Cystic Duct Metastasis from Renal Cell Carcinoma

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Abstract:
We herein report a 69-year-old man who underwent right nephrectomy 1 year previously to remove renal cell carcinoma (RCC). On our examinations, contrast-enhanced computed tomography revealed a tumor with intensive early enhancement near the cystic duct of the gallbladder. Endoscopic ultrasonography showed a low echoic mass in the cystic duct. We diagnosed the patient’s condition as cystic duct metastasis from RCC and performed open cholecystectomy. Histopathology indicated a metastatic tumor of clear cell RCC in the cystic duct wall. In patients with a medical history of RCC, hypervascular lesions suggest the possibility of metastasis. Therefore, detailed imaging examinations should be performed.

Key words: cystic duct, renal cell carcinoma, metastasis, gallbladder, EUS, imaging findings

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Introduction
Renal cell carcinoma (RCC) represents 2-3% of all cancers and accounts for approximately 90% of all kidney malignancies (1). One-third of patients have metastatic disease at the initial presentation; however, gallbladder metastasis from RCC is rare, and only few cases have been reported (2-5). To our knowledge, cystic duct metastasis from RCC has never been reported.

We herein report an extremely rare case of cystic duct metastasis from RCC preoperatively diagnosed in a patient. We also discuss its imaging and pathological characteristics, as well as its mechanism and treatment.

Case Report
A 69-year-old man visited our hospital for the evaluation of a cystic lesion in the pancreatic head that had been found during a routine health checkup. One year previously, he had undergone right nephrectomy to remove clear cell RCC. Histology of the resected specimen showed slight vessel invasion, but no lymphatic vessel invasion. The postoperative staging was T2, N0, Stage II according to the Union for International Cancer Control (7th edition). His recent physical examination findings were unremarkable, although his blood examination revealed slight elevation in his creatinine level (Table 1). Computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) showed multilocular cysts connecting with the main pancreatic duct, so the cystic lesion was diagnosed as a branch duct type intraductal papillary mucinous neoplasm. However, an oval tumor was found coincidently near the cystic duct, prompting us to perform detailed imaging examinations.

Abdominal ultrasonography (US) showed a smooth marginated mass with a homogeneous echo pattern near the cystic duct and a swollen gallbladder with stones (Fig. 1). Contrast-enhanced CT revealed the presence of a 13-mm-diameter tumor with intensive early enhancement located near the cystic duct (Fig. 2). On magnetic resonance imaging, the tumor showed a low signal intensity on T1-weighted images and a high signal intensity on T2-weighted images compared with the normal liver parenchyma. On diffusion-weighted imaging, the tumor showed a high signal intensity, and the apparent diffusion coefficient value was 1.5×10⁻³ mm²/s. MRCP showed a smooth signal defect in the cystic duct (Fig. 3). Endoscopic ultrasonography showed a well-circumscribed, oval, low-echoic mass surrounded by a cystic duct wall, suggesting the presence of a tumor in the cystic duct (Fig. 4). Endoscopic retrograde cholangiography...
Cancer metastasis to the cystic duct is extremely rare, and there were no operation-related adverse events, and the patient was followed up without adjuvant therapy in an outpatient clinic. He remained disease-free until seven months of follow-up.

**Table 1. Laboratory Data on Admission.**

|          | Complete blood count | Reference ranges | Blood chemistry | Reference ranges |
|----------|----------------------|------------------|-----------------|-----------------|
| WBC (×10^9/L) | 3.510               | 3,500-9,400      | Total bilirubin (mg/dL) | 0.7 | 0.2-1.0 |
| RBC (×10^12/L) | 442                 | 420-570          | AST (IU/L)          | 24  | 10-38   |
| Hemoglobin (g/dL) | 14.1               | 13.0-17.5        | ALT (IU/L)          | 23  | 6-38    |
| Hematocrit (%) | 40.1                | 39.8-51.8        | ALP (IU/L)          | 295 | 110-390 |
| Platelet (×10^12/L) | 11.4              | 13.0-38.0        | γ-GTP (IU/L)        | 21  | 7-70    |
|            |                     |                  | LDH (IU/L)          | 161 | 115-255 |
|            |                     |                  | Amylase (IU/L)      | 101 | 40-126  |
|            |                     |                  | Sodium (mEq/L)      | 142 | 136-147 |
|            |                     |                  | Potassium (mEq/L)   | 4.3 | 3.5-5.0 |
|            |                     |                  | Chloride (mEq/L)    | 109 | 95-110  |
|            |                     |                  | Total protein (g/dL)| 5.8 | 6.3-8.5 |
|            |                     |                  | Albumin (g/dL)      | 4.0 | 3.3-5.1 |
|            |                     |                  | BUN (mg/dL)         | 25.3 | 7-22   |
|            |                     |                  | Creatinine (mg/dL)  | 1.18 | 0.61-1.10 |
|            |                     |                  | Blood sugar (mg/dL) | 97  | 70-110  |
|            |                     |                  | CRP (mg/dL)         | 0.79 | <0.20   |

WBC: white blood cell count, RBC: red blood cell count, CEA: carcinoembryonic antigen, CA 19-9: cancer antigen 19-9, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γ-GTP: gamma-glutamyl transpeptidase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, CRP: C-reactive protein

**Figure 1. Abdominal ultrasonography showing a smooth margined mass with a homogeneous echo pattern near the cystic duct (yellow arrow) and a swollen gallbladder with stones (red arrow).**

showed a smooth defect in the cystic duct and displacement of the common bile duct from the gallbladder side (Fig. 5). Although a biopsy using a peroral cholangioscope (POCS) was attempted to establish a pathological diagnosis, the biopsy could not be performed because the POCS could not pass through the cystic duct. These imaging findings indicated the presence of a tumor in the cystic duct wall. Endoscopic ultrasonography (EUS)-guided fine needle aspiration was not performed due to the risk of bile leakage and tumor bleeding and seeding. Based on these imaging findings, we diagnosed the patient’s condition as cystic duct metastasis from RCC. As other metastatic sites were not observed, open cholecystectomy was performed.

Histopathology showed a 13×11-mm solid metastatic tumor of clear cell RCC in the cystic duct wall. The tumor had an alveolar architecture of cells with a clear or eosinophilic cytoplasm, separated by a delicate branching network of vascular tissue. A normal epithelium remained in some part of the tumor surface. The tumor was present in the lamina propria of the cystic duct and was elevated towards the mucosal side, resembling a polypoid lesion (Fig. 6). There was no lymph node component at the peripheral lesion. Immunohistochemistry showed tumor cell expressions of AE1/AE3, CD10, and vimentin, which were consistent with the diagnosis of metastatic clear cell RCC. The histopathological and immunohistochemical staining results of the cystic duct metastasis were the same as those of the primary kidney cancer.

There were no operation-related adverse events, and the patient was followed up without adjuvant therapy in an outpatient clinic. He remained disease-free until seven months of follow-up.

**Discussion**

RCC has a high metastatic potential. Indeed, one-third of patients present with metastatic disease at the diagnosis (6). In addition, up to 50% develop metastatic disease metachronously after surgical resection. The most common sites of distant metastasis are the lung, bone, liver, adrenal gland, brain, and contralateral kidney (2, 3). RCC metastasis to the gallbladder is rare and has only been found in 0.58% of cases at necropsy (7). Neves et al. reported a review of 52 patients published in the English and Japanese literature (3). Metachronous gallbladder metastasis was found in 69.2% of patients with a median disease-free interval from nephrectomy of 4 years. Clear cell type was identified in 97.4% of patients, and polypoid lesions were observed in 92% of patients.

Cancer metastasis to the cystic duct is extremely rare, and only three cases have been reported thus far in the literature.
Regarding the imaging features of metastatic gallbladder cancer, a polypoid tumor with intensive early enhancement was detected on contrast-enhanced CT, and a smooth marginated lesion with a superficial hyperechoic band was noted on US (4, 5). In the present case, the smooth marginated cystic duct tumor showed intensive early enhancement, so the patient was able to be diagnosed preoperatively with cystic duct metastasis from RCC.

Cancer metastasis is considered to result from hematogenous, lymphatic, disseminated, and direct invasion. Cancer often metastasizes hematogenously to the lamina propria of the gallbladder wall (10), and gallbladder metastasis shows characteristic polypoid lesions (3). We consider that cancer that has metastasized to the lamina propria of the gallbladder wall can spread easily to the mucosal side because the muscularis propria is located under the lamina propria. Therefore, metastatic tumors of the gallbladder show polypoid lesions. In the present case, the cystic duct tumor was also present in the lamina propria and showed polypoid growth, as reported previously (3, 10). RCC has a high potential for hematogenous metastasis, and the most common metastatic sites are vascular-rich organs. In addition, the frequency of lymph node metastasis from RCC is low in cases without other organ metastasis (11). In the present case, imaging examinations revealed no metastatic tumors, except for in the cystic duct. The primary lesion did not have lymphatic vessel invasion. Furthermore, histopathological findings revealed that the tumor was present in the lamina propria of the cystic duct without any lymph node component around the tumor. Therefore, hematogenous metastasis to the cystic duct occurred.
Figure 4. Endoscopic ultrasonography showing a well-circumscribed, oval, low-echoic mass surrounded by a cystic duct wall, suggesting the presence of the tumor in the cystic duct. CBD: common bile duct, CD: cystic duct, GB: gallbladder

Figure 5. Endoscopic retrograde cholangiography showing a smooth defect in the cystic duct and the displacement of the common bile duct from the gallbladder side.

Surgical resection is a curative treatment for RCC only if all of the tumor burden can be removed. Metastasectomy may be justified in select patients with local metastatic disease. A systematic review reported that complete metastasectomy in any organs except the brain and bone benefited metastatic RCC patients in terms of their survival and delaying systemic therapy (12). In patients with metastatic clear cell RCC, chemotherapy has been shown to have little or no efficacy (13). A number of targeted agents have recently become available (14). However, there is still no evidence to support the use of adjuvant therapy after RCC surgery (14-16). Thus, cholecystectomy and careful follow-up
without adjuvant therapy were considered adequate treatment for this patient.

In conclusion, we encountered an extremely rare case of cystic duct metastasis from RCC. This cystic duct tumor showed the characteristics of hematogenous metastasis to the gallbladder—namely hypervascularity and polypoid growth. In patients with a medical history of RCC, the presence of a hypervascular lesion suggests the possibility of metastasis.

Table 2. Summary of Cancer Metastasis to the Cystic Duct.

| Reference | Age (years) | Sex | Primary cancer | Opportunity for diagnosis | Operation | Macroscopic appearance | Other metastasis |
|-----------|------------|-----|----------------|---------------------------|-----------|------------------------|------------------|
| 1         | 8          | 59 F | Breast         | Acalculous cholecystitis  | Cholecystectomy | polypoid                | None             |
| 2         | 9          | 73 F | Breast         | Acalculous cholecystitis  | Cholecystectomy | Mass                   | Lymph node Liver |
| 3         | 10         | 67 M | Rectal         | Intraoperative appearance| Colon and liver resection + Cholecystectomy | polypoid                | Liver             |
| 4         | Present case | 69 M | Kidney         | Preoperative imaging findings | Cholecystectomy | polypoid                | None             |

Figure 6. Histopathological findings (hematoxylin and eosin staining). a. 13 ×11 mm solid metastatic tumor of clear cell RCC in the cystic duct wall. b. Normal epithelium remained on part of the tumor surface. c. The tumor was present in the lamina propria of the cystic duct and elevated towards the mucosal side.
from RCC. Therefore, detailed imaging examinations should be performed to definitively identify the lesion site and determine the optimal treatment strategy.

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

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