Abstract

A 23-year-old man was admitted to our department due to hemorrhage from gastric varices. He had been diagnosed as having Wilson’s disease at the age of 17. Abdominal ultrasonography and computed tomography (CT) showed portal thrombosis and a large mass occupying most of the right lobe in the liver. The tumor was diagnosed as hepatocellular carcinoma (HCC) by image views and tumor markers. He died 3 months after the diagnosis, and an autopsy was performed. Histologic examination of the tumor showed moderately to poorly differentiated HCC. The nontumorous lesion of the liver revealed cirrhosis. HBX-DNA sequence was not detected in the liver. Hepatic cirrhosis is a well-recognized complication of Wilson’s disease, but HCC is extremely rare. We describe the clinical findings of this patient and discuss the relationship of the development of HCC with a review of the relevant literature.

Introduction

Hepatocellular carcinoma (HCC) is rarely associated with Wilson’s disease. Only 11 cases of Wilson’s disease complicated by HCC have been reported (1–11). It has been suggested that a protective effect of hepatic copper against oncogenesis may account for the infrequent development of HCC in this disease. On the other hand, based on reports in the literature, it appears that men with long-standing Wilson’s disease treated with penicillamine have the highest risk of developing HCC. We present here a male patient with HCC associated with Wilson’s disease after 6 years of penicillamine therapy.

Case report

A 23-year-old man was admitted to our department on July 22, 1998 because of hemorrhage from gastric varices. He had been diagnosed as having Wilson’s disease at the age of 17 on the basis of histologic findings indicating liver cirrhosis, a low serum ceruloplasmin level and the presence of Kayser-Fleischer rings in his eyes on slit-lamp examination. He had been treated with a low copper diet and D-penicillamine 400 mg/day for 6 years. He had no history of blood transfusion or drug allergy and had no alcoholic habit or family history of liver disease. Physical examination showed anemia and enlargement of the liver extending 3 cm below the right costal margin, but no jaundice, leg edema or neurological abnormality.

The results of laboratory examination were as follows: hemoglobin, 9.6 g/dl; WBC, 11,000/μl; PLT, 19.2 K/μl; AST, 56 IU/l; ALT, 38 IU/l; ALP, 295 IU/l (normal, 125–335 IU/l); GGT, 130 IU/l (normal, 7–55 IU/l); total bilirubin, 2.7 mg/dl; ferritin 140 ng/ml (normal 27–320 ng/ml), serum copper, 42 μg/dl (normal, 90–130 μg/dl); ceruloplasmin, 10.6 mg/dl (normal, 25–45 mg/dl); urinary copper excretion, 615 μg/l (normal, 14–63 μg/l). Hepatitis B surface (HBs) antigen, HBe antigen and HBe antibody were negative, but HBs antibody and HB core (HBC) antibody were positive. HBC antibody was negative at 1:200 serum dilution. Serological tests for hepatitis A and C (HCV) were negative. Serum HCV antibody and HCV-RNA were negative. Antimitochondrial and antinuclear antibodies were negative. Alpha-fetoprotein was
235,720 ng/ml (normal, 0–8.5 mg/dl) and PIVKA-II was 33 mAU/ml (normal, <40 mAU/ml).

Because endoscopic examination revealed ruptured gastric fundal varices, endoscopic injection sclerotherapy (EIS) was performed. After the sclerotherapy, there was no recurrence of the varices or evidence of bleeding.

Abdominal ultrasonography and computed tomography (CT) showed portal thrombosis and a large mass occupying most of the right lobe in the liver (Fig. 1A and B). The tumor was diagnosed as HCC by image views and tumor markers.

His condition was too severe to undergo chemotherapy. Therefore, he received therapy of management for whole body, mainly control of ascites or hepatic encephalopathy, after EIS. He died 3 months after the diagnosis, and an autopsy was performed.

On autopsy, the liver weighed 1,623 g, and massive ascites (6,700 ml) was observed. A 14×12×10 cm in size, confluent and necrotic carcinoma was seen in the right lobe (Fig. 2), accompanied by many small satellite nodules directly invading the right diaphragm and portal tract, resulting in tumor emboli extending from the portal vein to superior mesenteric and splenic veins. Histologic examination of the tumor showed moderately to poorly differentiated HCC (Fig. 3A). The nontumorous lesion of the liver revealed cirrhosis showing macronodular pseudo-lobules throughout the liver (Fig. 3B). Several metastases of HCC, up to 2 cm in diameter, were found in both lungs. The related findings included pleural effusion, splenomegaly and esophagogastric varices with ulcer formation caused by endoscopic variceal sclerotherapy. Positive staining of copper in hepatocytes was seen in the nontumorous region, but not in HCC. Immunohistochemical assay for HBsAg or HBCAg was negative in the liver.

The polymerase chain reaction (PCR) analysis for hepatitis B virus X (HBX)-DNA in the liver was performed according to the methods described elsewhere (12). As shown in Fig. 4, HBX-DNA sequence was not detected in the tumor or nontumorous lesion. We cannot conclude completely however that there had not been occult HBV in this patient’s liver because the sensitivity of the PCR system was unclear.

**Discussion**

Hepatic cirrhosis is a well-recognized complication of Wilson’s disease, but HCC is extremely rare. It is assumed that hepatic copper has a protective effect against malignant transformation (7, 13). In animal models, copper treatment was shown to have an inhibitory effect on the induction of liver neoplasms (14, 15). To date, only 11 cases of HCC
associated with Wilson’s disease have been reported in the literature (1–11).

Recently, Walshe et al reviewed the case records of about 363 patients of Wilson’s disease seen at multi-centers and reported that abdominal malignancy developed in 9 patients of 159 patients (5.7%), who were followed-up for more than 10 years. There were only 2 HCC cases among the 159 patients (1.2%) (16). As shown in Table 1, 8 of 11 cases occurred in males aged 14 to 61 years. All their livers showed cirrhosis as was seen in the present case. The duration of treatment with D-penicillamine varied from 1 week to 33 years.

Cheng et al suggested that men with long-standing Wilson’s disease treated with D-penicillamine have the highest risk of developing HCC, because of a decrease in copper content in the liver (11).

On the other hand, Polio et al reported that the liver copper level was increased in 4 of 7 HCC patients with Wilson’s disease (10). Thus, the protective effect of hepatic copper may not be absolute; HCC occurred in cases of Wilson’s disease not treated with penicillamine and in cholestatic syndromes, in which the hepatic copper level would be expected to be increased. In short, the role of the liver in the pathogenesis of HCC in Wilson’s disease is still unclear.

In addition, it has been shown that copper is required as a cofactor for many key mediators of angiogenesis, such as basic fibroblast growth factor (FGF) matrix metalloproteinase, and angiogenin (17–20). Several clinical trials have been carried out in recent years to evaluate the antiangiogenic effects of copper chelators on solid tumors. D-penicillamine suppressed the growth of brain tumors in a rat model by inhibiting angiogenesis (21). Recently, the copper chelator trientine dihydrochloride, which has a lower incidence of side effects than D-penicillamine, showed an antiangiogenic effect on HCC (22).

This patient had been infected with HBV before, as was indicated by anti-HBc Ab positivity. HBV can cause HCC by transient infection, even if the patient does not know of a previous infection. It has been shown that HBV-DNA may be inserted into cellular DNA at an earlier stage, and that the X gene or a truncated preS/S gene in HBV-DNA can initiate tumorigenesis. Thus, the previous HBV infection might have been responsible for the development of HCC in this case. However, HBX-DNA was not detected in the liver. Since the reported cases all showed liver cirrhosis, the development of HCC may not be related to HBV infection. In fact, there were no HBs antigen-positive cases in the reported cases.
Hepatocellular Carcinoma Associated with Wilson’s Disease

Table 1. Clinical Data for Patients with Wilson’s Disease Complicated by Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Age</th>
<th>Duration of clinical dis. (yr)</th>
<th>Duration of penicillamine therapy (yr)</th>
<th>Therapy for HCC</th>
<th>Outcome</th>
<th>HBsAg</th>
<th>HBsAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Lygren (1959) (1)</td>
<td>M</td>
<td>14</td>
<td>1.5</td>
<td>0</td>
<td>–</td>
<td>Died</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2 Girard (1968) (2)</td>
<td>M</td>
<td>41</td>
<td>22</td>
<td>5</td>
<td>–</td>
<td>Died</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3 Kamakura (1975) (3)</td>
<td>M</td>
<td>32</td>
<td>6</td>
<td>1.5</td>
<td>–</td>
<td>Died</td>
<td>Negative</td>
<td>NA</td>
</tr>
<tr>
<td>5 Buffet (1984) (5)</td>
<td>M</td>
<td>57</td>
<td>12</td>
<td>12</td>
<td>–</td>
<td>Died</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>7 Guan (1983) (7)</td>
<td>F</td>
<td>27</td>
<td>6</td>
<td>0.02</td>
<td>NA</td>
<td>Died</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>8 Madden (1985) (8)</td>
<td>M</td>
<td>61</td>
<td>26</td>
<td>3.5</td>
<td>Chemotherapy</td>
<td>Chemotherapy</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>9 Imhof (1985) (9)</td>
<td>M</td>
<td>40</td>
<td>22</td>
<td>NA</td>
<td>Chemotherapy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>10 Polio (1989) (10)</td>
<td>M</td>
<td>33</td>
<td>1.25</td>
<td>1.2</td>
<td>–</td>
<td>Died</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>12 Present case</td>
<td>M</td>
<td>23</td>
<td>6</td>
<td>6</td>
<td>–</td>
<td>Died</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

NA: not available.

HCC in this case was already in an advanced stage, when it was found. After the diagnosis of Wilson’ disease, proper screening for HCC was not performed, because little was known of HCC associated with Wilson’s disease, and the patient was young. Of the 11 patients in the literature, 9 were younger than 40 years old. Cirrhotic patients with Wilson’s disease should be examined frequently regardless of age to find HCC in an early stage.

References