[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 (CBD) and main pancreatic duct (MPD). 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. Pancreatoduodenectomy was then performed later. The final diagnosis was goblet cell carcinoid, pT2N0M0, pStage IIA (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, 1b) 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 ultrasonography

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showed a low-echoic, round-shaped, 6-mm mass with an un-
clear margin (Fig. 2b and c) at the papilla of 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 neuroen-
docrine tumor was diagnosed according to the 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 speci-
men 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 tu-
mor size was less than 10 mm. Complete en bloc resection
was performed using a snare (MEDICO’S HIRATA INC,
Tokyo, Japan) and ICC200 (ERBE, Tübingen, Germany),
and the cut mode was ENDO-CUT (CUT 120W, COAG 30
W) (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 treat-
ment 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. 6a-f). There were
no lymph node metastases. The final diagnosis was pT2N0
M0, pStage IIA (UICC 7th). Two years have passed since
surgery, and the patient remains alive without recurrence.

**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 pre-
sent as carcinomas that grow into small, solid alveolar-

### Table 1. Blood Examination Results.

<table>
<thead>
<tr>
<th>Complete blood count</th>
<th>Biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC 463 ×10⁴/μL</td>
<td>TP 7.3 g/dL</td>
</tr>
<tr>
<td>Hb 13.6 g/dL</td>
<td>Alb 3.2 g/dL</td>
</tr>
<tr>
<td>Ht 40.5 %</td>
<td>AST 47 U/L</td>
</tr>
<tr>
<td>WBC 6,980 /μL</td>
<td>ALT 78 U/L</td>
</tr>
<tr>
<td>Neut 76.7 %</td>
<td>ALD 194 U/L</td>
</tr>
<tr>
<td>Eosin 2.3 %</td>
<td>BUN 18 mg/dL</td>
</tr>
<tr>
<td>Baso 0.5 %</td>
<td>Cr 0.64 mg/dL</td>
</tr>
<tr>
<td>Mono 8.8 %</td>
<td>γ-GTP 203 U/L</td>
</tr>
<tr>
<td>lymph 11.7 %</td>
<td>LAP 863 U/L</td>
</tr>
<tr>
<td>Ptt 36.4 ×10⁴/μL</td>
<td>T.Bil 2.1 mg/dL</td>
</tr>
<tr>
<td>Coagulation</td>
<td>D.Bil 1.4 mg/dL</td>
</tr>
<tr>
<td>APTT 29.8 sec</td>
<td>Na 137 mmol/L</td>
</tr>
<tr>
<td>PT-INR 1.32</td>
<td>K 4.2 mmol/L</td>
</tr>
<tr>
<td>Tumor marker</td>
<td>Cl 101 mmol/L</td>
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<tr>
<td>CEA 3.0 ng/mL</td>
<td>Ca 8.6 mg/dL</td>
</tr>
<tr>
<td>CA19-9 33.3 U/mL</td>
<td>Serology</td>
</tr>
<tr>
<td>DUPAN-2 25&gt; U/mL</td>
<td>CRP 0.99 mg/dL</td>
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</table>

**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 dilata-
tion of the CBD and MPD from the ampulla of Vater
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.

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 (H&E) 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 INC, 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 (H&E 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 (H&E staining).

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 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 pancreatoduodenectomy, 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 unknown, 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, pancreatoduodenectomy 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 μm 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 detected 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.

<table>
<thead>
<tr>
<th>Table 2. Clinicopathological Features of Goblet Cell Carcinoid.</th>
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<tbody>
<tr>
<td><strong>Common site</strong></td>
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<tr>
<td>Frequency</td>
</tr>
<tr>
<td>Pathological findings</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Prognosis</td>
</tr>
</tbody>
</table>
Table 3. Review of the Literature of Ampullary GCC.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Age</th>
<th>gender</th>
<th>Symptom</th>
<th>treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>1989</td>
<td>64</td>
<td>Female</td>
<td>Abdominal discomfort, jaundice</td>
<td>surgery</td>
<td>alive (35 months)</td>
</tr>
<tr>
<td>5</td>
<td>1998</td>
<td>63</td>
<td>Female</td>
<td>Abdominal pain, jaundice, body weight loss</td>
<td>surgery</td>
<td>alive (24 months)</td>
</tr>
<tr>
<td>Our case</td>
<td>2016</td>
<td>70</td>
<td>Female</td>
<td>Jaundice</td>
<td>Endoscopic papillectomy—surgery</td>
<td>alive (24 months)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CT</th>
<th>MRCP</th>
<th>EUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Dilatation of pancreatic and biliary ductal system</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Hyper vascular, round shaped mass</td>
<td>Dilatation of pancreatic and biliary ductal system</td>
<td>Low echoic lesion with unclear border</td>
</tr>
</tbody>
</table>

3-2 Pathological findings

<table>
<thead>
<tr>
<th>Reference</th>
<th>HE</th>
<th>Tumor size</th>
<th>Immunohistochemistry</th>
<th>Ki67LI (%)</th>
<th>Mitotic counts (HPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>The predominant pattern was small, tightly packed tubuloglandular structures, focally transition from tubuloglandular to goblet cell differentiated was seen.</td>
<td>15mm</td>
<td>Chromogranin+, Carcinoembryonic antigen+, Cytanophysin-</td>
<td>NE</td>
<td>rare</td>
</tr>
<tr>
<td>5</td>
<td>The tumor predominantly displayed an acinar and trabecular pattern. Focally there was mucin production with scattered goblet cells present.</td>
<td>15mm</td>
<td>Chromogranin+, neurospecific enolase+</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Our case</td>
<td>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</td>
<td>6mm</td>
<td>Chromogranin+ Synaptophysin+ CDX2+</td>
<td>10</td>
<td>4/10</td>
</tr>
</tbody>
</table>

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

References


