonic antigen and CA 19-9, were within the reference ranges. The patient had type 2 diabetes. Left lateral segmentectomy for the liver mass was performed. Macroscopically, the tumor measured $3.5 \times 2.5 \times 2.5$ cm and was pale gray, well defined, non-encapsulated, rubbery and solid (fig. 1). The background liver showed macronodular cirrhosis. Histologically, the tumor was composed of two components: an adenocarcinoma that formed irregular small glands and a lymphoepithelioma-like carcinoma that exhibited sheets of undifferentiated epithelial cells with lymphoid stroma (fig. 2). Lymphoplasmacytic infiltrates were more predominant in the lymphoepithelioma-like carcinoma than in the adenocarcinoma. Significant desmoplasia was not observed even in the adenocarcinoma area. Both components were roughly divided, but they gradually merged. The nuclei of the tumor cells were similar in both components, and they were ovoid or pleomorphic with an irregular nuclear membrane, vesicular chromatin and occasional macronucleoli. The background liver showed cirrhotic nodules surrounded by fibrous bands and a considerable portal infiltration of lymphocytes. Immunohistochemically, the adenocarcinoma component was diffusely positive for AE1/AE3, cytokeratin (CK) 7, CK19 and epithelial membrane antigen (EMA), while the lymphoepithelioma-like carcinoma component was focally positive for AE1/AE3, EMA, CK7 and CK19 (fig. 3). Both components were diffusely positive for p53 protein, but they were negative for polyclonal carcinoembryonic antigen, HepPar1, alpha-fetoprotein, CK20, vimentin, c-kit and CD56. In situ hybridization using EBV-encoded RNA 1 was negative in both components. Based on the histological analysis of the resected liver mass, the patient was diagnosed with intrahepatic lymphoepithelioma-like cholangiocarcinoma. Examination of a resected para-aortic lymph node revealed metastasis exclusively of the lymphoepithelioma-like carcinoma component. The postoperative ^{18}F -FDG PET-CT demonstrated no evidence of extrahepatic tumors, including nasopharyngeal cancer. After the operation, a radiation therapy performed to ablate the enlarged lymph nodes in the porta hepatis and retropancreatic areas was successful.

Three years later, a follow-up abdominal CT revealed two well-defined heterogeneous low-attenuated nodular lesions that measured 5 cm and 2 cm in greatest dimension, respectively. A needle biopsy of the nodule was performed, and histologically, a well-differentiated hepatocellular carcinoma was diagnosed. The patient underwent chemoembolization for the hepatocellular carcinoma. He is currently alive, without recurrence of lymphoepithelioma-like cholangiocarcinoma 54 months after surgery.

Discussion

Lymphoepithelioma-like carcinoma is composed of undifferentiated epithelial cells with an intense lymphocytic infiltrate. Unlike carcinomas of other organ sites, the majority of lymphoepithelioma-like cholangiocarcinomas are composed of two different components – an adenocarcinoma and a lymphoepithelioma-like carcinoma. There is

only 1 reported case of the pure form of lymphoepithelioma-like carcinoma without well-formed tubules [4]. In the present case, the adenocarcinoma and lymphoepithelioma-like carcinoma components presented several identical characteristics; for example, both had a considerable amount of lymphocyte infiltrate without any conspicuous desmoplastic stroma, the nuclei of the adenocarcinoma and the lymphoepithelioma-like carcinoma resembled each other, and both components revealed diffuse immunoreactivity for p53 protein. However, immunohistochemically, some differences between the two components could be observed, e.g. contrary to the adenocarcinoma, the lymphoepithelioma-like carcinoma showed only focal positivity for epithelial markers such as AE1/AE3, EMA, CK7 and CK19. The histological and immunohistochemical findings in the present patient suggest that the adenocarcinoma component may have transformed to the lymphoepithelioma-like carcinoma.

Although the majority of reported lymphoepithelioma-like carcinomas of the liver were considered to be cholangiocarcinoma, to the best of my knowledge, 3 cases of lymphoepithelioma-like hepatocellular carcinoma have been reported [12–14]. In this patient, the presence of glandular structures showing diffuse positivity for bile duct markers, such as CK7 and CK19, and negativity for hepatocyte markers, such as alpha-fetoprotein and HepPar1, was considered to be an indicator for the diagnosis of cholangiocarcinoma.

The majority of lymphoepithelioma-like cholangiocarcinomas are associated with EBV infection. EBV infection is detected in both the adenocarcinoma and lymphoepithelioma-like carcinoma components [1]. Most of these lymphoepithelioma-like cholangiocarcinoma cases except for 2 [1, 3] were reported in the oriental countries, which are known as endemic areas of EBV infection. It has been suggested that EBV may play a role in the tumorigenesis of lymphoepithelioma-like cholangiocarcinoma. To the best of my knowledge, 7 of the 16 reported cases of lymphoepithelioma-like cholangiocarcinomas, including the present case, were negative for EBV [4, 8, 10, 11]. One of the 7 EBV-negative patients had HCV cirrhosis [4] and 4 cases, including the present case, had HBV cirrhosis [6, 10]. This finding suggests that HBV and HCV are also related with the pathogenesis of lymphoepithelioma-like cholangiocarcinoma. However, further collective studies are needed to confirm this hypothesis.

According to the literature, the lymphocytes within lymphoepithelioma-like carcinomas are known to be predominantly T cells [6, 8]. However, in the present case, the B and T cells infiltrated in nearly equal proportions and, interestingly, many plasma cells were mixed with them.

Jeng et al. [7] and Szekely [8] reported that the prognosis of lymphoepithelioma-like cholangiocarcinoma seems to be better than that of ordinary cholangiocarcinoma. However, there is limited information regarding the prognosis and treatment of lymphoepithelioma-like cholangiocarcinomas because of the only limited number of reported cases. The present case was associated with metastasis to a para-aortic lymph node at the time of operation. Postoperative radiation was given to the regional lymph nodes, and the patient is alive without recurrence of lymphoepithelioma-like cholangiocarcinoma 54 months after tumor removal, although a metachronous hepatocellular carcinoma developed recently.

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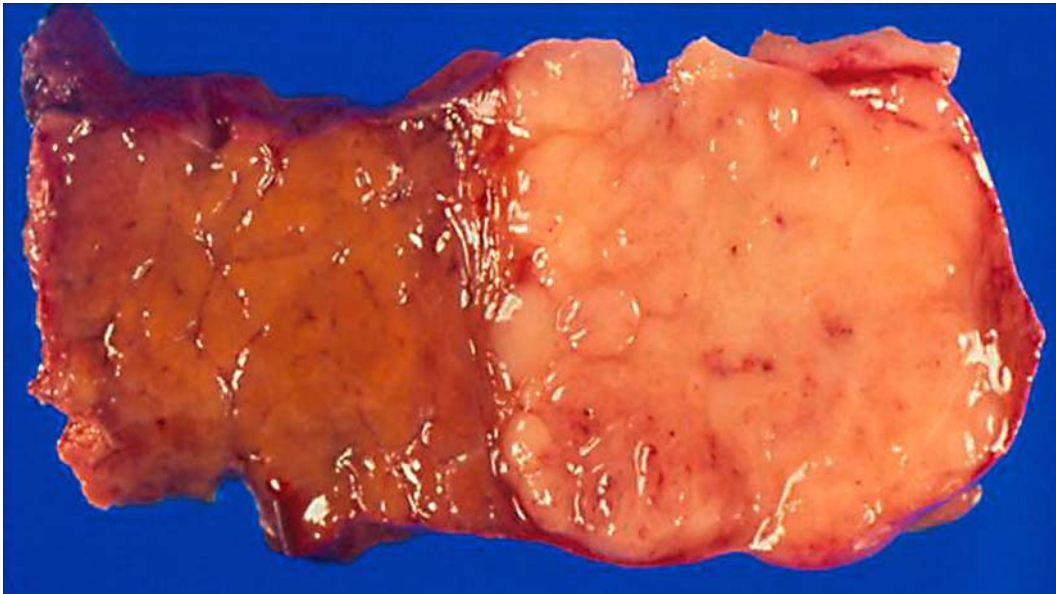


Fig. 1. Macroscopic photograph of the resected liver specimen. The sectioned surface shows a pale gray, well-defined, non-encapsulated, solid tumor with a background of cirrhosis.

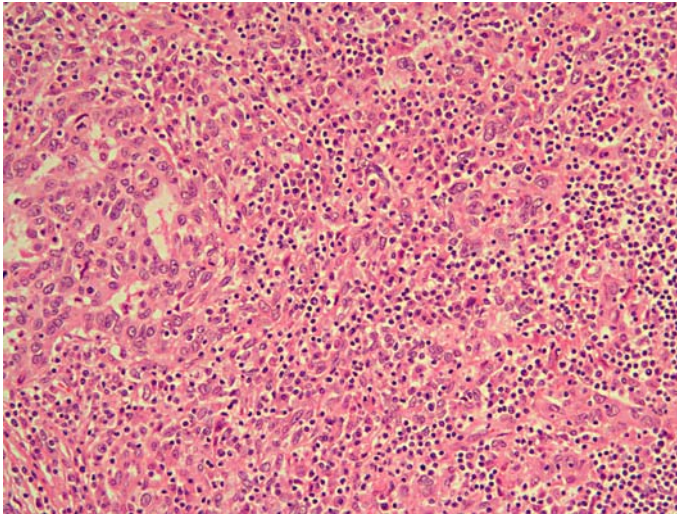


Fig. 2. Microscopic photograph of the tumor. The lymphoepithelioma-like cholangiocarcinoma is composed of a glandular component (left) and undifferentiated epithelial cells intimately admixed with abundant lymphoplasmic cells (right). HE, $\times 200$.

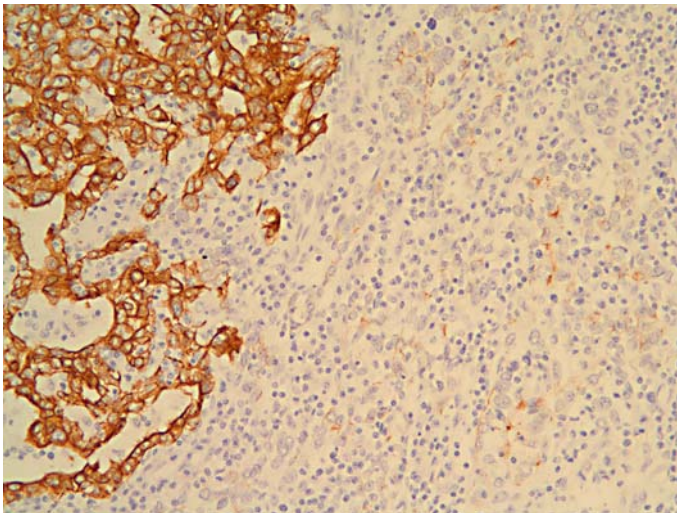


Fig. 3. Microscopic photograph of the immunohistochemistry. The adenocarcinoma component (left) is diffusely positive for CK19, while the lymphoepithelioma-like carcinoma component (right) is focally positive for CK19. Immunohistochemistry, $\times 200$.

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