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【 CASE REPORT 】

Duodenal Obstruction Caused by the Long-term Recurrence of Appendiceal Goblet Cell Carcinoid

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Abstract:
A 38-year-old Japanese man who had been diagnosed with appendiceal carcinoid and undergone ileocecal resection 8 years before presented with duodenal obstruction caused by a submucosal tumor-like appearance. He was diagnosed with long-term recurrence of appendiceal goblet cell carcinoid (GCC) with a multimorphological pattern based on the histological assessment of a duodenal biopsy and his previously resected appendix. He underwent subtotal stomach-preserving pancreaticoduodenectomy combined with resection of an ileo-colic anastomotic lesion. The GCC recurred at the nearby ileo-colic anastomosis and invaded the duodenum. This late recurrence might have resulted from the unique features of his GCC, which contained cells with different degrees of malignancy.

Key words: duodenal obstruction, goblet cell carcinoid, recurrence

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Introduction

Goblet cell carcinoid (GCC) is a rare malignant neoplasm, with over 90% of cases arising from the appendix (1-3). Despite the inclusion of carcinoid in the disease term, GCC resembles an adenocarcinoma in the pathological features rather than a neuroendocrine tumor (NET) (4). The histological hallmark of GCC is the presence of clusters or nests of neoplastic cells with goblet cell morphology, over half of which are cells with signet-ring or poorly differentiated cell morphology, a high-grade malignant component (5). A consensus regarding the optimal treatment has yet to be established because of the histological complexity and rarity of GCC.

Through this case of late recurrence, we describe the pathological characteristics of appendiceal GCC, which may help guide the proper clinical management.

Case Report

A 38-year-old Japanese man was referred to our hospital for duodenal obstruction with unidentified cause in late 2018. He had suffered from abdominal bloating and postprandial vomiting for several months before the initial consultation to the referring hospital. In his past history, he had been diagnosed with acute appendicitis and undergone appendectomy in 2010. The resected appendix had contained neoplastic cells with sparse immunopositivity of chromogranin A, synaptophysin and Ki-67 index <20% spread from the mucosal layer into the serosal adipose tissue (pT3), resulting in a diagnosis of appendiceal carcinoid. Because of the positive surgical margin, additional ileocecal resection with D3 lymphadenectomy had been performed. There had been no residual tumor in the additionally resected tissues. No manifestation of recurrence had been noted on annual computed tomography (CT) surveillance for five years without any adjuvant treatment, and no medication had been received for three years since the end of the surveillance.

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Table 1. The Results of Laboratory Workup.

Complete blood count		Serum biochemistry		Na	143 mmol/L
WBC	3.8 $\times 10^3$/μL	TP	7.2 g/dL	K	4.0 mmol/L
RBC	521 $\times 10^4$/μL	Alb	4.3 g/dL	Cl	100 mmol/L
Hb	15.8 g/dL	T-bil	0.9 mg/dL	Hormone levels	
Ht	47.2 %	AST	19 U/L	(U) 5-HIAA	1.9 mg/day
Plt	17.4 $\times 10^4$/μL	ALT	19 U/L	(S) Gastrin	397 pg/mL
Coagulation factors		LDH	166 U/L		
PT-INR	0.99	ALP	248 U/L		
APTT	26.2 s	g-GTP	9 U/L		
Tumor makers		BUN	12 mg/dL		
CEA	0.3 ng/mL	Cre	0.92 mg/dL		
CA19-9	5.8 U/mL	Amy	60 U/L		
DUPAN-2	25 U/mL	Glu	109 mg/dL		
IL-2R	427 U/mL	CRP	0.03 mg/dL		

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit,Plt: platelet, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, DUPAN-2: duke pancreatic monoclonal antigen type 2, IL-2R: interleukin-2 receptor, TP: total protein, Alb: albumin, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate Dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyltransferase, BUN: blood urea nitrogen, Cre: creatinine, Amy: amylase, Glu: glucose, CRP: c-reactive protein, Na: sodium, K: potassium, Cl: chlorine, (U) 5-HIAA; urinary 5-hydroxyindoleacetic acid, (S) Gastrin: serum gastrin

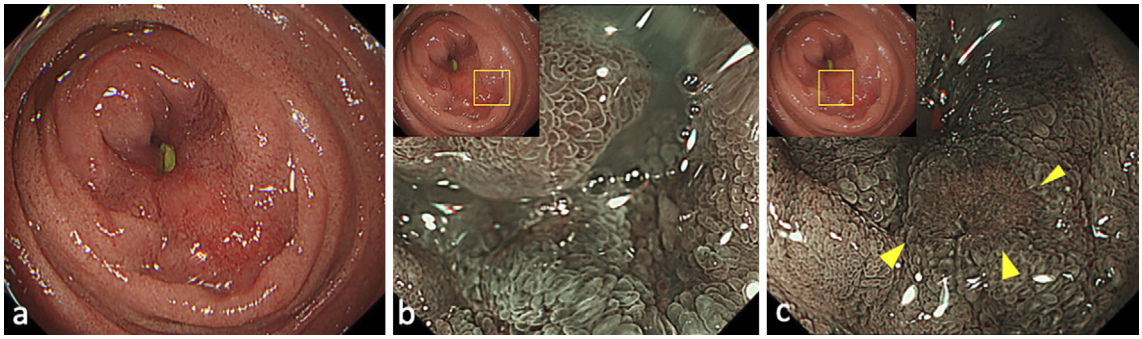

Figure 1. Endoscopic images of the duodenal obstructed lesion. White-light imaging on EGD demonstrated the circumferentially compressed lumen of the distal descending duodenum with slight ulceration (a). A magnified NBI examination showed that almost the whole surface of the obstructed lesion had elongated villous mucosa (b). In the small area adjacent to the ulcer (yellow triangle), the normal duodenal microstructure could not be identified (c). EGD: esophago-gastro-duodenoscopy, NBI: narrow-band imaging

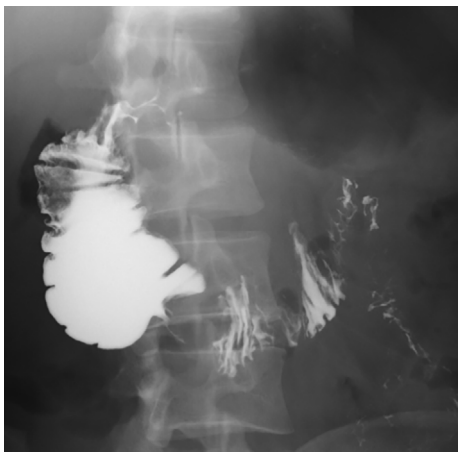

Figure 2. Hypotonic duodenography. The duodenal lumen was obstructed circumferentially at the inferior flexure.

The laboratory examination findings at our hospital were within normal limits except for a slight increase in serum gastrin levels caused by the administration of potassium-competitive acid blocker (Table 1). White-light imaging (WLI) on esophago-gastro-duodenoscopy (EGD) demonstrated that the duodenal lumen was circumferentially compressed by a submucosal tumor-like object accompanied by slight ulceration (Fig. 1). An area with an ambiguous mucosal pattern can be seen beside the ulcer. Magnified narrow-band imaging (NBI) using an H260Z endoscope (Olympus, Tokyo, Japan) revealed elongated villi without apparent irregularity of the duodenal mucosal pattern over almost the whole surface, while the area with the obscure mucosal pattern in the WLI endoscopic study revealed a demarcated appearance of the invisible microstructure. Hypotonic duodenography with water-soluble contrast medium

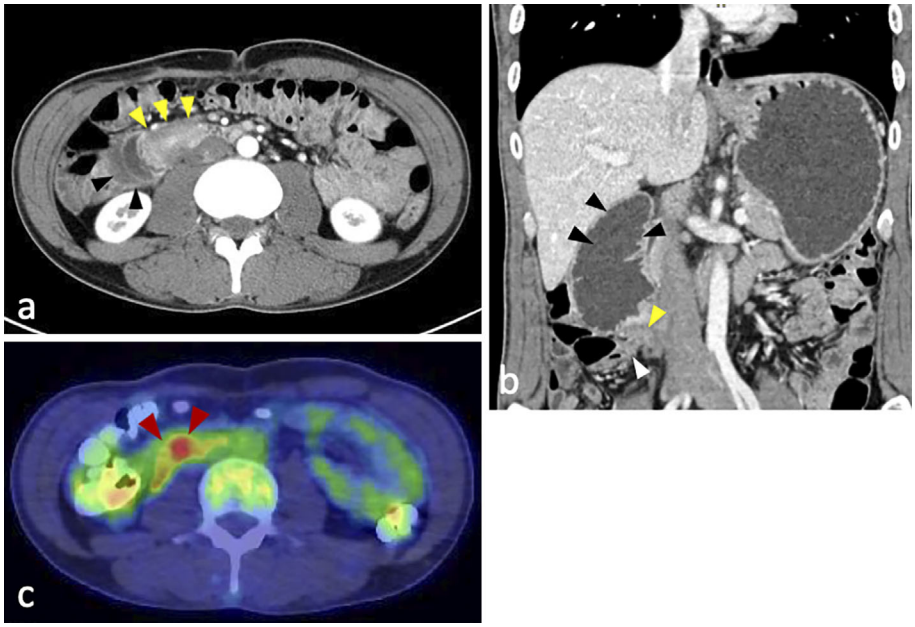

Figure 3. **The findings of contrast-enhanced CT and ^{18}F-FDG-PET/CT. The wall of the inferior duodenal was thickened and enhanced heterogeneously (yellow triangle), findings that were accompanied by dilation of the proximal duodenum (black triangle) (a: axial view). The tumor compressing the duodenum (yellow triangle) was adjacent to the proximal colon close to the ileo-colic anastomosis after ileocecal resection (white triangle) (b: coronal view). The duodenal lesion showed an increased FDG uptake (SUV_{max}=4.8) (c). No other lesions with an elevated FDG uptake were observed. ^{18}F-FDG-PET/CT: ^{18}F-fluorodeoxyglucose positron emission tomography, SUV_{max}: maximum standard uptake value**

(Gastrografin®) revealed an annular constriction with circumferential involvement of the duodenal lumen at the inferior flexure (Fig. 2). Contrast-enhanced abdominal CT showed a thickened intestinal wall in both the duodenum and adjacent colon, distal from the ileo-colic anastomosis, leading to dilatation of the proximal side of the duodenal lumen (Fig. 3). ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET)/CT showed a maximum standard uptake value (SUV_{max}) of 4.8 in this lesion. No other findings suggestive of metastasis were detected.

A pathologic review of the duodenal biopsy specimens showed the infiltration of goblet cell morphology with a signet-ring cell type that presented sparse immunopositivity of chromogranin A, synaptophysin and immunopositivity of pan-cytokeratin marker (AE1/AE3), suggesting GCC (Fig. 4). A histological re-assessment of the previously resected appendix revealed close similarity to that of the duodenum. Furthermore, the neoplastic cells of the appendix contained non-mucinous cells of undistinguished to poorly differentiated adenocarcinoma with a multi-morphological pattern. Colonoscopy showed a focal circumferential lesion with erythema and multiple small erosions at the distal part from the ileo-colic anastomosis, despite the absence of neoplastic changes in the biopsy specimens (Fig. 5).

The patient was diagnosed with duodenal obstruction caused by the focal recurrence of appendiceal GCC eight years after surgery, and he underwent subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) combined with resection of the ileo-colic anastomosis in early 2019 (Fig. 6a). The histological findings of the surgically resected tissue revealed that poorly cohesive cells with a signet-ring cell morphology had developed sequentially between the duodenal and colonic wall without dysplastic formation of the mucosal surface gland (Fig. 6). In addition to sparse immunopositivity of synaptophysin and chromogranin A, the tumor cells were positive for mucin subtype A and C (MUC 5AC) and mucin 2 (MUC2), which is characteristic of mucin in GCC (6). The Ki-67 index did not exceed 20%. The infiltration of cells just under the mucosal surface caused the duodenal glands to become sparse in the area with an ambiguous mucosal pattern on the endoscopic examination. In contrast, hemorrhaging and infiltration of inflammatory cells were found without GCC in the lamina propria mucosae of the colon. The GCC was exposed to the peritoneal cavity, and several lymph node metastases were observed, but no definitive malignancy was seen on intraoperative peritoneal lavage cytology.

Postoperatively, the patient completed the adjuvant chemotherapy regimen with six cycles of cisplatin combined with etoposide, and no signs of recurrence were observed for six months after chemotherapy.

Discussion

GCC is a type of mixed endocrine-exocrine neoplasm that is mostly seen in the appendix (1). It appears in 0.3% to

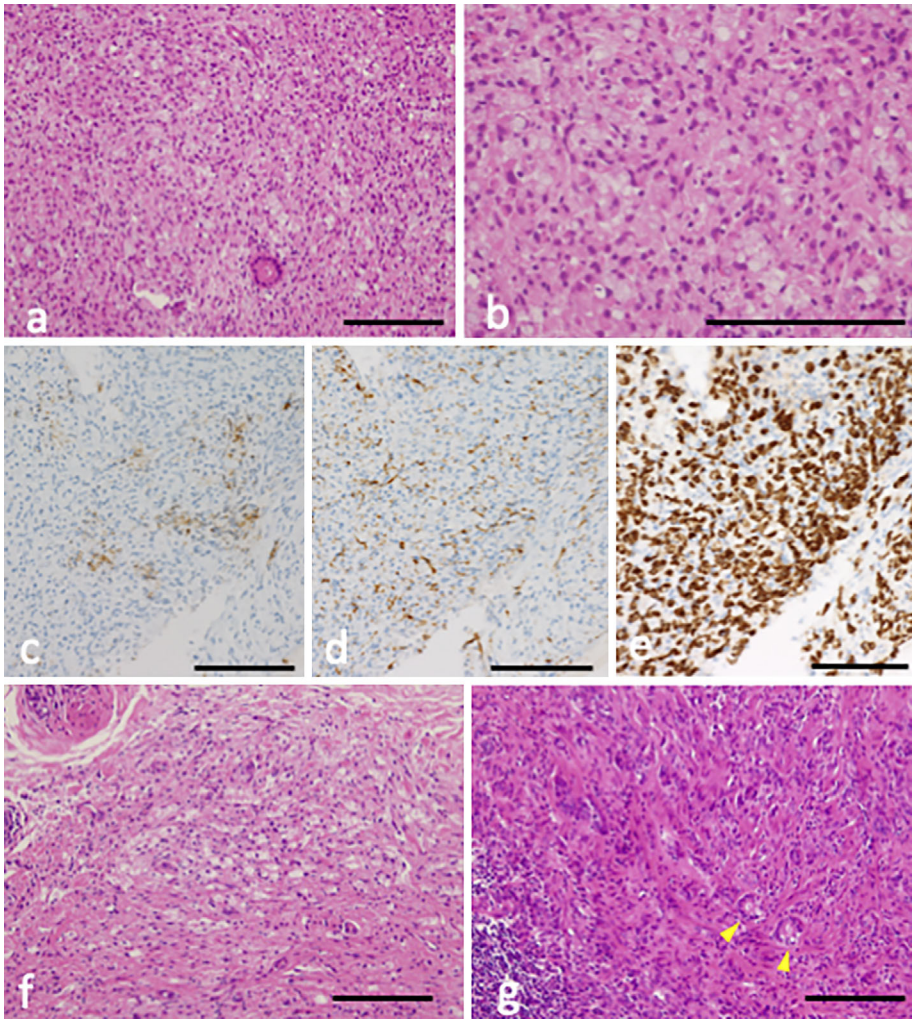

Figure 4. **The histological findings of the duodenal biopsy specimens. Atypical cells with conspicuous intracytoplasmic mucin and prominent nuclear atypia arranged in an irregular, large clusters. [a, b: Hematoxylin and Eosin (H&E) staining]. Immunostaining of chromogranin A (c) and synaptophysin (d) showed focally positivity, and pan-cytokeratin marker (AE1/AE3) (e) was positive in the tumor cells. The appendix that had been resected eight years earlier contained a cluster of cells distended by abundant mucin and compressed nuclear with ill-defined acinar (f: H&E staining) as well as infiltration of non-mucinous, poorly differentiated adenocarcinoma-type cells that formed a few gland-like structure (yellow triangle) (g: H&E staining). Bar indicates 100 μm.**

0.9% of appendectomies, accounting for 35% to 58% of all appendiceal neoplasms and about 14% of malignant neoplasms of the appendix (1-3). True extra-appendiceal GCC may be extremely rare and GCCs found in locations other than appendix could be extra-appendiceal presentations of an occult appendiceal primary (7). In many cases, GCC is diagnosed post-operatively by a histological examination after the diagnosis of acute appendicitis (2).

Although GCC has been the preferred term in the literature, the inclusion of the term "carcinoid" can cause confusion with well-differentiated NET, which might lead to inappropriate treatments (4). In addition, GCC is distinct from the type of NET termed mixed adenoneuroendocrine carcinoma (MANEC). In contrast to NET, immuno-positivity to endocrine markers is sometimes sparse, and hormone-related syndromes are unusual with GCC (8). GCC should be regarded as a variant of adenocarcinoma, although whether it is a variant of NET or a hybrid remains controversial (9, 10). GCC develops diffusely and spreads through a trans-coelomic and peritoneal route, so metastasis and recurrence to solid organs, such as the liver or lung, is uncommon (5). The general prognosis for GCC is reported to be worse than that of NET and better than that of adenocarcinoma (11).

While the 5-year survival rates for stages I, II, III and IV have been reported to be 100%, 76%, 22% and 14%, respectively, the prognosis of patients with GCC is greatly influenced by the tumor cell morphology (5, 12). The classification reported by Tang et al. divided GCC cases into group A (typical GCC, goblet cell type without apparent atypia), B (adenocarcinoma ex GCC, signet ring cell type) and C (adenocarcinoma ex GCC, poorly differentiated adenocarcinoma

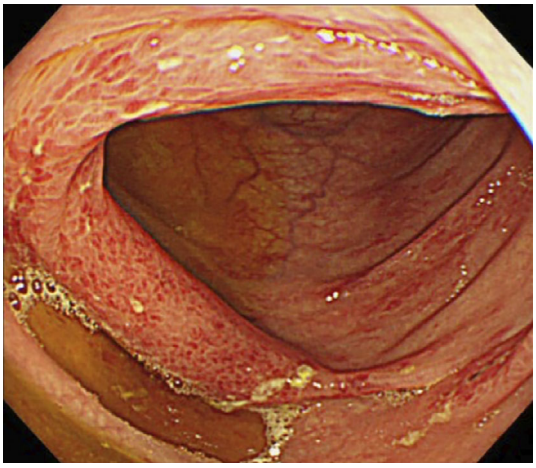

Figure 5. **Endoscopic image on colonoscopy. Edematous haustrum with erythema and multiple small erosions were observed in the proximal colon close to the anastomosis of the ileocecal resection.**

type), with the grouping correlated with the survival outcomes (5-year overall survival rates of 100%, 38% and 0%, respectively) (5). In addition, GCC often consists of mixed components of different morphological cells (13-15). DNA sequencing and histopathologic studies have revealed that the divergent cell morphology in GCC reflects various grades of differentiation with a single developmental linage, and the mixture or proportion of high-grade malignant components dictates the prognosis of patients (5, 13, 16, 17). Although the primary appendiceal GCC in the current case contained a component in group C according to Tang's classification, the remnant GCC cells might have possessed low-grade malignancy and very slow growth features, resulting in long-term recurrence.

Thus far, there has been no consensus regarding the optimal treatment for GCC. Several studies have recommended right hemicolectomy with adequate lymph node sampling for cases with tumors of higher stage than pT3 (invasion to

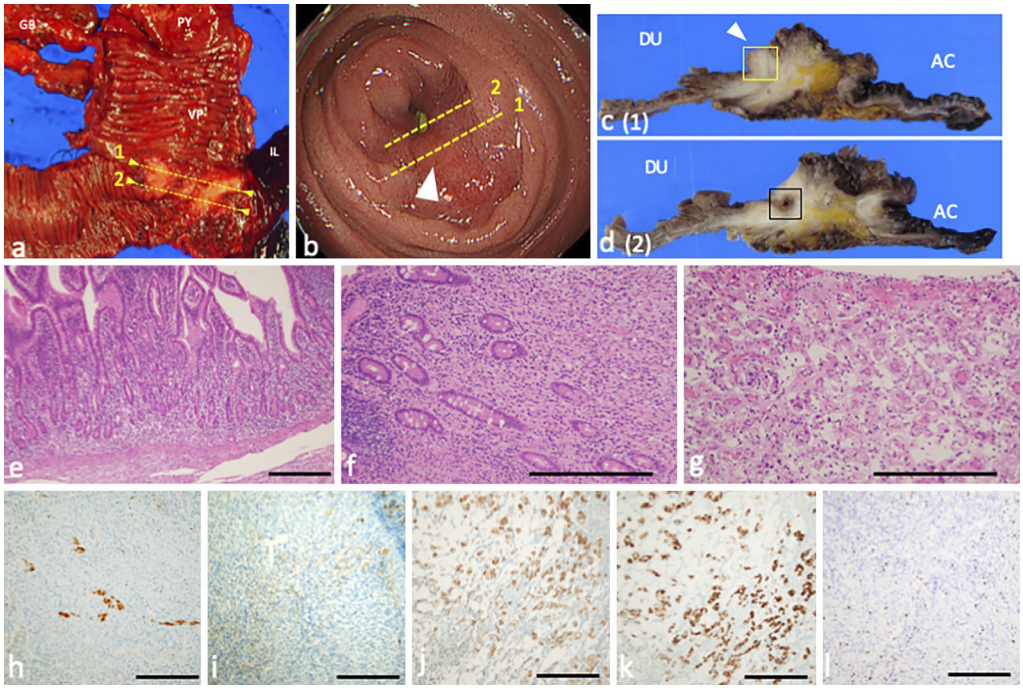

Figure 6. **A comparison among the endoscopic images, surgical specimens and histological findings. The patient underwent SSPPD combined with resection of the previous ileo-colic anastomotic region at the time of ileocecal resection (a). The duodenum was opened by cutting along the bowel, opposite the papilla of Vater. The yellow dotted line in the surgical specimen and WLI endoscopic image (b) indicates the location of the formalin-fixed specimens (c, d). The white triangle indicates the area of the fine mucosal pattern on the duodenal surface (b, c). The GCC tumor occupied the whole layer of the duodenal wall, which was connected to the colonic wall (c). There were almost no apparent mucosal abnormalities across the entire duodenal surface, and the GCC had mainly infiltrated up to the deep mucosal layer [e: Hematoxylin and Eosin (H&E) staining]. The histological findings in the magnified yellow-lined box (c) revealed that the poorly cohesive signet-ring cells had infiltrated just under the mucosal surface, which caused the duodenal glands to become sparse (f: H&E staining). The histological findings in the magnified black-lined box (d) revealed that the GCC was exposed to the duodenal surface, causing the ulceration (g: H&E staining). Immunostaining for chromogranin A (h), synaptophysin (i), MUC5AC (j), MUC2 (k) and Ki-67 (l). Bar indicates 200 μm. AC: ascending colon, DU: duodenum, GB: gallbladder, IL: ileum, PY: pylorus, VP: papilla of Vater, SSPPD: subtotal stomach-preserving pancreaticoduodenectomy, WLI: white-light imaging, GCC: goblet cell carcinoid**

Table 2. Reported Cases of GCC with Late Recurrence (over 5 Years).

Case	Age (year)/ Sex	TMN classification	Histological type of the GCC	Treatment	Recurrence free survival	Location of the recurrence	Prognosis after the recurrence (treatment)
Ref. 20	57/female	T2N0M0	Signet-ring cell	Appendectomy	9 years	Peritoneum	NA
Ref. 21	60/female	T2N0M0	Signet-ring cell	Appendectomy	24 years	Peritoneum	NA
Ref. 22	45/male	T4aN1M0	Signet-ring cell	Ileocecal resection + UFT/LV (3 months)	5 years 3 months	Peritoneum	SD for 7 months (FOLFOX)
Ref. 23	49/female	TxN0M1	Signet-ring cell	Right hemi-colectomy + ovariectomy	8 years	Uterus	NR for 2 years (surgery)
Our case	38/male	T3N0M0	Poor differentiated cell	Ileocecal resection	8 years	Ileo-colic anastomosis	NR for 1 year (Surgery/ CDDP+VP-16)

CDDP+VP-16: cisplatin+etoposide, FORFOX: folinic acid+fluorouracil+oxaliplatin, GCC: goblet cell carcinoid, UFT/LV: uracil-tegafur/leucovorin, SD: stable disease, NR: no recurrence, NA: not available

subserosa or mesoappendix), positive surgical margins observed on appendectomy or high-grade malignant type aside from typical GCC (9, 11, 13, 15). Adjuvant chemotherapy is recommended for GCC in which the tumor staging is higher than pT3 as well as in the setting of metastasis, and is likely to improve the overall survival (9, 18). Chemotherapy regimens based on 5-fluorouracil (5-FU) are commonly used (3, 11), but the effectiveness of platinum-based agents and DNA synthesis inhibitors, such as etoposide, has also been reported (19).

Because of the lack of large cohort studies, the time to relapse in GCC has not been fully evaluated. However, as with the current case, several studies have reported GCC cases with extremely slow growth or long-term recurrence despite metastasis or curable resection (Table 2) (20-23). In 4 of the 5 cases, right hemicolectomy was not performed despite the high tumor stage (>pT3) and/or mixture of high-grade malignant cells. The Ki67 index, a prognostic parameter for NET, has no prognostic value for GCC, and decisive hallmarks for malignant grading have yet to be determined (4).

We herein report a case of recurrent appendiceal GCC that obstructed the duodenum long after surgery had been performed. Given the unique histological features of GCC, extended surgical resection, such as right hemicolectomy, followed by careful surveillance may be needed to manage this neoplastic disease in cases of an advanced stage or with high-grade malignant cells.

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

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