Abstract

A 45-year-old man was admitted to our hospital because of chronic hepatitis C and a large liver tumor accompanied by increased serum levels of alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), the tumor markers for hepatocellular carcinoma. Endoscopic examination revealed advanced gastric cancer. Biopsy specimens of the stomach and liver showed gastric adenocarcinoma and its metastasis to the liver. Immunohistochemical studies demonstrated that adenocarcinoma cells both of the stomach and liver, were positive for the antibodies against AFP as well as DCP. Expression of AFP mRNA was shown in the cancer cells of the stomach. Accordingly, we diagnosed this patient with AFP- and DCP-producing adenocarcinoma of the stomach together with liver metastasis.

Case Report

A 45-year-old man was admitted to our hospital because of abdominal distension. He had no history of transfusion or alcohol abuse. On physical examination, the elastic and firm liver was palpable 10 cm below the right costal margin.

The laboratory data were as follows: serum levels of transaminase and biliary enzymes were moderately increased, whereas that of lactate dehydrogenase (LDH) was extremely high. The serum level of bilirubin was normal. Hepatitis C virus (HCV) antibody and HCV-RNA were both positive and hepatitis B virus surface (HBs) antigen was negative. As for tumor markers, serum AFP and DCP levels were both extremely high at 13,827 ng/ml and 405 mAU/ml, respectively, whereas serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were normal (Table 1).

An abdominal ultrasound and computed tomography (CT) scan showed numerous nodules throughout the liver (Fig. 1).
Endoscopic examination of the stomach revealed the simultaneous presence of Borrmann II type advanced cancer at the greater curvature to the posterior wall of the antrum, and IIc type early cancer at the angle and lesser curvature of the antrum (Fig. 2).

Gastric biopsy demonstrated moderately differentiated adenocarcinoma. To differentiate metastatic lesions of gastric cancer to the liver from gastric cancer complicated with HCC, we performed needle liver biopsy. The tumorous liver also showed moderately differentiated adenocarcinoma, as was seen in the gastric lesion (Fig. 3). The adjacent region showed a moderate fibrosis and infiltration of lymphocytes, suggesting a state of chronic hepatitis. Accordingly, we diagnosed the patient with adenocarcinoma of the stomach with metastasis to the liver.

To study the origin of elevated serum levels of AFP and DCP, we performed immunohistochemical analysis using an anti-alpha-1-fetoprotein polyclonal antibody (Dako Cytomation A/S, Copenhagen, Denmark) for AFP and a MU-3 monoclonal antibody (Eisai, Tokyo, Japan) for DCP. Immunoreaction for both AFP and DCP was significantly demonstrated in both the gastric cancer and in the metastatic lesion of the liver, suggesting AFP- and DCP-producing gastric cancer and its metastasis to the liver (Fig. 4).

Furthermore, we examined the expression of AFP mRNA in the gastric cancer, and compared it to that in the non-tumorous gastric lesion by reverse transcriptional polyn-
Figure 3. Both gastric biopsy (A) and liver biopsy (B) demonstrated moderately differentiated adenocarcinoma (HE stain, ×40).

Figure 4. Immunoreaction for both AFP (A, C) and DCP (B, D) was significantly demonstrated in primary gastric lesion and metastatic lesion of the liver. A and B; gastric lesion, C and D; metastatic lesion of the liver (×160).
AFP- and DCP-producing Gastric Cancer

Figure 5. Electrophoresis after reverse transcriptional polymerase chain reaction (RT-PCR) revealed a transcript of AFP gene in the gastric cancer (lane 1), while AFP-mRNA was not expressed in the non-tumorous gastric lesion (lane 2). Lane 3: HepG2 (positive control), M: marker.

AFP is a glycoprotein whose molecular weight is 65 to 70 kD, and it has been recognized as being a useful marker in the diagnosis of HCC. DCP, another tumor marker for HCC, is a prothrombin precursor and is elevated in serum in vitamin K-deficient conditions, such as obstructive jaundice or medication with warfarin. In HCC, the specificity of serum level of DCP is superior to that of AFP (10).

Because the mechanism behind the production of these tumor markers in cancer cells excluding HCC cells has not been elucidated, we attempted to clarify the expression of AFP at the transcriptional level. We, therefore, speculate that genetic abnormality associated with the transcription of AFP occurs in AFP-producing gastric cancer.

 Particularly in this case where the patient had chronic hepatitis C, the distinction between metastatic lesions of gastric cancer, and double cancer comprising gastric cancer and HCC, was critically important. In many cases of HCC, the percentage of the fraction of lens culinaris agglutinin-reactive AFP (AFP-L3) is increased at more than 15%. In the present case, AFP analysis showed a broadband pattern of AFP, different from the typical pattern of HCC.

A Medline search of the literature found eight reported cases with DCP-producing gastric cancer (5–7, 11–15) (Table 2). All eight reported cases had high serum levels of AFP. Moreover, all cases showed advanced gastric cancer and they were accompanied by liver metastasis, except for the first case reported by Kudo et al (5). Histologically, poor differentiation is generally thought to be a feature of either AFP- or AFP- plus DCP- producing gastric cancer. Moreover, hepatoid, fetal intestinal, and yolk sac-like types have also been reported (16, 17). However, the present case showed moderately differentiated adenocarcinoma without hepatoid cells, leading to the speculation that gene injury in only a small area, including some of the regions associated with AFP and DCP production, may have occurred.

AFP-producing gastric cancer has often been reported, however, gastric cancer, which produces both AFP and DCP is very rare. Even in HCC, the level of AFP and DCP do not always rise and fall together. Accordingly, one can assume that there must also be gastric cancer, which produces DCP,

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/Sex</th>
<th>Macroscopic type</th>
<th>Histological type</th>
<th>Hepatoid cell</th>
<th>Liver metastasis</th>
<th>AFP (ng/ml)</th>
<th>DCP (AU/ml)</th>
<th>Survival</th>
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<tbody>
<tr>
<td>5</td>
<td>56/M</td>
<td>Iic</td>
<td>PD and WD adenocarcinoma</td>
<td>+</td>
<td>–</td>
<td>2,810</td>
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<td>11</td>
<td>43/M</td>
<td>Borrmann III</td>
<td>PD adenocarcinoma</td>
<td>–</td>
<td>+</td>
<td>483,380</td>
<td>134</td>
<td>78 days</td>
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<td>12</td>
<td>42/F</td>
<td>Borrmann III</td>
<td>PD adenocarcinoma</td>
<td>–</td>
<td>+</td>
<td>190</td>
<td>2.9</td>
<td>102 days</td>
</tr>
<tr>
<td>6</td>
<td>63/M</td>
<td>Borrmann I and Iic</td>
<td>PD and MD adenocarcinoma</td>
<td>+</td>
<td>+</td>
<td>120,000</td>
<td>&gt;8.0</td>
<td>45 days</td>
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<tr>
<td>7</td>
<td>55/M</td>
<td>Borrmann I and Iic</td>
<td>PD and MD adenocarcinoma</td>
<td>–</td>
<td>+</td>
<td>247,000</td>
<td>320</td>
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<td>13</td>
<td>71/M</td>
<td>Borrmann III</td>
<td>MD adenocarcinoma</td>
<td>–</td>
<td>portal thrombus</td>
<td>18,552</td>
<td>1.08</td>
<td>5 months</td>
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<tr>
<td>14</td>
<td>49/M</td>
<td>Borrmann II</td>
<td>MD adenocarcinoma</td>
<td>+</td>
<td>+</td>
<td>215,553</td>
<td>3.7</td>
<td>5 months</td>
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<tr>
<td>15</td>
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<td>–</td>
<td>+</td>
<td>490,200</td>
<td>2.28</td>
<td>42 days</td>
</tr>
<tr>
<td>present</td>
<td>45/M</td>
<td>Borrmann II and Iic</td>
<td>MD adenocarcinoma</td>
<td>–</td>
<td>+</td>
<td>13,827</td>
<td>0.41</td>
<td>6 months</td>
</tr>
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</table>

but not AFP.

The prognosis of AFP-producing gastric cancer has been reported to be very poor. The cancer cells have a high level of malignant potential and the cancer progresses rapidly. In addition, most of these cases are accompanied by metastasis and show resistance to anti-cancer drugs. Recently, TS-1, a novel oral derivative of 5-fluorouracil, was developed, and its effectiveness against advanced gastric cancer was reportedly seen in approximately 45% of the patients (18–20). Its effect against some cases of AFP-producing gastric cancer has also been reported (21, 22), however, further investigations are called for.

The present patient showed resistance against several anti-cancer drugs. Although we attempted treatment with TS-1, even this novel drug did not show any obvious effect on the clinical course of this AFP- and DCP-producing gastric cancer which had metastasized to the liver.

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References