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A Case of Well-differentiated Hepatocellular Carcinoma Arising in Primary Biliary Cirrhosis

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Primary biliary cirrhosis (PBC) is a chronic progressive, autoimmune liver disease that increases the risk of hepatobiliary malignancies at a late stage. We report a 66-year-old woman with PBC combined with hepatocellular carcinoma (HCC) accompanied by hypoglycemia. Two large tumors were detected on admission and the patient died because of tumor rupture and subsequent liver failure. Histological analysis revealed well-differentiated HCC in both of the tumors. Sometimes the patient had suffered from hypoglycemic attacks of unknown origin, but serum immunoreactive insulin (IRI) was within the normal range. It was interesting that such large well-differentiated hepatocellular carcinomas were generated in PBC.
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Hepatocellular carcinoma (HCC) is the most common hepatobiliary malignancy that occurs mostly in the liver containing hepatitis virus (1,2). Primary biliary cirrhosis (PBC) is a chronic autoimmune liver disease (3), and several reports have shown that it can be a risk factor in hepatobiliary malignancies (4). We report a case of PBC with two large tumors both of which were well-differentiated carcinomas.

The patient also demonstrated hypoglycemic attacks of unknown origin. HCC is sometimes complicated with paraneoplastic syndromes (5), and some reports have shown that insulin-like growth factor-II (IGF-II) production in cancer cells causes hypoglycemia (6,7). We investigated the involvement of IGF-II in the cancer cells of our case.

CASE REPORT

A 66-year-old woman was admitted to our hospital on March 31, 2001 because she was detected a large space occupying lesions in the liver and severe esophageal varices. At the age of 40 she was pointed out liver dysfunction, but she got no treatment. At the age of 52 she was diagnosed with PBC based on elevated serum hepatobiliary enzyme and positive antimitochondrial antibody (AMA). She was followed up with conservative therapy with ursodeoxycholic acid (UDCA) (600mg/day) without regular imaging studies. She had no history of diabetes mellitus or blood transfusion.

Upon admission physical examinations revealed anemia and icterus in her eyes and edema in her legs. Laboratory examinations showed pancytopenia; WBC 2,700/mm^3, Hb 10.5g/dl, PLT $8.4x10^4/mm^3$, elevated hepatobiliary enzymes; asparate aminotransferase (AST) 120IU/l, alanine aminotransferase (ALT) 61IU/l, alkaline phosphatase 983IU/l, γ-glutamyl

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transpeptidase 107IU/l, total bilirubin 3.2mg/dl, and low albumin (2.4g/dl) and cholinesterase (2.0IU/ml) levels. Serum HBs-Ag and anti-HCV were negative. Tumor markers were elevated: α-fetoprotein (AFP) 1722ng/ml and protein induced by vitamin K antagonist-II (PIVKA-II) 1610mAU/ml. AMA was positive (x640) and immunoglobulin (IgM 324mg/dl) was elevated. Abdominal computed tomography (CT) showed two large nodules in both lobes (Fig.1a). On day 25 after admission, abruptly falling blood pressure, progressing anemia and increased ascites indicated rupture of liver tumor. Transarterial angiography was carried out on day 27, and only numerous tumor vessels were detected and embolization was carried out to the mass in the right lobe (Fig.1b). Although signs of bleeding stopped, liver failure progressed thereafter and the patient died on day 84. Autopsy disclosed two large masses in the right (56x58mm) and left (62x50mm) lobes accompanied by small satellite nodules in the 750-gram atrophic liver (Fig.2a). The mass in the right lobe was almost necrotic because of transarterial embolization (TAE) and massive bleeding. On the other hand, the tumor in the left lobe was the viable massive type tumor expanding with bleeding and necrosis, and partially green areas indicative of bile production were observed. Histologically almost the same well-differentiated hepatocellular carcinoma was detected in both of the tumors (Fig.2b). Surrounding liver tissue was classified as of stage IV of PBC (8).

Fig.1.
(a) Abdominal CT showing two large nodules. The tumor was partially enhanced, but most of the lesions were not, even at a late phase, suggesting necrosis.
(b) Transarterial angiography showing numerous tumor vessels.

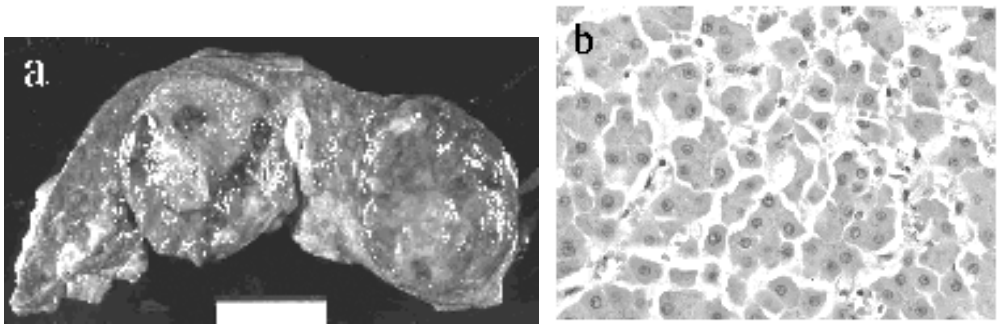

Fig.2.
(a) Autopsy specimen. Two large tumors were detected in the cirrhotic liver. The tumor was composed of dark red lesions suggesting bleeding, and viable green lesions suggesting bile production.
(b) Histological findings. The tumor was well-differentiated carcinoma. (H&E stain, x400)

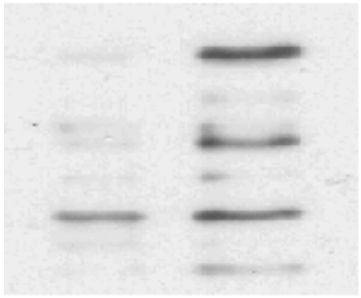

Fig.3. Western blot analysis. In the right lane positive control showing 7.5kDa (normal type) and 14kDa (abnormal type) IGF-II protein bands. A 14kDa high molecular protein band was not detected.

From days 46 to 50 the patient had sometimes suffered loss of consciousness because of hypoglycemia without any symptoms before the attacks. Her plasma glucose was about 20 to 50 mg/dl and symptoms improved after the injection of glucose. Her sera contained a low concentration of immunoreactive insulin (8 μU/ml) and insulin-like growth factor (IGF)-I (11 ng/ml), whereas the IGF-II level was normal (312 ng/ml). Immunohistochemical and Western blot analyses did not show IGF-II in cancer cells (Fig.3).

DISCUSSION

PBC, a chronic autoimmune cholestatic disease, is sometimes associated with other autoimmune diseases. In complications associated with malignant neoplasms, the risk of extrahepatic malignancies is not high (9). Previous reports have described HCC as a rare complication of PBC (10,11). Recent reports have, however, described that it is not rare in PBC patients without viral hepatitis (4,12). Especially, patients at late stages of PBC are at a higher risk of HCC, and the incidence is almost similar to that in hepatitis C virus related cirrhosis (13). Moreover, HCV superinfection in patients with PBC plays a crucial role in the development of HCC (14,15). Several other cases of HCC in PBC have also been reported (14,16).

Poorly differentiated component becomes predominant according to tumor growth because HCC progression is accompanied with dedifferentiation of the primary lesion. Interestingly, the cancer in our case was well-differentiated carcinoma in spite of the large size. It is supposed that poorer-differentiated lesions may lead to necrosis due to the tumor progresses and bleeding. But the carcinogenesis from PBC might be different from that from viral associated cirrhosis. Indeed, large well-differentiated HCCs associated with PBC has been described (6,17). The incidence of well-differenciated HCC is still unclear, and it is possible that the incidence of HCC from PBC is higher than that from virus associated cirrhosis.

Hypoglycemia is a complication in approximately 3% of HCC cases because of malnutrition and a decrease of gluconeogenesis in the liver (5). Hypoglycemia associated with HCC has been controlled by treating the HCC (18). IGF-II produced by cancer cells is associated with hypoglycemia; especially, high molecular weight IGF-II (14kDa) is crucial in the inception of hypoglycemia (6,7,19). Even if the level of serum IGF-II is within a normal range, cancer cells may produce high molecular weight IGF-II and induce hypoglycemia (6). In this case, we investigated the level of this factor in cancer cells by Western blotting. High molecular weight IGF-II was not detected, indicating that hypoglycemia in HCC is not always associated with this growth factor.

The carcinogenesis of HCC was associated with hepatitis virus itself (20, 21). The mechanism of the progression of HCC in PBC is expected to be different from that of other

hepatitis viral diseases. Further studies and histological analyses are needed on a larger number of cases to elucidate the mechanism.

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