Carcinosarcoma of the Extrahepatic Bile Duct Presenting with Stone-like Radiological Findings

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Abstract

A 73-year-old woman was referred to our hospital due to epigastralgia and jaundice. The radiological findings showed a stone-like tumor in the extrahepatic bile duct. The patient was initially thought to have adenocarcinoma of the bile duct based on the findings of a pathological examination of the bile duct biopsy specimen and underwent pancreaticoduodenectomy; the final diagnosis of the lesion was so-called carcinosarcoma of the extrahepatic bile duct. She died of liver metastasis six months after the surgery. This case suggests that surgical resection is not adequate for achieving a radical cure, and the optimal treatment for extrahepatic bile duct carcinosarcoma should be established immediately.

Key words: so-called carcinosarcoma, extrahepatic bile duct, epithelial-mesenchymal transition, choledochal stone

(Intern Med 54: 1747-1751, 2015) (DOI: 10.2169/internalmedicine.54.3082)

Introduction

Carcinosarcoma of the biliary tract is a very rare malignant neoplasm characterized by the presence of both carcinomatous and sarcomatous components that intermingle. To date, only five such cases have been reported in the literature worldwide (1-5). Although the histogenesis of these biliary tract malignancies remains the subject of much debate due to their rarity, it is possible to subdivide them into two groups: one group exhibiting apparent carcinomatous and sarcomatous differentiation, called true carcinosarcoma, and one group presenting with both carcinomatous and sarcomatous components that undergo a transition between the two types of cells, known as so-called carcinosarcoma (3).

We herein present a rare case of so-called carcinosarcoma of the extrahepatic bile duct and discuss the features of this tumor in six reported cases, including the current case.

Case Report

A 73-year-old woman presented with epigastralgia and jaundice. She had previously undergone cholecystectomy for cholecystolithiasis approximately 10 years earlier. Biochemical tests performed at that time showed elevated bilirubin, transaminase and alkaline phosphatase levels (Table 1). A plain computed tomography (CT) scan revealed bilateral intrahepatic bile duct dilatation, while magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiography (ERC) disclosed a 25×14-mm oval-shaped filling defect in the extrahepatic bile duct (Fig. 1) that appeared to be the result of a bile duct stone. However, the detection of high-intensity signals on diffusion-weighted magnetic resonance imaging (DWI) suggested the possibility of a malignant tumor (Fig. 2A), and enhanced CT demonstrated a high-density mass (Fig. 2B, C). Based on these imaging findings, we suspected the lesion to be bile duct cancer. After the patient recovered from the obstructive jaundice with endoscopic retrograde biliary drainage, we performed a
endoscopic retrograde forceps biopsy, which showed that the tumor had rapidly become enlarged (30×15 mm). The biopsy specimen exhibited circular and spindle cells similar to that seen in poorly differentiated adenocarcinoma. Consequently, the patient underwent subtotal stomach-preserving pancreaticoduodenectomy approximately one month after the first ERC procedure.

A gross examination of the resected specimen revealed a nodular and polypoid tumor located in the extrahepatic bile duct measuring 6.5×3.5 cm in size (Fig. 3). Histologically, the tumor displayed a biphasic pattern of carcinomatous and sarcomatous elements. Most of the tumor was composed of spindle cells, with the remainder consisting of glandular cells; the carcinomatous areas were surrounded by the sarcomatous areas (Fig. 4). On an immunohistological examination, some of the sarcomatous areas were positive for epithelial markers, such as keratins (AE1/AE3), in addition to the carcinomatous areas (Fig. 5) (Table 2). Furthermore, the sarcomatous areas included no mesenchymal elements, such as cartilage, bone or skeletal muscle. The carcinomatous and sarcomatous elements were obviously intermingled in the tumor, with apparent morphological transition between the two components, known as the epithelial-mesenchymal transition (EMT).

These histological findings indicated a diagnosis of so-called carcinosarcoma of the extrahepatic bile duct. Three months later, follow-up CT confirmed the presence of large liver metastases of the carcinosarcoma (Fig. 6). The disease progressed rapidly, and the patient died six months after receiving surgical treatment.

Discussion

We herein reported an extremely rare case of carcinosarcoma of the extrahepatic bile duct. Carcinosarcoma itself is a very rare lesion of the hepatobiliary pancreatic system. To our knowledge, only five cases of carcinosarcoma of the extrahepatic bile duct have been reported to date (1-5). Carcinosarcoma is described as a malignant tumor composed of both epithelial and mesenchymal elements intermingled with

| Table 1. Laboratory Data at the Time of Admission. |
|-----------------------------|-----------------------------|
|                 |                |
| CBC            | Biochemistry   |
| WBC 3,800 /μL  | TP 8.5 g/dL    |
| Neu 80.5 %     | FBS 91 mg/dL   |
| Eos 0.5 %      | HbA1c 5.4 %    |
| Ly 12 %        | BUN 10.1 mg/dL |
| Mono 1 %       | Cr 0.71 mg/dL  |
| RBC 426×10⁶ /μL| AST 399 IU/L   |
| Hb 13.1 g/dL   | Na 138 mEq/L   |
| Ht 40 %        | ALT 634 IU/L   |
| MCV 94 g/L     | Cl 98 mEq/L    |
| Plt 22×10⁴ /μL | LDH 321 IU/L   |
| Tcho 244 mg/dL | Ca 10.4 mg/dL  |
| TG 81 mg/dL    | ALP 1,880 IU/L |
| Fe 116 μg/dL   | γ-GTP 685 IU/L |
| GTP 685 IU/L   | IP 3.3 mg/dL   |
| Amy 45 IU/L    | CRP 1 mg/dL    |
| CK 97 IU/L     | <Tumor marker> |
| Tcho 244 mg/dL | T-Bil 7.12 mg/dL|
| RBC 426×10⁶ /μL| T-Bil 7.12 mg/dL|
| Hb 13.1 g/dL   | T-Bil 7.12 mg/dL|
| MCV 94 g/L     | T-Bil 7.12 mg/dL|
| Plt 22×10⁴ /μL | T-Bil 7.12 mg/dL|
| Tcho 244 mg/dL | T-Bil 7.12 mg/dL|
| TG 81 mg/dL    | T-Bil 7.12 mg/dL|
| Fe 116 μg/dL   | T-Bil 7.12 mg/dL|
| GTP 685 IU/L   | T-Bil 7.12 mg/dL|
| Amy 45 IU/L    | T-Bil 7.12 mg/dL|
| CK 97 IU/L     | T-Bil 7.12 mg/dL|
| Tcho 244 mg/dL | T-Bil 7.12 mg/dL|
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| Tcho 244 mg/dL | T-Bil 7.12 mg/dL|
| TG 81 mg/dL    | T-Bil 7.12 mg/dL|
| Fe 116 μg/dL   | T-Bil 7.12 mg/dL|
| GTP 685 IU/L   | T-Bil 7.12 mg/dL|
| Amy 45 IU/L    | T-Bil 7.12 mg/dL|
| CK 97 IU/L     | T-Bil 7.12 mg/dL|
| Tcho 244 mg/dL | T-Bil 7.12 mg/dL|
| RBC 426×10⁶ /μL| T-Bil 7.12 mg/dL|
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| GTP 685 IU/L   | T-Bil 7.12 mg/dL|
| Amy 45 IU/L    | T-Bil 7.12 mg/dL|
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| Fe 116 μg/dL   | T-Bil 7.12 mg/dL|
| GTP 685 IU/L   | T-Bil 7.12 mg/dL|
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| GTP 685 IU/L   | T-Bil 7.12 mg/dL|
| Amy 45 IU/L    | T-Bil 7.12 mg/dL|
| CK 97 IU/L     | T-Bil 7.12 mg/dL|
| Tcho 244 mg/dL | T-Bil 7.12 mg/dL|

Figure 1. A: Magnetic resonance cholangiopancreatography shows an oval-shaped filling defect in the extrahepatic bile duct with bilateral intrahepatic bile duct dilatation. B: Endoscopic retrograde cholangiography shows the same findings.
Carcinosarcomas are divided into true and so-called entities. True carcinosarcomas exhibit apparent differentiation, such as rhabdoid, osteoid or chondroid differentiation. A recent immunohistochemical and ultrastructural study showed immunoreactivity to epithelial markers and intercellular junctions in the sarcomatous component in the majority of carcinosarcomas of the aerodigestive organs, known as so-called carcinosarcomas (3, 7). The exact histogenesis of carcinosarcomas has not been clearly elucidated. To date, two opposing theories have been hypothesized to explain the origin of these morphologically diverse tumors. The multiclonal theory (convergence hypothesis) regards a carcinosarcoma as being a collision tumor composed of the derivatives of two or more stem cells of separate epithelial and mesenchymal origin. In contrast, the monoclonal theory (divergent hypothesis) proposes that the carcinomatous and sarcomatous elements are derived from a single pluripotent stem cell that subsequently undergoes divergent differentiation along separate epithelial and mesenchymal pathways (8, 9). The histogenesis of carcinosarcoma remains controversial, although the results of recent immunohistochemical, ultrastructural and genetic engineering studies support the monoclonal theory (6, 9, 10). Polypoid growth and ossification in the tumor have also been reported to be typical characteristics of the gross and radiographic findings of carcinosarcoma (1, 6). In the present case, polypoid growth was observed; however, no findings of ossification were noted on CT. There is often no ossification in so-called carcinosarcomas, as these lesions do not always exhibit apparent differentiation to mesenchymal tissue. The radiographic features observed in the current patient, including an oval-shaped filling defect on ERC due to polypoid growth, are consistent with those of choleodochal stones, although there were no signs of ossification. In addition, the patient’s past history of cholecystolithiasis and symptoms such as epigastralgia and jaundice may have been associated with the choleodocholithiasis. Few cases involving a preoperative diagnosis of chole-
Hematoxylin and Eosin staining shows that most of the tumor is composed of sarcomatous areas, with the carcinomatous areas surrounded by sarcomatous components (arrows) (A: Scale bar=10 mm, B: Scale bar=100 μm).

Immunohistological staining shows both the sarcomatous and carcinomatous areas to be positive for epithelial markers (A: AE/AE3, Scale bar=20 μm, B: CK7, Scale bar=20 μm).

Table 2. Differential Expression of Immunohistochemical Markers between the Carcinomatous and Sarcomatous Components.

| Marker     | Carcinomatous component | Sarcomatous component |
|------------|-------------------------|-----------------------|
| S-100 protein | -                       | +                     |
| keratin 20   | -                       | -                     |
| keratin 7    | ++                      | focal +               |
| AE1/AE3      | ++                      | focal +               |
| α-SMA        | -                       | +                     |
| Vimentin     | -                       | ++                    |
| MUC1         | +                       | -                     |
| MMP7         | -                       | -                     |
| CD10         | -                       | ++                    |

++: Intense positive staining, +: positive staining, -: negative staining

Follow-up CT performed three months after surgery shows recurrence of the tumor in the right lobe of the liver.

dochoal stones have been reported (1, 3). In the present case, with respect to distinguishing the disease from choledocholithiasis, it was helpful that the tumor displayed high intensity on DWI MRI images. Obtaining a diagnosis of carcinosarcoma prior to resection is difficult. Endoscopic retrograde forceps biopsies often identify only the epithelial component of the tumor. If the specimens fortunately reveal both the epithelial and mesenchymal components, the lesion is diagnosed as carcinosarcoma. There are no previous cases in
which an exact preoperative diagnosis of carcinosarcoma in the extrahepatic bile duct was made (1-5). In the present case, retrospectively, it may have been possible to diagnose the tumor as carcinosarcoma based on the specimens for the bile duct biopsy, which showed spindle cells. However, even if we had been able to diagnose the tumor as carcinosarcoma, the patient would have received the same surgical treatment, as the best treatment option for extrahepatic bile duct carcinosarcoma is currently surgical excision.

In the previous five cases and present case, the carcinosarcomas of the extrahepatic bile duct showed various features (Table 3). There are three characteristic findings in these six cases. First, the patients usually presented with abdominal pain or jaundice. Second, the lesions were located in the middle or lower bile duct. Finally, the prognosis of so-called carcinosarcoma was inferior to that of true carcinosarcoma. Due to the limited number of cases, it is difficult to entirely clarify the features of carcinosarcoma of the extrahepatic bile duct. In the Japanese literature in particular, carcinosarcoma of the extrahepatic bile duct has been reported in more than 10 cases (11), which suggests that Asians more easily suffer from this disease than other races. Further case accumulation is required to investigate this issue.

The prognosis of patients with carcinosarcoma of the extrahepatic bile duct remains uncertain. Generally, carcinosarcomas tend to metastasize systemically and exhibit an aggressive form of malignancy, even in early stages (12). The present patient died of tumor recurrence six months after undergoing surgery. This outcome suggests that surgical resection is not adequate for achieving a radical cure. However, the only currently recognized treatment for carcinosarcoma is surgery, and there are no previous reports of effective chemotherapy or radiotherapy, irrespective of the affected organ. Therefore, the development of other treatment strategies for carcinosarcoma is required, and the optimal treatment for extrahepatic bile duct carcinosarcoma should be established immediately.

The authors state that they have no Conflict of Interest (COI).

Table 3. Reported Cases of Carcinosarcomas of Extrahepatic Bile Duct.

| References | Age | Gender | Symptom | Preoperative diagnosis | Site | Surgical treatment | Macroscopic tumor type | Pathology | Prognosis |
|------------|-----|--------|---------|------------------------|------|-------------------|------------------------|-----------|-----------|
| 1          | 35  | F      | Jaundice| Choledochal stone      | Middle | CBD resection     | Polypoid               | NR        | NR        |
| 2          | 78  | M      | Abdominal pain and jaundice | NR     | Middle to lower | PD | Infiltative | So-called | Died, 2 years of local recurrence |
| 3          | 75  | F      | Jaundice| Choledochal stone      | Middle | CBD resection     | Polypoid               | True      | Alive, 5 years disease-free |
| 4          | 64  | F      | Appetite loss | NR     | Middle to lower | PD | Infiltative | So-called | True |
| 5          | 73  | F      | Jaundice| Cholangiocarcinoma     | Lower  | PD                | Polypoid               | True      | Alive, 7 months disease-free |
| Present case | 73  | F      | Abdominal pain and jaundice | Cholangiocarcinoma | Middle | PD                | Polypoid               | So-called | Died, 6 months of local recurrence |

M: man, F: female, NR: not reported, CBD: common bile duct, PD: pancreaticoduodenectomy, POD: postoperative day

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