

[CASE REPORT]

A Rare Case of Ampullary Goblet Cell Carcinoid

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Abstract:

An asymptomatic 70-year-old woman was referred to our hospital because of liver enzyme elevation. Enhanced abdominal computed tomography demonstrated a small, round-shaped tumor with dilation of the common bile duct and main pancreatic duct. A biopsy specimen from the papilla showed mucin-containing cells that were positive for endocrine markers on immunohistochemical staining. Endoscopic snare resection was done, and there was a positive vertical margin on pathology. Pancreaticoduodenectomy was then performed later. The final diagnosis was goblet cell carcinoid, pT2N0M0, pStage IIA [Union for International Cancer Control (UICC) 7th edition]. Ampullary goblet cell carcinoid is an extremely rare disease of which there have been no recent reports.

Key words: goblet cell carcinoid, papilla of Vater, neuroendocrine tumor

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Introduction

Duodenal neuroendocrine tumor (NET) accounts for only 2% of gastrointestinal NETs (1), with ampullary NET accounting for only 8% of duodenal NETs. Thus, ampullary NET is a very rare tumor. Of the duodenal NETs, atypical histological types, such as neuroendocrine adenocarcinoid, enterochromaffin, goblet, and composite histology, account for less than 0.7% of duodenal NETs (2). Since only 0.08% of all ampullary malignant tumors are ampullary goblet cell carcinoid (GCC) (3), ampullary GCC is an extremely rare tumor. There have been only two reports of ampullary GCC (4, 5).

We herein report a case of ampullary GCC treated by endoscopic snare resection, followed by additional surgical treatment because of a positive vertical margin.

Case Report

An asymptomatic 70-year-old woman was referred to our hospital because her blood tests showed elevated liver enzyme and bilirubin levels; the blood examination results at the first visit are shown in Table 1. Enhanced abdominal computed tomography (CT) demonstrated a small, round-shaped, 6-mm tumor that was enhanced during the arterial phase with a dilated common bile duct (CBD) and main pancreatic duct (MPD). (Fig. 1a and b) Contrast enhancement was prolonged until the delayed phase. There were no metastases to other organs or the lymph nodes. Magnetic resonance imaging (MRI) did not show the mass, and magnetic resonance cholangiopancreatography (MRCP) showed only the dilated CBD and MPD (Fig. 1c). Duodenoscopy showed a yellow-whitish expanded tumor similar to a submucosal tumor at the papilla of Vater (Fig. 2a). The surface of the mass appeared smooth with dilated capillaries, and erosion could be seen at the papilla of Vater. Endoscopic ul-

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trasound showed a low-echoic, round-shaped, 6-mm mass with an unclear margin (Fig. 2b and c) at the papilla of

Table 1. Blood Examination Results.

Complete blood count		Biochemistry	
RBC	463 ×10 ⁴ /μL	TP	7.3 g/dL
Hb	13.6 g/dL	Alb	3.2 g/dL
Ht	40.5 %	AST	47 U/L
WBC	6,980 /μL	ALT	78 U/L
Neutro	76.7 %	LDH	194 U/L
Eosino	2.3 %	BUN	18 mg/dL
Baso	0.5 %	Cr	0.64 mg/dL
Mono	8.8 %	γ-GTP	203 U/L
lympho	11.7 %	ALP	863 U/L
Plt	36.4 ×10 ⁴ /μL	T.Bil	2.1 mg/dL
Coagulation		D.Bil	1.4 mg/dL
APTT	29.8 s	Na	137 mmol/L
PT-INR	1.32	K	4.2 mmol/L
Tumor marker		Cl	101 mmol/L
CEA	3.0 ng/mL	Ca	8.6 mg/dL
CA19-9	33.3 U/mL	Serology	
DUPAN-2	25> U/mL	CRP	0.99 mg/dL

RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, WBC: white blood cell, Neutro: neutrophils, Eosino: eosinophils, Baso: Basophils, Mono: monocytes, Lympho: lymphocytes, Plt: platelet, CEA: carcinoembryonic antigen, CA19-9: carbohydrate antigen 19-9, DUPAN-2: pancreatic cancer associated antigen-2, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate Dehydrogenase, BUN: blood urea nitrogen, Cr: creatinine, γ-GTP: γ-glutamyltransferase, ALP: alkaline phosphatase, T.Bil: total bilirubin, D.Bil: direct bilirubin, Na: sodium, K: potassium, Cl: chlorine, Ca: calcium, CRP: c-reactive protein

Vater. The mass had not spread to the CBD and MPD. An endoscopic biopsy was done, and the pathology showed small cells with round-shaped nuclei including mucin (Fig. 3) that were positive on immunohistochemical staining for endocrine markers, and the Ki67 labeling index was < 2%. A neuroendocrine tumor was diagnosed according to the World Health Organization (WHO) 2010 classification; the mass was Grade 1.

Endoscopic snare resection was selected as the treatment based on four findings, as follows: First, the biopsy specimen showed a neuroendocrine tumor of Grade 1 according to the WHO 2010 classification. Second, the tumor had not spread to the cholangiopancreatic duct. Third, imaging showed no lymph node or distant metastases. Fourth, the tumor size was less than 10 mm. Complete en bloc resection was performed using a snare (MEDICO'S HIRATA, Tokyo, Japan) and ICC200 (ERBE, Tübingen, Germany), and the cut mode was ENDO-CUT (CUT 120W, COAG 30W) (Fig. 4). The pathological findings included tumor cells containing mucus and a round nucleus with salt-and-pepper-like chromatin (Fig. 5a-d). This was diagnosed as a goblet cell carcinoid (GCC). The horizontal margin was negative, but vascular invasion was positive, and the vertical margin was positive (Fig. 5e-g). The Ki-67 labeling index (LI) was 10%.

Given the pathological results, additional surgical treatment was performed. Pancreatoduodenectomy was done, and the surgical specimen showed a micro mucous lake in the duodenal muscularis propria, with aggregations of atypical cells with mucus, and atypical ducts suspended in the mucus were observed in a range of 800 μm. (Fig. 6). There were no lymph node metastases. The final diagnosis was pT2N0M0, pStage IIA [Union for International Cancer Control (UICC) 7th]. Two years have passed since surgery, and the patient remains alive without recurrence.

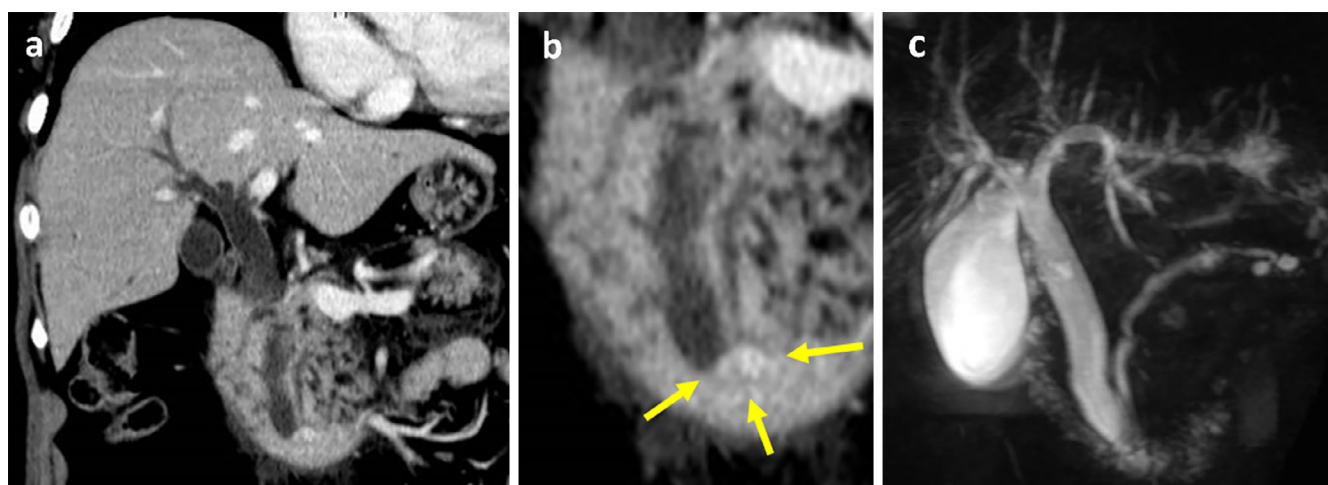


Figure 1. Imaging findings. a: Contrast CT (arterial phase): An enhanced mass is detected in the ampulla of Vater. The CBD and MPD are dilated from the ampulla of Vater. No swollen lymph nodes or distant metastases can be seen. b: Enlarged image of the ampulla of Vater. c: MRCP showing dilation of the CBD and MPD from the ampulla of Vater. CBD: common bile duct, MPD: main pancreatic duct

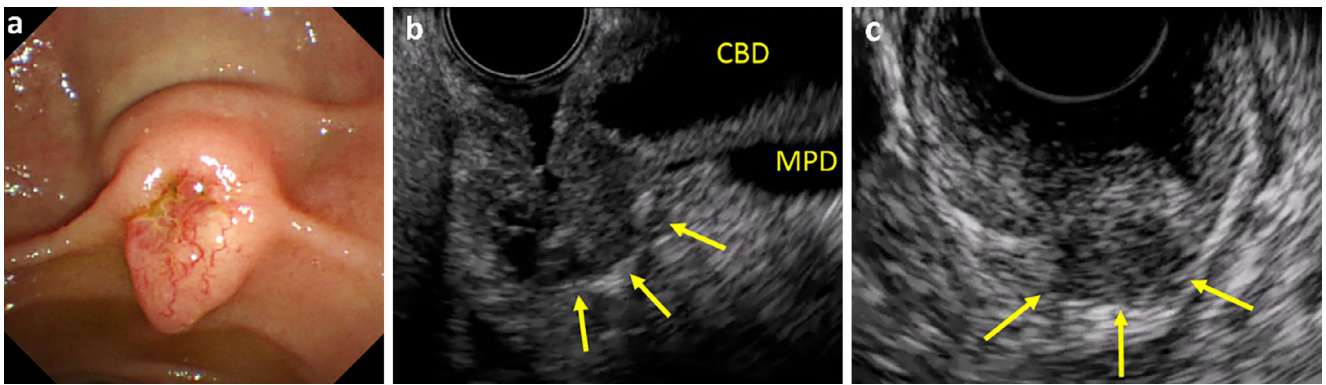


Figure 2. Endoscopic examination findings. a: Duodenoscopy shows a tense, yellowish-white tumorous lesion consistent with the duodenal papilla. Its surface is covered with a normal mucous membrane with dilated capillary vessels, and erosion of the greater duodenal papilla is seen. b: Endoscopic ultrasound (convex), c: Endoscopic ultrasound (radial): A low-echoic, round-shaped, 6-mm mass with an unclear margin is seen in the ampulla of Vater. The mass has not spread to the CBD and MPD. CBD: common bile duct, MPD: main pancreatic duct

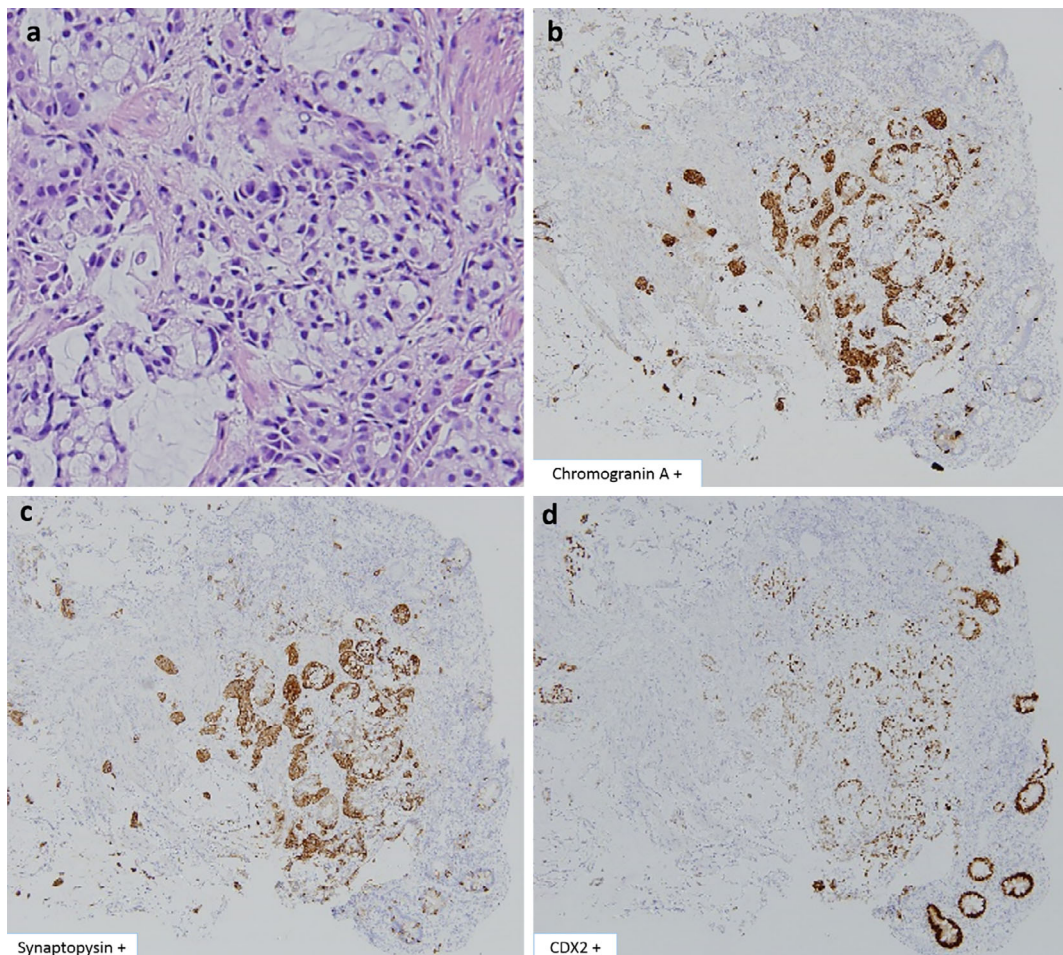


Figure 3. Histopathological findings of the tumor. a: A component in which cells with a small round nucleus are growing in solid fashion and a component that grows with mucus production are seen. (Hematoxylin and Eosin staining). b to d: Immunohistochemical: Chromogranin A (+); synaptophysin (+); CDX2 (+).

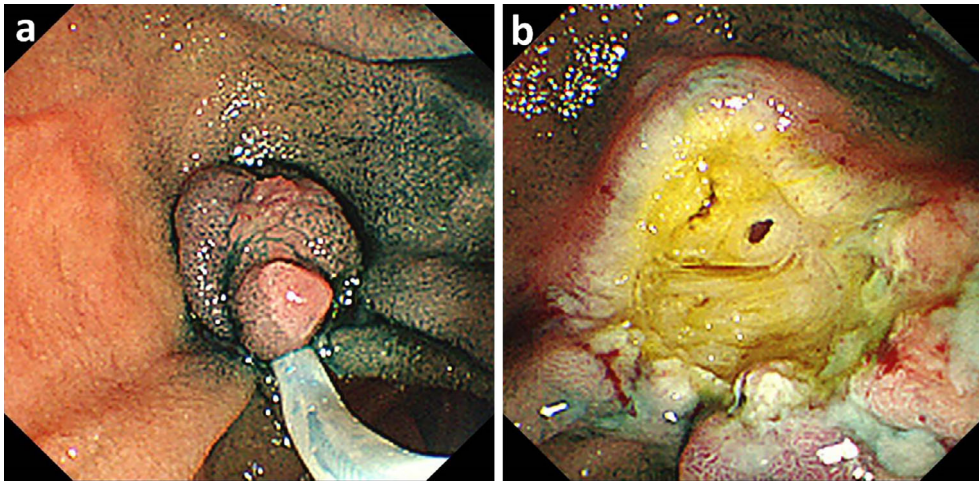


Figure 4. Endoscopic snare resection. a, b: Complete en bloc resection using a snare (MEDICO'S HIRATA, Tokyo, Japan) and ICC200 (ERBE, Tübingen, Germany), with cut mode ENDO-CUT (CUT 120W, COAG 30W).

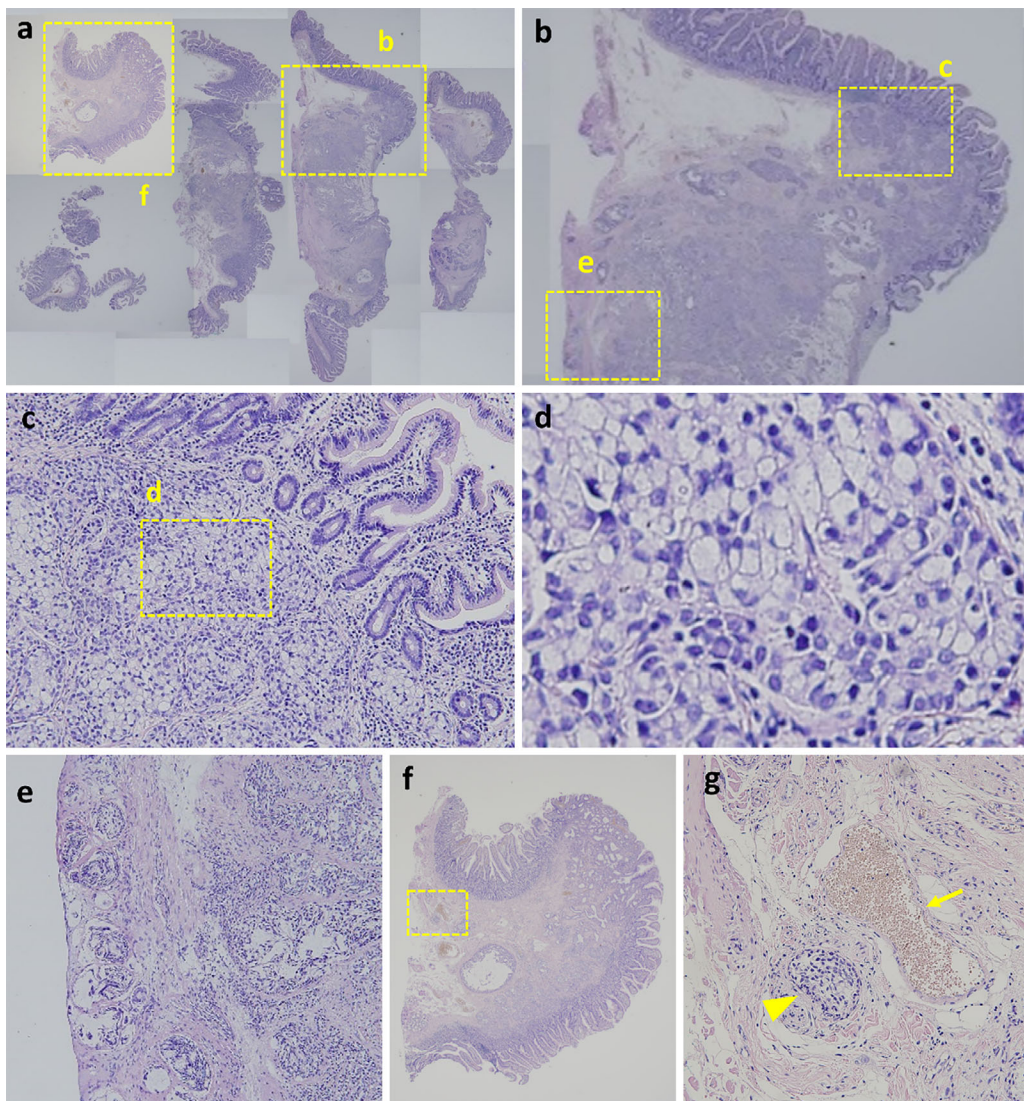


Figure 5. The resected specimen of endoscopic snare resection (Hematoxylin and Eosin staining). a to d: Mucus-containing tumor cells with a round nucleus showing salt and pepper-like chromatin are seen. e: The vertical margin is positive. f, g: There is the possibility of vascular and lymphatic duct invasion. Cluster of tumor cell (arrow head) can be seen around vein (arrow) very closely.

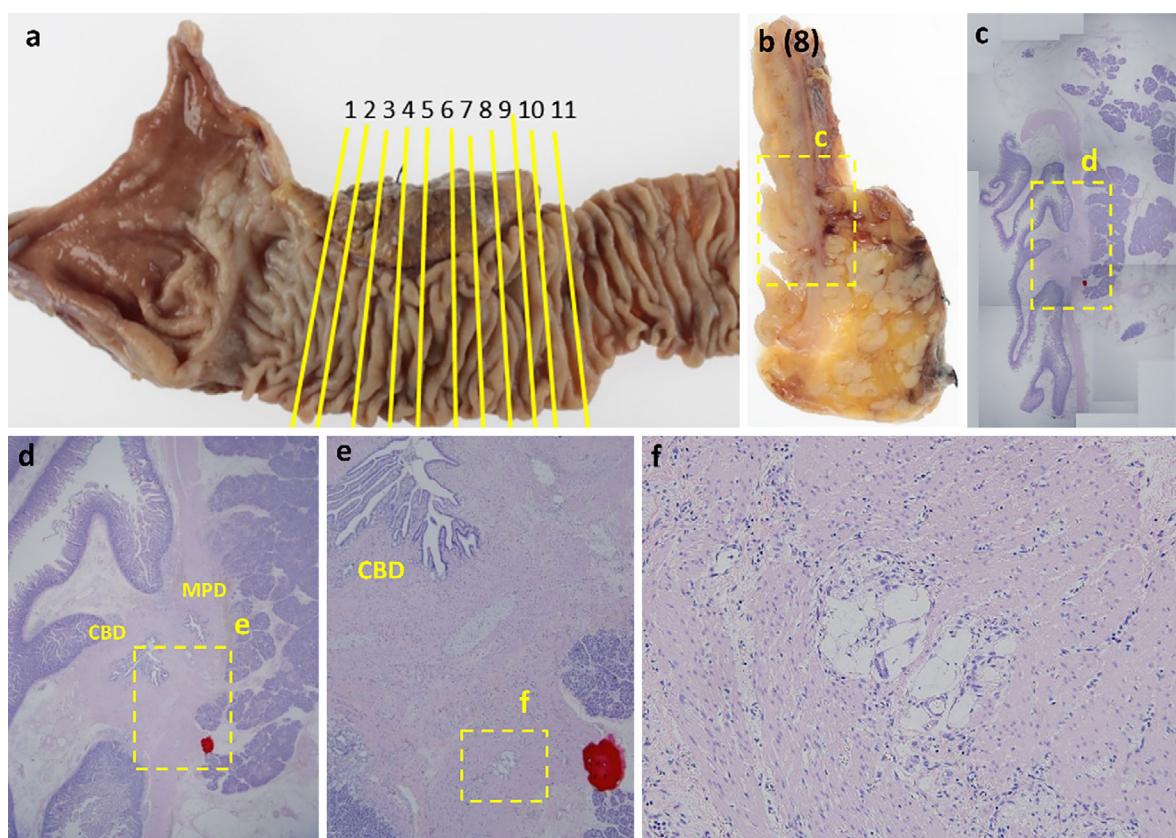


Figure 6. The resected specimen of pancreaticoduodenectomy. **a, b:** Scar of the snare resection. **c to f:** Micro mucous lake is found around the common duct in the duodenal muscularis propria, suggesting residual tumor tissue. Aggregations of atypical cells with mucus, and atypical ducts suspended in the mucus are observed in a range of about 800 μm (Hematoxylin and Eosin staining).

Discussion

The present case of GCC originating from the papilla of Vater is an extremely rare case. GCC is a subtype of NET, typically arising from the appendix. Histopathologically, GCC is composed of mucus-producing cells, such as goblet-like cells and/or signet ring-like cells, and endocrine cells, and sometimes also cancer cells showing differentiation into Paneth cells. These cells coexist in various ratios and present as carcinomas that grow into small, solid alveolar-, cord-, or duct-like forms. While GCCs differentiate into epithelial tumors, they are special tumors in that they have dual properties, since they also contain endocrine granules.

GCC was first reported by Warkel et al. in 1978 in three patients with tumors of the appendix that contained foci rich in enterochromaffin cells and mucus-producing ductal structures (6). The definition of GCC was uncertain for a time, being reported by various names, such as GCC, mucinous carcinoid tumor, mucous-secreting carcinoid tumor, crypt cell carcinoma, mucin-producing carcinoid, argyrophilic mucin-secreting adenocarcinoma, composite carcinoid, and composite carcinoma-carcinoid (5). For this reason, although the degree of malignancy was previously unknown, it is now

known to be between that of carcinoid and adenocarcinoma, but closer to adenocarcinoma (7, 8). GCC is included in the WHO 2010 pathological classification as a subtype of mixed adenoneuroendocrine carcinoma (MANEC) originating from the appendix, gallbladder, and extrahepatic bile ducts (9). Because of the tumor location, the present tumor was diagnosed as consistent with the subtype of MANEC originating from extrahepatic bile ducts. The clinicopathological features of GCC are summarized in Table 2.

Ampullary NETs behave more aggressively than those located elsewhere in the duodenum, with a high frequency of poorly differentiated tumors, marginal lymph node metastases, and distant metastases. The median overall survival of patients with ampullary NETs is shorter than that of patients with proximal small bowel NETs (2). However, on comparison with only locally resected cases, no significant difference was observed in the overall survival (median overall survival 100 vs. 171 months; hazard ratio 1.37, 95% confidence interval 0.76-2.48, $p=0.291$). This means that, although ampullary NET has high overall malignancy compared to duodenal non-papillary NET, in only localized cases, the same prognosis as in duodenal non-papillary NET can be obtained by local treatment. The imaging findings of ampullary NETs are fairly obvious if a round-shaped tumor

Table 2. Clinicopathological Features of Goblet Cell Carcinoid.

Common site	Appendix
Frequency	Appendix: less than 1% of appendectomy specimens (19, 20) Other site: the detail is unknown
Pathological findings	The tumors consist of uniform nests of mature-looking goblet cells arranged in small smooth-bordered cell nests, small tight cellular clumps, cellular rosettes, and signet ring cells. Most cells contain abundant intracytoplasmic mucin; smaller numbers of endocrine cells with finely granular eosinophilic cytoplasm are also normally present, as are Paneth cells (21).
Treatment	Resectable case: Surgery (optimal procedure is not decided) Unresectable case: Systemic chemotherapy (optimal regimen is lacking. The optional regimen is similar to colorectal adenocarcinoma)
Prognosis	Intermediate between NETs and adenocarcinoma. It leans a little to the adenocarcinoma (7, 8)

is seen in the ampulla of Vater. However, a previous report noted that the average size of ampullary NETs at the time of the diagnosis was 23 mm, and 66% (47/71) of all cases were less than 20 mm in size (10). These small tumors may be difficult to detect by CT or magnetic resonance imaging (MRI). Typically, ampullary NETs are visualized as round-shaped, hypoechoic lesions with clear borders on endoscopic ultrasound (11-14). The findings in the present case differed from the typical findings, instead showing a small hypoechoic lesion with an unclear border. This unclear border made it difficult to distinguish whether the findings were the mass or the papilla of Vater itself, and there were no distinctive findings that were correlated with the mucus lake of GCC.

The European Neuroendocrine Tumor Society (ENETS) consensus guidelines published in 2016 recommend surgical treatment for ampullary NETs, regardless of the size (15). Even though the recommended surgical method is pancreaticoduodenectomy, this method is far too invasive for small, localized tumors. A review of duodenal papillary NET (10) reported that, if the tumor diameter is ≤ 20 mm with no lymph node and/or distant metastases, adequate treatment results can be achieved simply by local surgical excision and lymph node dissection, with a survival rate of 90%. The same paper reported that, even for tumors ≤ 20 mm, liver or lymph node metastasis was confirmed in 47% of cases, almost all of which were described as lymph node metastases. These results support our belief that there is no doubt that surgical treatment with lymph node dissection should be considered as the basic treatment approach.

However, there have been several case reports of endoscopic snare resection (11-13) and endoscopic submucosal dissection (14) for localized ampullary NETs. These 4 cases were 7 to 20 mm in size, and pathologically complete en bloc resection was achieved in all cases. The WHO tumor grade classification was G1 in two cases, G2 in one, and unknown in one. These cases are alive without recurrence at a follow-up of 6 to 24 months. The long-term prognosis is un-

known, but even from the viewpoint of the postoperative quality of life (QOL) in the elderly and those anticipated to be unable to tolerate surgery, we believe that minimally invasive endoscopic papillectomy can be a treatment option, as long as there are no lymph node or distant metastases. The above review (10) stated that lymph node metastases were seen in 39% of cases. However, a 2015 investigation (16) of nine cases of papillary NET found no metastases in G1 cases. In contrast, metastases were observed in 25% of G2 cases (1/4). In one patient with metastasis, the Ki-67 LI was as high as 18%. All G3 cases (3/3 cases) were positive for lymph node metastases. The factors predictive of the presence of potential lymph node and distant metastases will need to be identified in order to select cases of papillary NET for which endoscopic papillectomy can be performed.

The present case needed additional surgical treatment after endoscopic resection because of a positive vertical margin. The first biopsy specimen showed that the tumor cells contained mucin and were positive for endocrine markers. These findings suggested a special type of tumor. The ENETS 2016 consensus guidelines recommend that GCC of the appendix be treated as adenocarcinoma (17, 18). Assuming that GCC is an atypical neuroendocrine tumor that has high malignant potential, pancreaticoduodenectomy should be selected as the first-line treatment. Indeed, following the additional resection in the present case, a micro mucous lake in the duodenal muscularis propria, aggregations of atypical cells with mucus, and atypical ducts suspended in the mucus were observed in a range of 800 μ m on a pathological examination. Since these areas of micro invasion and metastases cannot be accurately evaluated before treatment, we recommend surgical treatment for ampullary GCC.

Extra-appendiceal GCC or tumors with similar histological findings are extremely rare, especially since there have been only two case reports of ampullary GCC in the English literature (4, 5). The present case and the two previous cases are summarized in Table 3. In each case, the tumor was de-

Table 3. Review of the Literature of Ampullary GCC.

3-1 Clinical findings						
Reference	Year	Age	Gender	Symptom	Treatment	Outcome
4	1989	64	Female	Abdominal discomfort, jaundice	surgery	alive (35 months)
5	1998	63	Female	Abdominal pain, jaundice, body weight loss	surgery	alive (24 months)
Our case	2016	70	Female	Jaundice	Endoscopic papillectomy→surgery	alive (24 months)

CT	MRCP	EUS
NE	NE	NE
No mass Dilation of pancreatic and biliary ductal system	NE	NE
Hyper vascular, round shaped mass Dilation of pancreatic and biliary ductal system	Dilation of pancreatic and biliary ductal system	Low echoic lesion with unclear border

3-2 Pathological findings					
Reference	HE	Tumor size	Immunohistochemistry	Ki67LI (%)	Mitotic counts (HPF)
4	The predominant pattern was small, tightly packed tubuloglandular structures, focally transition from tubuloglandular to goblet cell differentiated was seen.	15 mm	Chromogranin+, Carcinoembryonic antigen+ Cynaptophysin-	NE	rare
5	The tumor predominantly displayed an acinar and trabecular pattern. Focally there was mucin production with scattered goblet cells present.	15 mm	Chromogranin+, neurospecific enolase+	NE	NE
Our case	A component in which cells with a small round nucleus are growing in solid fashion and a component that grows with mucus production are seen	6 mm	Chromogranin+ Synaptophysin+ CDX2+	10	4/10

tected while it was still small due to symptoms from bile duct obstruction. Furthermore, all cases underwent surgical treatment, with no recurrence after surgery. These results suggest that the early detection of such tumors due to symptoms from obstruction of the biliary and pancreatic ducts contributes to a good prognosis despite the high malignant potential.

We herein reported a subtype of NET that occurred in the ampulla of Vater. GCC has several specific clinicopathological features, and physicians must learn to recognize such findings in order to select the appropriate treatment.

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

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