

[CASE REPORT]

Endoscopic Ultrasound-guided Fine Needle Aspiration for the Diagnosis of Duodenal Stenosis Due to Urothelial Carcinoma

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Abstract:

Upper tract urothelial carcinoma (UTUC) initially presents with hematuria and hydronephrosis. We report a case of UTUC presenting with initial findings of duodenal stenosis before the appearance of hydronephrosis. A 59-year-old man presented with upper abdominal symptoms on his initial visit. Esophagogastroduodenoscopy (EGD) revealed circumferential stenosis at the descending part of the duodenum. However, the underlying cause of duodenal stenosis was unknown as repeated histopathological examinations of endoscopic biopsy specimens showed no specific findings. We then performed endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of the thickened duodenal wall, and successfully diagnosed duodenal metastasis of UTUC. EUS-FNA is an effective diagnostic method in cases in which the cause of duodenal stenosis is unknown.

Key words: urothelial carcinoma, duodenal stenosis, EUS-FNA

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Introduction

The many causes of duodenal stenosis include both neoplastic and non-neoplastic disease. In cases of duodenal stenosis caused by non-neoplastic disease, including retroperitoneal panniculitis, Crohn's disease, tuberculosis, and vasculitis, stenosis is induced by chronic inflammation (1-3). On the other hand, neoplastic stenosis results from the growth of duodenal or metastatic duodenal cancer, direct invasion of pancreatic or bile duct cancer into the duodenum, or infiltration of peritoneal dissemination into the duodenal wall (4-7). The identification of primary cancer is therefore challenging for clinicians when computed tomography (CT) does not identify a primary site, and endoscopic biopsy reveals no cancer cells.

We herein report a case of upper tract urothelial carcinoma (UTUC) presenting with duodenal stenosis resulting from lymphatic metastasis to the duodenal wall. However, the diagnosis was difficult because repeated endoscopic bi-

opsies were negative for cancer due to poor mucosal change, and CT scans obtained at the initial visit showed no urinary tract lesions or hydronephrosis, as secondary signs of advanced disease (8). Finally, endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) revealed cancer cells in the duodenal wall, and a primary diagnosis of UTUC was reached based on an immunohistochemical study.

Case Report

A 59-year-old man was admitted for abdominal fullness, vomiting, and body weight loss of 5 kg. A physical examination revealed upper abdominal distension and a laboratory examination revealed mild renal dysfunction without hematuria or proteinuria. Abdominal CT showed wall thickening of the descending part of the duodenum at the initial visit, suggesting duodenal stenosis as the underlying cause of the symptoms (Fig. 1a). In addition, the concentration of fatty tissue surrounding the right kidney was slightly increased. No other abnormal findings were observed. Consequently,

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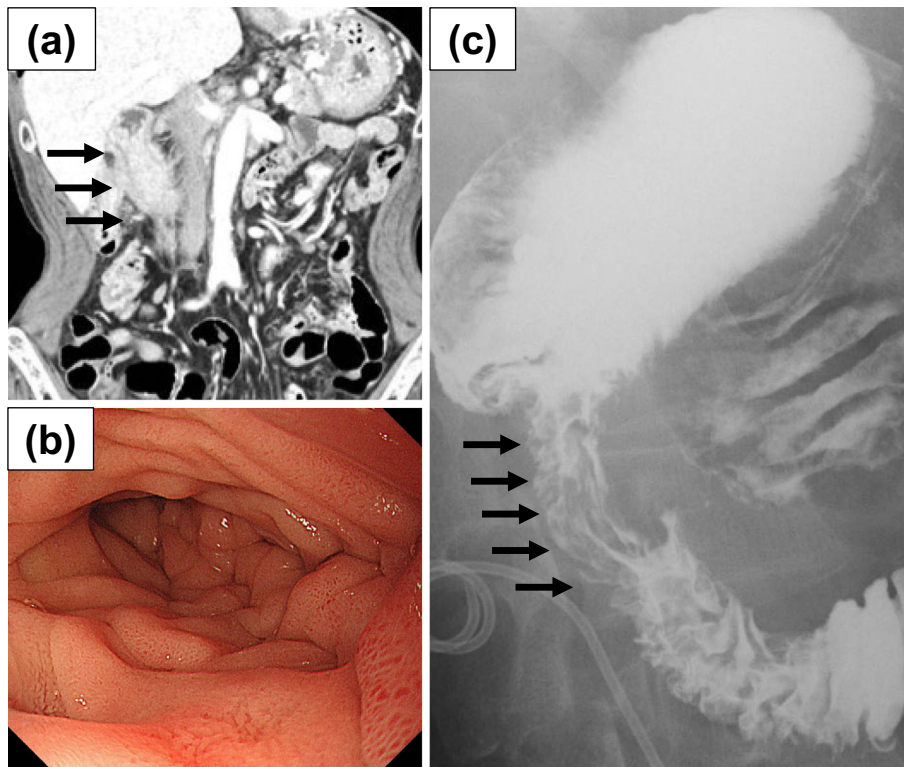


Figure 1. The appearance of the duodenal stenosis on the initial visit. (a) Abdominal computed tomography on the first visit showed thickening of the duodenal wall with no other specific findings. (b) Esophagogastroduodenoscopy revealed circumferential stenosis without erosion or ulceration at the descending part of the duodenum. (c) Hypotonic duodenography using barium revealed smooth stenosis in the lumen (arrows).

esophagogastroduodenoscopy (EGD) and hypotonic duodenography were performed. These tests revealed circumferential stenosis of 3 cm in length with multiple red spots at the descending part of the duodenum (Fig. 1b, c). However, the underlying cause of the duodenal stenosis could not be determined because no specific findings were observed in the histopathological examination of 15 endoscopic biopsy specimens. The patient's serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were 3.8 ng/mL (normal <3.4 ng/mL) and 14 U/mL (normal <37 U/mL), respectively.

Follow-up abdominal CT three months after the initial visit showed thickening of the right ureter wall and right hydronephrosis (Fig. 2a, b), and retrograde urography revealed irregular ureteral stenosis (Fig. 2c). No abnormal findings of the bile duct or pancreas were observed. The immunoglobulin G subclass 4 (IgG4) serum level was 24.3 mg/dL (normal 11-121 mg/dL). Based on these findings, the assumed differential diagnoses were diffuse duodenal cancer with peritoneal dissemination to the ureter or urothelial carcinoma with duodenal metastasis. EUS-FNA of the duodenal lesion and ureteroscopy were therefore performed. EUS showed a thickened duodenal wall (thickness: 5.4 mm) and a swollen superior anterior pancreatic lymph node (size: 15 mm). EUS-FNA of both lesions was successfully performed using a 22 G needle (Acquire, Boston Scientific, Marlbor-

ough, USA) (Fig. 3). In particular, we punctured the thickened duodenal wall at the duodenal bulb at a shallow puncture angle. Finally, a pathological analysis revealed cancer nests in the duodenal wall, which seemed to have spread into the lymphatic vessels. An immunohistochemical analysis revealed that the cancer cells were positive for cytokeratin 7 (CK7), cytokeratin 20 (CK20) and GATA binding protein 3 (GATA3) (Fig. 4). Cancer nests were also identified in the lymph node, which were positive for CK7, CK20 and GATA3 and negative for caudal-related homeobox 2 (CDX2) (data not shown). These immunostaining characteristics strongly suggested urothelial carcinoma. Additionally, ureteroscopy showed ureteral stenosis with sessile tumor architecture, and a histological examination of biopsy specimens obtained by ureteroscopy showed CK7-, CK20- and GATA3-positive transitional cell carcinoma (Fig. 5). All findings were consistent with those of the duodenal and lymph node specimens, and the final diagnosis was urothelial carcinoma with lymph node and duodenal metastasis. The clinical disease stage, according to the tumor-node-metastasis staging system of the Union for International Cancer Control, was T4N2M1, stage IV.

The patient received gastrojejunostomy for duodenal stenosis alongside treatment with gemcitabine plus cisplatin. The best response to chemotherapy was stable disease across four cycles of chemotherapy. However, the right hilar lymph

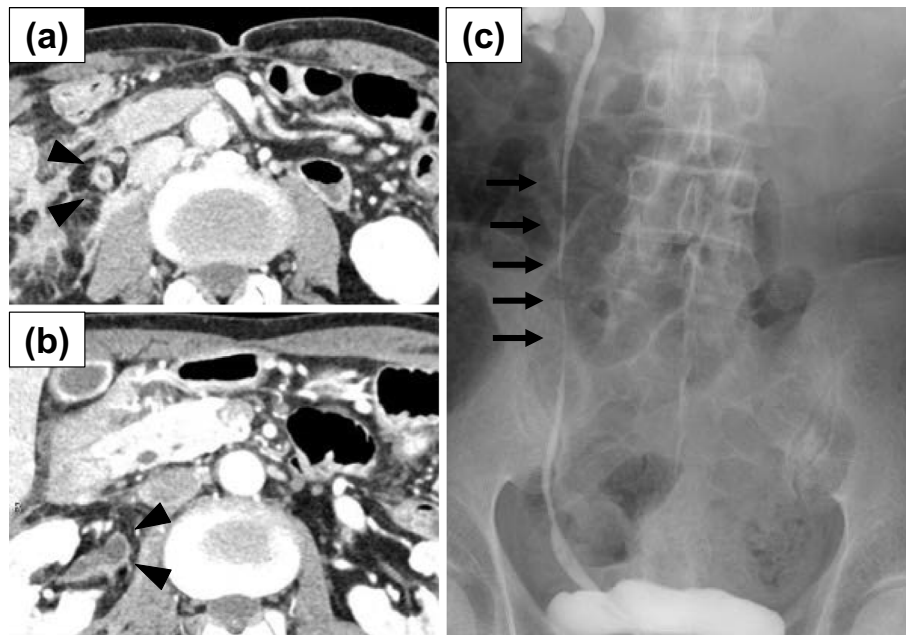


Figure 2. Appearance of the ureteral stenosis at three months after initial visit. (a), (b) Abdominal computed tomography showed right hydronephrosis and wall thickening of the right ureter (arrowheads). (c) Retrograde urography showed irregular ureteral stenosis (arrows).

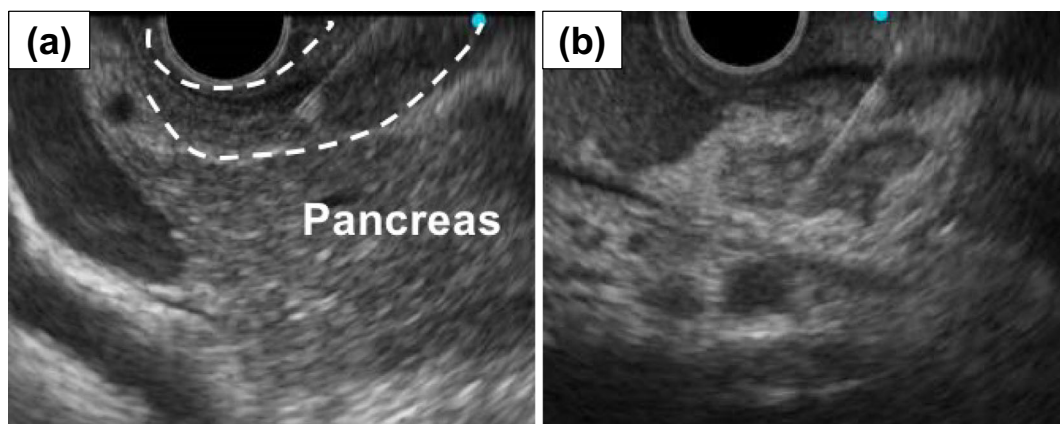


Figure 3. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). EUS revealed duodenal thickening (a) and irregular abdominal lymph node swelling (b). FNA of both lesions was successfully performed using a 22 G needle.

nodes progressed five months after the initiation of first-line chemotherapy. Thus, pembrolizumab treatment was initiated.

Discussion

The initial findings in UTUC are generally visible or non-visible hematuria and hydronephrosis due to ureter stenosis (8-10), although circumferential stenosis of the duodenum has occasionally been described in previous reports (11-14) (Table). The present case therefore highlights two important clinical points. The first is that upper abdominal symptoms due to duodenal stenosis may appear before hematuria and hydronephrosis; the other is that EUS-FNA was a conclusive minimally invasive method for diagnosing

duodenal stenosis of unknown cause. As a result, the patient avoided unnecessary invasive diagnostic surgical procedures and could receive chemotherapy.

Duodenal metastasis from a distant origin is an uncommon event. UTUC usually metastasizes to the lung, liver, and bone with lymph node metastasis (15). The current case showed duodenal metastasis earlier than those organs; thus, we focused on the metastatic pathway of UTUC to the duodenum. Previously, advanced UTUC has been reported to cause duodenal stenosis via direct invasion, and lymphatic and peritoneal dissemination (11-14). Ando et al. demonstrated that cancer cells reached the duodenum through lymphatic metastasis in an autopsy case of recurrent UTUC (12). Their findings revealed that high-grade urothe-

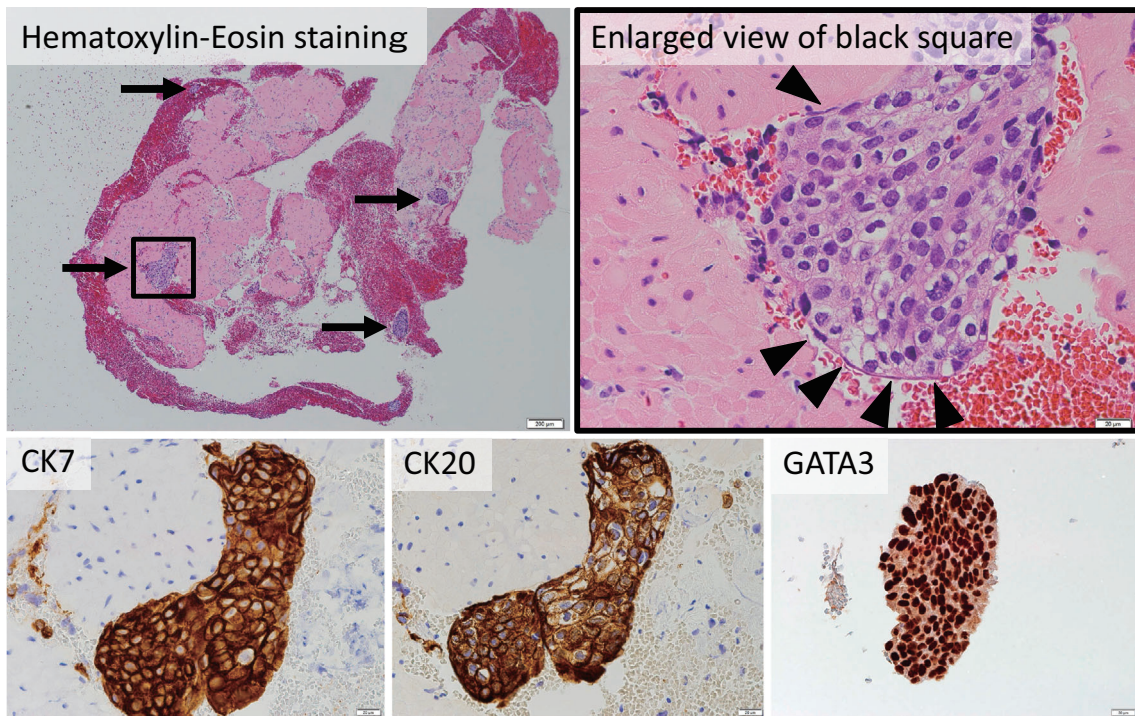


Figure 4. The histopathological examination of EUS-FNA specimens. Cancer nests surrounded by lymphatic endothelial cells (arrowheads) were identified in the duodenal tissues (arrows). The immunostaining findings were as follows: CK7, positive; CK20, positive; and GATA3, positive. EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

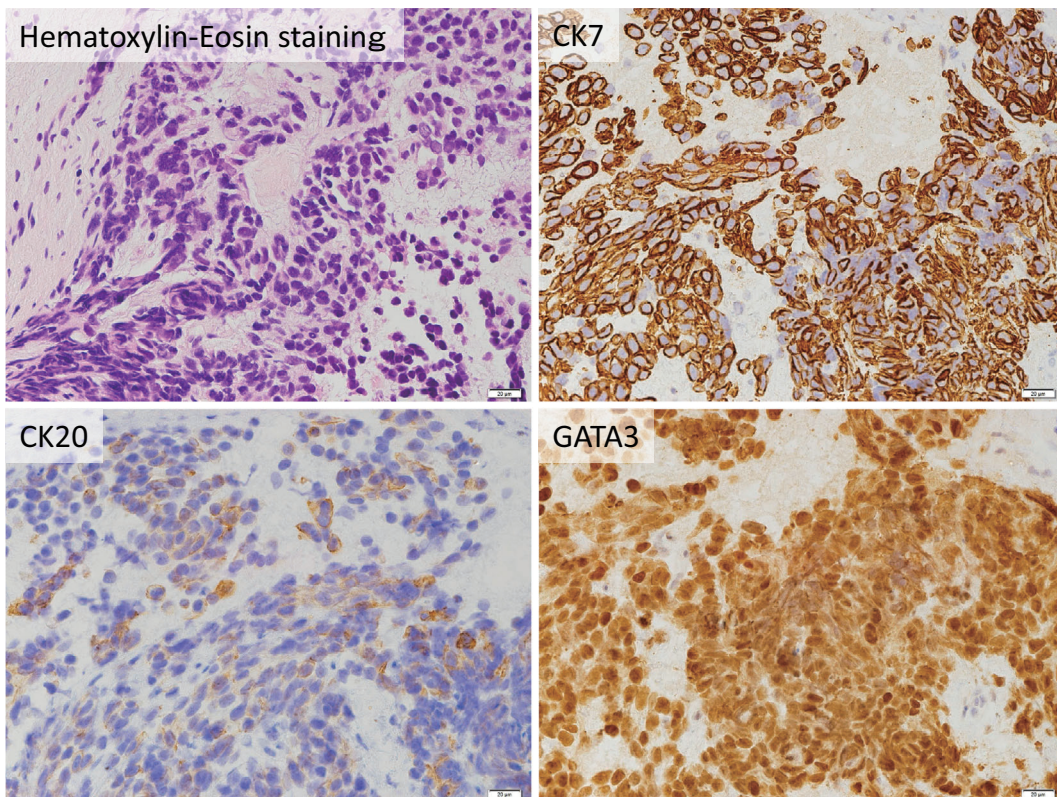


Figure 5. The histopathological examination of the tumor biopsy specimens by ureteroscopy. The pathological examination revealed transitional cell carcinoma of the right ureteral tract. The immunostaining findings were as follows: CK7, positive; CK20, positive; and GATA3, positive.

Table. Reported Cases of Duodenal Stenosis with Upper Tract Urothelial Carcinoma.

No	Reference	Age	Sex	Initial symptom	Endoscopy	CT	Clinical diagnosis	Diagnosis method	The pathway to the duodenum
1	13	61	M	Dysphagia Upper abdominal pain	Generalized inflammation	Duodenal compression at horizontal part Left upper ureteric mass Left hydronephrosis	Urinary carcinoma	Laparoscopic biopsy	Direct invasion
2	14	68	F	No abdominal symptoms	Duodenal stricture with edematous mucosa	Low density areas surrounding the duodenum Bilateral hydronephrosis	Urinary carcinoma	EUS-FNA	Peritoneal dissemination
3	11	66	M	Vomiting Upper abdominal pain	Circumferential duodenal stenosis at descending part	Low density area at pancreatic head Right hydronephrosis	Groove pancreatitis	surgery	Peritoneal dissemination
4	12	83	M	Vomiting Upper abdominal pain	Circumferential duodenal stenosis at descending part	Duodenal obstruction at descending part Right hydronephrosis	Unknown primary cancer	autopsy	Lymphatic metastasis
5	Our case	59	M	Vomiting Upper abdominal pain	Circumferential duodenal stenosis at descending part with multiple red spot	Duodenal wall thickness of descending part Right hydronephrosis	Duodenal cancer	EUS-FNA	Lymphatic metastasis

M: male, F: female, CT: computed tomography, EUS-FNA: endoscopic ultrasound-guided fine needle aspiration

lial carcinoma infiltrated the walls of the bladder, rectum and duodenum. Considering the clinical course, they concluded that recurrent cancer in the bladder wall had infiltrated the rectum and duodenum as it spread widely into the retroperitoneal lymphatic vessels. On the other hand, in cases of peritoneal dissemination, cancer cells are considered to mainly be concentrated in the serosal layer of the duodenum; these cases frequently co-occur with massive ascites or pancreatic findings (11). In our present case, cancer cells seemed to be identified in the lymphatic vessels of the duodenal wall, although specimens obtained by EUS-FNA were tiny in comparison to the surgically resected specimens. These findings strongly suggested that the metastatic pathway of UTUC to the duodenum was via lymphatic dissemination.

The tumor architecture of UTUC is macroscopically categorized as either papillary or sessile. The sessile growth pattern of UTUC has been reported to be associated with a higher tumor grade, more advanced stage, lymphovascular invasion, and lymph node metastasis (16). Ricardo et al. demonstrated that the decreased expression of E-cadherin was associated with sessile architecture (17). Murakami et al. reported that the expression of N-cadherin independently predicted recurrence after radical nephroureterectomy (18). Recent studies have demonstrated that a switch from E-cadherin to N-cadherin in cancer cells plays an important role in the malignant progression by enhancing the motile and invasive potential (18, 19). These results may support that the duodenal stenosis appeared before hematuria and hydronephrosis in the present case, which showed sessile architecture.

The safety and outcomes of EUS-FNA have previously been analyzed (20-22), and its methods have been well established for sampling unexplained thickening of the esophagogastric wall and the diagnosis of linitis plastica in

cases with negative endoscopic biopsy findings (23-27). Among 10 patients with unexplained thickening of the esophagogastric wall, five were diagnosed with carcinoma (esophageal carcinoma, n=2; gastric carcinoma, n=3) without complications using EUS-FNA (25). In cases of linitis plastica, the diagnostic accuracy of EUS-FNA was 87.5% (14/16), without severe hemorrhage or perforation (27). However, few studies exist regarding the use of EUS-FNA for duodenal lesions, except for the ampulla of Vater (28, 29). Indeed, only one case report has demonstrated the usefulness of EUS-FNA in the diagnosis of undiagnosed wall thickening of the duodenum due to diffuse large B-cell lymphoma and UTUC (14). In previous reports on the diagnosis of UTUC with duodenum involvement, the diagnosis was made during surgery or autopsy because of poor mucosal change in the duodenum (11-13) (Table). In our case, EUS-FNA provided an accurate diagnosis, and we could select the appropriate treatment without the need for invasive surgical procedures. We therefore suggest EUS-FNA should be performed for the diagnosis of unexplained thickening of the duodenum in cases that meet the following criteria: 1) a conventional forceps biopsy has failed to diagnose the lesion; 2) duodenal wall thickening (>5 mm) is present; and 3) no visible interposing vessels are present on the estimated puncture line.

In conclusion, we experienced a case of UTUC with upper abdominal symptoms due to duodenal stenosis that presented before the appearance of hydronephrosis, in which EUS-FNA was useful for reaching a diagnosis. EUS-FNA can be an effective method for investigating unexplained thickening of the duodenal wall in cases with negative endoscopic biopsy findings.

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

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