Small Cell Carcinoma of the Extrahepatic Bile Duct Diagnosed with EUS-FNA and Effectively Treated with Chemoradiation

Norikazu Arakura¹, Takashi Muraki¹, Kenichi Komatsu¹, Yayoi Ozaki¹, Hideaki Hamano¹, Eiji Tanaka¹ and Shigeyuki Kawa²

Abstract

Small cell carcinoma of the bile duct system is extremely rare, and surgical procedures have been complicated by early hematogenous dissemination. In this study, we report a patient with small cell carcinoma of the bile duct system presenting with jaundice. The diagnosis was made early by endoscopic ultrasonography-guided fine needle aspiration biopsy (EUS-FNA). We performed radiation therapy of a total of 30 Gy, resulting in a marked decrease of serum neuron specific enolase levels and amelioration of jaundice, which had been resistant to drainage procedures. The patient was then treated with combined chemotherapy of cisplatin and CPT-11, which resulted in the disappearance of the tumor mass by image tests.

Key words: small cell carcinoma of bile duct, EUS-FNA, chemotherapy, radiation

(Inter Med 47: 621-625, 2008) (DOI: 10.2169/internalmedicine.47.0663)

Introduction

Small cell carcinoma of the bile duct system is extremely rare, and surgical procedures have been complicated by early hematogeneous dissemination. For effective therapeutic modalities, it is better to apply radiation and chemotherapy; however, most patients have been treated with surgical procedures based on tentative diagnoses of ordinary bile duct cancer. Here, we report a patient with small cell carcinoma of the bile duct system that was diagnosed early by endoscopic ultrasonography-guided fine needle aspiration biopsy and effectively treated with radiation and chemotherapy.

Case Report

A 75-year-old man was admitted to our hospital because of anorexia and jaundice. Blood tests showed liver dysfunction suggestive of obstructive jaundice, normal levels of CEA and elevated levels of CA19-9,682 U/ml (normal<37 U/ml) (Table 1). Computed tomography (CT) and magnetic resonance imaging (MRI) revealed a tumor mass completely surrounding the wall from the lower to the hilar bile ducts (Fig. 1 and Fig. 2). Endoscopic retrograde cholangiopancreatography (ERCP) showed a smooth narrowing of the corresponding bile duct region but a normal pancreateogram (Fig. 3). A biopsy specimen obtained through the papilla of Vater disclosed no tumor tissue. Endoscopic ultrasonography (EUS) showed a tumor mass of 6.5 × 4.5 cm around the narrowed bile ducts. EUS-FNA was performed to get a histological diagnosis. Convex linear-array echoendoscopy (GF-UCT240; Olympus Optical Co., Ltd., Tokyo, Japan) from the duodenal bulb clearly displayed the biliary tumor and tube stent in the bile duct and the needle knife [22-gauge needle (NA10J-1; Olympus)] inserted into the biliary tumor. The biopsy specimen showed a nest of round to spindle-shaped small tumor cells with hyperchromatic chromatin, sparse cytoplasm and dysplasia, which were immunoreactive for synaptophysin and chromogranin A (Fig. 4), suggesting the diagnosis of small cell carcinoma. Reevaluation of the blood test revealed an elevated level of NSE, 33 ng/ml (normal<10 ng/ml) (Table 1). We found no other lesions includ-
Table 1.  Laboratory Data

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>T.Bil</th>
<th>16.5 mg/dl</th>
<th>Serological examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro (-)</td>
<td>D.Bil</td>
<td>11.1mg/dl</td>
<td>CRP 0.38mg/dl</td>
</tr>
<tr>
<td>Glu (-)</td>
<td>AST</td>
<td>81 IU/l</td>
<td>ANA (-)</td>
</tr>
<tr>
<td>OB (-)</td>
<td>ALT</td>
<td>148 IU/l</td>
<td>IgG 1869 mg/dl</td>
</tr>
<tr>
<td>Bil (3+)</td>
<td>ALP</td>
<td>597 IU/l</td>
<td>IgG4 117 mg/dl</td>
</tr>
<tr>
<td></td>
<td>γ-GTP</td>
<td>263 U/l</td>
<td>β 2MG 1.9 mg/l</td>
</tr>
</tbody>
</table>

Hematology

| WBC 4390 /mm³ | Amy 73 U/l | LDH 222 U/l | CEA 1.9 ng/ml |
| RBC 477×10⁶/mm³ | BUN 20 mg/dl | CA19-9 682 U/ml |
| Hb 15.2 g/dl | Cr 0.85 mg/dl | NSE 33 ng/ml |
| Ht 43.7% | Na 136 mEq/l | pro-GRP 17.8 pg/ml |
| Plt 22.5×10⁹/mm³ | K 4.3 mEq/l | HBs Ag (-) |
|            | Cl 100 mEq/l | HCV Ab (-) |

Blood chemistry

Ca 9.2 mg/dl
TP 7.9 g/dl
FPG 132 mg/dl
Alb 4.2 g/dl
HbA1c 5.2%

Figure 1.  Abdominal CT scan on admission. The arrowheads indicate a tumor in the pancreatic head.

Figure 2.  Abdominal MRI on admission. The arrowheads indicate a tumor throughout the region from the lower bile ducts to the hilar bile ducts.

Figure 3.  ERCP showed smooth narrowing of the bile ducts from the lower bile ducts to hilar bile ducts.

ing pulmonary small cell carcinoma, so the patient was diagnosed with small cell carcinoma of the bile duct. Because of severe obstructive jaundice that was resistant to drainage procedures, the patient developed intolerance to chemotherapy. Alternatively, we performed radiation therapy totaling
Figure 4. (A) EUS-FNA cytology specimen showed a nest of small tumor cells with abundant chromatin, high N/C ratio and dysplasia (Hematoxylin and Eosin staining, original magnification x40) Immunostaining for (B) synaptophysin and (C) chromogranin A.

Figure 5. Abdominal CT image at end of treatment. Splenic vein slice identical to that in Figure 1 showed complete disappearance of the tumor.

30 Gy, resulting in a marked decrease of serum levels of NSE and amelioration of jaundice which was resistant to drainage procedures. Then, the patient was treated with combined chemotherapy of cisplatin and CPT-11, which resulted in the disappearance of the tumor mass by image tests (Fig. 5). After therapy, his condition was markedly improved and he was treated at an outpatient clinic. However, he died of disseminated lesions 10 months after therapy, and autopsy disclosed metastatic tumors in pleura, peritoneum and systemic lymph nodes. Detailed pathological analysis of total bile ducts revealed a small residual lesion in the subserous layer, but not in the mucosal surface. No tumor disseminations were found around the duodenal region where EUS-guided FNA was performed.

Discussion

Almost all small cell carcinomas occur in the pulmonary region; extrapulmonary cases comprise only 4% (1). To date there have been only 10 reported cases of small cell carcinoma of the bile duct in the English-language literature (including the present case); these cases show a preponderance of elderly males (mean age 63.7, male to female ratio 9:1) (Table 2), and have been pathologically classified as pure type (small cell carcinoma) or combined type (small cell carcinoma and adenocarcinoma) for therapeutic purposes be-
cause adenocarcinoma is resistant to chemotherapy (2-11). Early diagnosis has been very difficult; only 3 cases were diagnosed before treatment. Image tests showed very similar findings to those of ordinary bile duct cancer, and ERCP showed a smooth protrusion like a submucosal tumor at the margin of the tumor. Surgical procedures were performed in 8 cases, but resulted in unfavorable outcomes due to systemic hematogenous dissemination similar to other extrapulmonary small cell carcinomas (12). For early and correct diagnoses, it is necessary to perform EUS-FNA, as in the present case, and to do intensive biopsy. If small cell carcinoma is diagnosed, chemoradiation therapy is recommended as in the case of pulmonary small cell carcinoma (13). Chemotherapeutic regimens are similar to those employed in pulmonary small cell carcinoma (e.g., cisplatin, etoposide and CPT-11), but still show insufficient results especially for metastatic lesions, indicating the need for a more effective regimen. In the present case, radiation therapy ameliorated the jaundice which had been resistant to drainage procedures, suggesting that humoral factors released from the tumor may contribute to the persistence of the liver dysfunction.

In conclusion, in the present case EUS-FNA facilitated early and correct diagnosis and chemoradiation provided effective treatment. Together, these procedures represent an effective diagnosis and best-practices treatment system for small cell carcinoma of the bile duct.

### References