Abstract:
A 61-year-old man who had undergone total nephroureterectomy eight months earlier for right ureteral carcinoma was referred for the investigation of elevated serum hepatobiliary enzymes. Computed tomography revealed a small mass invading the lower bile duct. Duodenoscopy revealed a central ulcerative tumor near the major papilla, and a biopsy histologically confirmed metastatic ureteral carcinoma. Endoscopic biliary stenting ameliorated the cholangitis, and gemcitabine-based chemotherapy was initiated. The patient was stable for a year until a duodenal stenosis developed and required duodenal stenting. Endoscopic procedures play important roles in the management of rare metastases to the duodenum.

Key words: ureteral carcinoma, duodenum, metastasis, stenosis, biliary stent, duodenal stent

Introduction
Metastasis to the duodenum has been reported on rare occasions in a limited number of cases of several human malignancies, including those of the breast (1), lung (2, 3), liver (4), colon (3), kidney (5), bladder (6), prostate (7), uterus cervix (8), bone (9), and skin (10). However, duodenal metastasis from ureteral cancer has seldom been reported, and its clinical course is unclear.

Malignancies invading the duodenum sometimes need treatment for obstructions of both the bile duct and the duodenum. In these cases, double metallic stenting for these tracts is a choice for palliative therapy. Double stenting has largely been applied in cases of pancreatobiliary or gastric cancer (11, 12). We herein report a case of ureteral cancer that was initially treated surgically but developed a metastatic recurrence to the periampullary region. This metastasis was first managed by biliary stenting and later by duodenal stenting, in addition to systemic chemotherapy.

Case Report
A 61-year-old man was referred from the Urology Division for the investigation of a sudden increase in serum hepatobiliary enzymes: aspartate aminotransferase (AST) (248 U/L, normal: 10-40 U/L), alanine aminotransferase (ALT) (293 U/L, normal: 5-40 U/L), and alkaline phosphatase (ALP) (1,403 U/L, normal: 115-359 U/L). He had a history of invasive carcinoma of the right ureter and had undergone right nephroureterectomy and partial cystectomy eight months earlier (pathology: pT3, 38 mm in size, G3>G2, positive for lymph ductal and venous permeation, and positive for right renal metastasis). Enhanced computed tomography (CT) revealed a faintly enhanced tumor close to the dilated lower bile duct and the ampullary region (Fig. 1). Abdominal ultrasound (US) also demonstrated a few enlarged lymph nodes near the inferior vena cava and the pancreas head. An endoscopic procedure was performed for biliary drainage. Duodenoscopy revealed a tumor showing central ulceration with a wavy margin, approximately 2 cm
in size, at the oral side of the major papilla (Fig. 2a, b). Endoscopic retrograde cholangiography revealed a short segment of the distal biliary stricture (Fig. 3a), and a plastic stent was placed (Fig. 3b). Histology obtained by a forceps biopsy from the duodenal tumor revealed carcinoma tissue with diffuse thrombomodulin expression and focally aggregated GATA-3 expression (Fig. 4a-c), quite compatible with that of the previously resected right ureter cancer (Fig. 4d-f) (13). Combining the imaging and pathological findings with the clinical course led to the suspicion of periampullary metastasis invading the bile duct.

Systemic chemotherapy with gemcitabine (1,000 mg/m$^2$/at days 1, 8, and 15) and cisplatin (70 mg/m$^2$/at day 2) (14) was initiated immediately after the relief of cholangitis with their doses adjusted based on the renal function (estimated glomerular filtration rate [EGFR: 30-45 mg/dL] (Fig. 5). Abdominal CT was repeated every two to three months for a therapeutic evaluation. The initial biliary stent was effective for a while, but it became occluded and was exchanged in the seventh month for a covered metallic stent (Supremo, 10×60 mm; Taewoong, Goyang, South Korea). At that time, a second portion of the duodenum became moderately stenotic, and the tumor extended very near to the papilla orifice (Fig. 2c, d), preventing endoscopic sphincterotomy (EST) of the required length. The next morning, a blood test revealed an increased level of serum amylase (1,934 U/L, normal: 37-125 U/L) without an accompanying increase in the level of white blood cells or complaints of abdominal pain. Abdominal US was performed to evaluate post-biliary stenting pancreatitis (15) but did not reveal any pancreatic swelling or peripancreatic effusion. Instead, it showed an increase in the size of a bulky peripancreatic lymph node to 66 mm. The chemotherapy regimen was then changed to gemcitabine and paclitaxel.

Four months later, the patient complained of nausea. Upper gastrointestinal endoscopy revealed advanced duodenal stenosis, so an uncovered metallic stent (WallFlex, 22×120 mm; Boston Scientific, Marlborough, USA) was placed between the bulbs and the transverse portion of the duodenum (Fig. 3c). Meals were started two days later and then gradually was changed to minced food in adjusted amounts. The patient sometimes experienced epigastric distress and needed a drip infusion, but he did not require any additional endoscopic procedures or interventions. The patient chose the best supportive care and succumbed 4 months later, 16 months after the initial diagnosis of duodenal metastasis.

Discussion

Duodenal metastasis from a distant origin is an uncommon event. Our PubMed literature survey using keywords of “duodenum or duodenal”, “metastasis or metastatic”, and “cancer or tumor”, did not identify any systematic analyses or reviews highlighting tumor metastases to the duodenum. Several case reports have individually described duodenal metastases from various distant organs, but these metastases mostly arose from the breast (1), lung (2, 3), kidney (5), prostate (7), and uterus (8), and on rare occasions from the liver (4), colon (3), bladder (6), bone (9), and skin (10), but never from the ureter. Upper urothelial tract cancers usually metastasize to the lung (4%), liver (12%), and bone (3%) (16). When metastasis is positive, they often accompany metastases to the lymph nodes (77%) (14). The current case also demonstrated swelling of the peripancreatic lymph nodes, suggesting a lymphatic metastasis. The current metastasis (Fig. 2) endoscopically looked quite similar to a primary duodenal cancer, as it showed a relatively well-demarcated mass with a central ulceration and a wavy margin. Therefore, a careful diagnosis using a forceps biopsy is essential for an accurate diagnosis and for the selection of suitable chemotherapy agents.

Recurrent upper urothelial carcinoma, such as in the cur-
Figure 2. Endoscopic view of the second portion of the duodenum at initial cholangitis, showing a mass lesion with a central ulcerative lesion and wavy margins (a) invading close to the major papilla (arrow pointing to the major papilla of Vater) (b). Endoscopic view seven months later showing a progressed tumor with large ulceration (c) extending to the major papilla replaced by a covered metallic stent (d).

Figure 3. Endoscopic retrograde cholangiography demonstrating a short length of stenosis at the lower bile duct (a) and a plastic stent placed across the stenotic site (b). Double stenting was performed with an additional duodenal metallic stent across the stenotic site, attaching to the lower end of the previously inserted biliary stent (c).
**Figure 4.** A high-magnification view of the biopsy material from the duodenal tumor consisted of invasive carcinoma cells with irregular nucleus and eosinophilic cytoplasm [Hematoxylin and Eosin (H&E) staining] (a), with a diffuse expression of thrombomodulin (b) and weak but focally aggregated expression of GATA-3 (c) (a-c: 200×), histologically and immunohistologically compatible with the primary urothelial carcinoma resected eight months previously (d: H&E staining, e: thrombomodulin, f: GATA-3, 100×).

**Figure 5.** The patient’s clinical course. †: death, *fentanyl was a patch drug, otherwise peroral drugs were used. ALP: alkaline phosphatase, ALT: alanine aminotransferase, B-PS: biliary plastic stent, B-EMS: biliary expandable metallic stent, D-EMS: duodenal expandable metallic stent, GEM+CDDP: gemcitabine and cisplatin, GEM+TXL: gemcitabine and taxol, NSAID: non-steroidal anti-inflammatory drug
rent case, is usually treated with gemcitabine and cisplatin as a standard regimen of systemic chemotherapy (14). For adjuvant chemotherapy, several retrospective studies have demonstrated a longer 5-year survival in patients given cisplatin-based chemotherapy than in those receiving non-cisplatin-based chemotherapy (63-96 months vs. 37-52 months) (17-19). A meta-analysis also confirmed the effect of cisplatin-based therapy in an adjuvant setting (17). However, a decline in the renal function due to nephroureterectomy has limited the use of cisplatin in the post-surgical course (20), as in the current case (70 mg/m² standard; 50 mg/m² in current case). One solution to this problem is to shift the chemotherapy to a neoadjuvant setting (20), especially in cases with a high risk of recurrence. Radiation therapy may also improve the prognosis, although the evidence supporting this approach is not solid (21).

The choice of stent is key in cases of malignant biliary obstruction, which may be largely affected by the response to chemotherapy. For instance, malignant lymphoma usually responds well initially to chemotherapy, so an easily withdrawable plastic stent is preferred in these cases. Similarly, in our case, we first placed a plastic stent and then later replaced it with a metallic stent upon confirmation of disease progression despite chemotherapy. The placement of a self-expandable metallic stent across the major papilla requires consideration of post-stenting pancreatitis (15), especially in cases with abundant pancreatic parenchyma and limited minor papilla excretion. In these cases, EST is viewed as effective for preventing pancreatitis (15). We were unable to perform a sufficient EST to place a metallic stent (10 mm) because of invasion of the cancer near the major papilla, which could have led to hyperamylasemia.

Regarding the technical aspects of double stenting, the addition of a duodenal stent is feasible in most cases when duodenal stenosis becomes severe. The average prognosis after double stenting has been reported to be relatively short in patients mostly with pancreaticobiliary carcinomas (81-91 days) (11, 12). In patients with a good physical status and an expectation of a long prognosis, a gastro-jejunal bypass can be considered for better nutrition and the quality of life. The application of double stenting in one endoscopic session in previous studies has involved duodenal stent placement for the first stenting, followed by biliary stenting (11, 12). In the current case, however, jaundice developed earlier and duodenal stenosis later, so the order of stenting was reversed; however, this stenting functioned for four months without additional procedures.

In summary, we reported a rare case of duodenal metastasis from a previously resected ureteral cancer. An accurate diagnosis and suitable subsequent treatment are necessary in such rare cases. In this sense, endoscopic procedures, including observation, a forceps biopsy, and biliary and duodenal stenting, play important roles in achieving a favorable outcome.

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

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