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CASE REPORT

Lymphoepithelioma-like hepatocellular carcinoma: A case report and a review of the literature

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Abstract

Lymphoepithelioma is a particular form of undifferentiated carcinoma, characterized by a prominent lymphoid stroma, originally described in the nasopharynx. Lymphoid stroma-rich carcinomas arising in other organs have been termed lymphoepithelioma-like carcinoma (LELC). In the liver, primary LELCs are very rare, and the majority has been identified as cholangiocarcinomas. Here a rare case of lymphoepithelioma-like hepatocellular carcinoma (HCC) is described. A 47-year old woman presented with abdominal pain. Ultrasonography revealed a liver nodule, 2.2 cm in diameter, localized in the right lobe, adjacent to the gallbladder. Viral markers for hepatic B virus (HBV), hepatic C virus (HCV) and Epstein-Barr virus (EBV) were negative. The nodule was hypoechogenic. The patient underwent surgery, with resection of the nodule. Histology showed hepatocellular carcinoma, characterized by a prominent lymphoid infiltrate. At immunocytochemistry, tumor cells were reactive for Hep Par1 and glypican 3. Immunophenotyping of tumor infiltrating lymphocytes evidenced the predominance of CD8+ cytotoxic suppressor T cells. The postoperative clinical outcome was favorable and the patient was recurrence-free 15 mo after resection. This case, to the best of our knowledge, is the first reported non EBV and non cirrhosis-associated lymphoepithelioma-like hepatocellular carcinoma. The association between the lack of EBV infection, the absence of cirrhosis, a "cytotoxic profile" of the inflammatory infiltrate and a good prognosis could identify a variant of lymphoepithelioma-like HCC with a favorable clinical outcome.

Key words: Liver; Hepatocellular carcinoma; Tumor infiltrating lymphocytes; Primary liver tumors; Liver lymphoepithelioma

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INTRODUCTION

Lymphoepithelioma is a particular form of undifferentiated carcinoma, characterized by a prominent lymphoid stroma, primarily described in the 1920's by Regaud and Schminke in the head and neck region of Asian subjects[1]. Subsequently, histologically similar carcinomas have been described in other organs, such as salivary glands[2], lung[3], stomach[4], colon[5], thymus[6], uterus[7], bladder[8,9] and urinary tract[10]. Lymphoid stroma-rich carcinomas in these locations have been termed Lymphoepithelioma-like carcinoma (LELC). The similarities among these neoplasms arising in diverse sites are not limited to the histological picture, i.e. to the presence of a heavy lymphocytic intratumoral infiltrate. The majority of these tumors, particularly those originating from the nasopharynx[11], salivary glands[2], thymus[12], lung and stomach[13], show relevant pathogenetic similarities: a close etiopathogenetic linkage with Epstein-Barr virus (EBV) infection. At the immunohistochemical level, EBV expression in these tumors has been associated

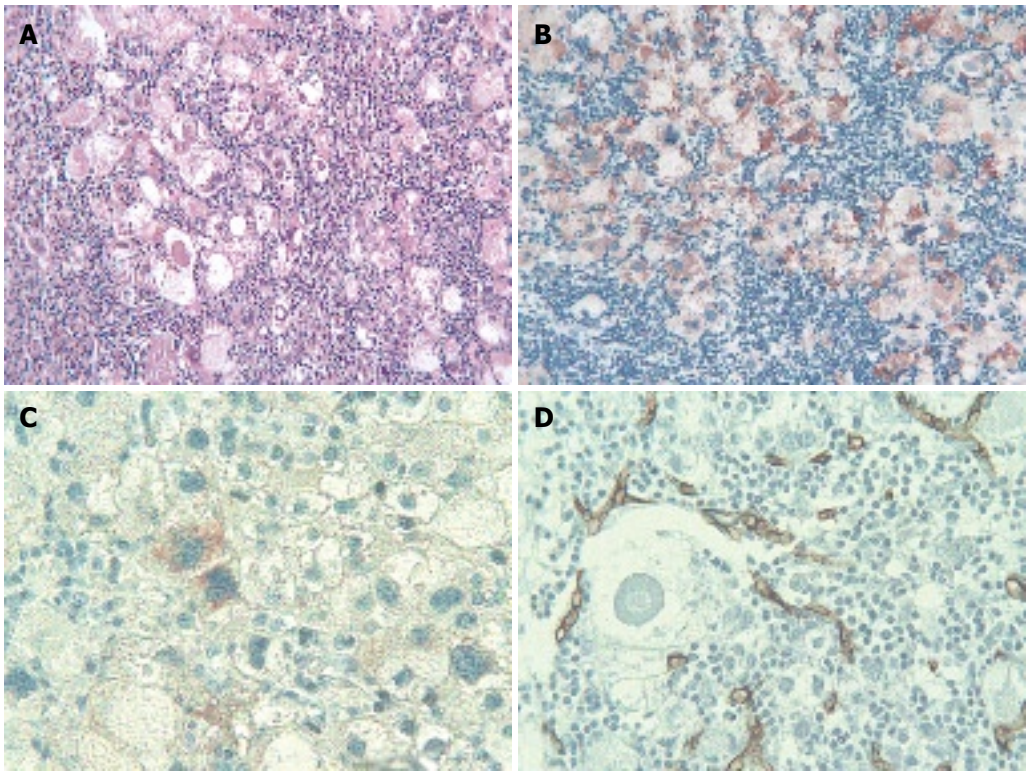

Figure 1 Histological picture characterized by a strong lymphoid intratumoral infiltrate (HE, x 250) (**A**), vast majority of neoplastic cells showing intense granular cytoplasmic reactivity for Hep Par 1 (x 250) (**B**), scattered atypical tumor cells showing cytoplasmic immunoreactivity for Glypican 3 (x 400) (**C**), and a large atypical tumor cell surrounded by CD34-positive newly formed capillaries (x 400) (**D**).

with p53 over expression in the nuclei of EBV-infected tumor cells[14] and hyperreactivity of tumor cells for bcl-2 and proliferating cell nuclear antigen (PCNA)[15].

Although it has been suggested by many authors that lymphoepithelioma-like carcinomas have a better prognosis than conventional carcinomas with a less marked lymphocytic infiltrate[10], given the few studies on the clinical course of lymphoepithelioma-like carcinomas in the literature to date, this topic needs further investigation.

In the liver, lymphoepithelioma-like primitive carcinomas are extremely rare. To the best of our knowledge, only nine cases of cholangiocarcinomas have been reported, and the majority was associated with EBV infection[16]. Here we report a rare case of hepatocellular carcinoma (HCC) characterized by a prominent lymphoid stroma, indistinguishable on morphological grounds from tumors called lymphoepithelioma-like carcinomas with a discussion on their histological, immunohistochemical and clinical findings.

CASE REPORT

A 47-year-old woman presented with acute abdominal pain, localized in the right liver lobe. Ultrasonography evidenced a hypoechogenic liver mass, 2.2 cm in diameter, adjacent to the gallbladder. At CT-scan, the nodule showed signs of a recent intranodular hemorrhage. Laboratory tests showed negativity for HBV (serum HBsAg, HbeAg, anti-HbcAg and HBV DNA), HCV, and EBV markers. Molecular analyses for detecting EBV DNA, performed in tumor samples by PCR and Southern blot hybridization, were negative. The patient underwent surgery, with resection of the liver nodule. Histological examination showed proliferation of atypical large cells, characterized by an eosinophilic cytoplasm, with large nuclei and prominent nucleoli. Epithelial cells were surrounded by a dense lymphoid stroma, extending inside the tumor (Figure 1A). At immunocytochemistry, tumor cells were diffusely Hep Par1-positive (Figure 1B) and focally immunoreactive for glypican 3 (Figure 1C). No reactivity for cytokeratins 7, 19 and 20 was observed. CD34 showed diffuse capillarization of intratumoral sinusoids (Figure 1D). The clinical outcome was favorable and the patient was recurrence-free after a 15-mo follow-up.

DISCUSSION

The case reported here is, to the best of our knowledge, the fourth reported case of Lymphoepithelioma-like HCC. The first case described in 2000 by Emile *et al* and defined as HCC with lymphoid stroma[17], was characterized by a good prognosis after liver transplant and negativity for EBV infection[18]. Subsequently, in a letter to the Journal, Szekely E. argued that the tumor was indistinguishable from LELC described in other organs, suggesting the final diagnosis of lymphoepithelioma-like HCC[19]. The second case of hepatocellular LELC, described in 2004 by Si MW and coworkers[20], showed some similarities and marked differences as compared with the first one. Both patients affected by end stage chronic liver disease underwent liver transplant. The patient described by Si was younger and infected with HCV and EBV, which was detected in tumor samples. The clinical course was precipitous, multiple recurrences appeared 3 mo after liver transplant and the patient expired within a few weeks. The third case of hepatocellular LELC was recently reported by Chen *et al*[21] in a 56-year old male patient with cirrhosis related

to HCV infection and negative EBV markers. The case reported here shows some peculiarities as compared with the previous 3 cases. It is the first case of hepatocellular LELC arising in a non cirrhotic liver. Moreover, the risk factor for Lymphoepithelioma-like HCC in our case was unknown since EBV, HBV and HCV markers were negative. The absence of EBV infection was associated with a favorable clinical outcome, as in two previously reported cases of EBV-negative lymphoepithelioma-like HCC[17,21], contrasting with the aggressive course of one case of EBV-positive hepatocellular LELC[20]. These data show that, even in LELCs arising in the liver, and in spite of a striking similarity of the histological picture of all tumors, the clinical aggressivity of HCC in a single case may be extremely variable. In our case, we observed the predominance of CD8+ cytotoxic T cells, in the inflammatory intratumoral infiltrate, suggestive of an effective immune response to the tumor[22].

Finally, this case is the first case of non EBV and non cirrhosis-associated lymphoepithelioma-like HCC. The association between the lack of EBV infection, the absence of cirrhosis, a CD8+/cytotoxic profile of the inflammatory infiltrate and a good prognosis could identify a variant of lymphoepithelioma-like HCC with a favorable clinical course.

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