INTERNAL MEDICINE

Gangliocytic Paraganglioma of the Minor Papilla of the Duodenum

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Abstract

A duodenal polyp was found during a health check of a 71-year-old asymptomatic man. Duodenoscopy demonstrated a pedunculated, smooth-surfaced tumor of 18 mm in size, protruding from the minor papilla. Endoscopic ultrasonography demonstrated a homogeneously low-echoic submucosal tumor. Enhanced computed tomography and magnetic resonance imaging demonstrated a well-enhanced duodenal tumor without obvious metastasis. A tumor biopsy revealed a well-differentiated neuroendocrine tumor, and laparotomic transduodenal polypectomy with regional lymph node dissection was performed. The histology of the surgical specimen revealed gangliocytic paraganglioma consisting of three cell types: endocrine, ganglion, and spindle cells. There has been no recurrence in >5 years after surgery.

Key words: gangliocytic paraganglioma, duodenum, minor papilla, diagnosis, treatment, prognosis

Introduction

Gangliocytic paraganglioma (GP) is a rare nonepithelial tumor mostly located in the 2nd and 3rd portion of the duodenum. There is a wide distribution in the age of the patients (15-84 years), with a slight predominance of males (114:76) (1). The biological behavior of GP is less aggressive when limited to the submucosal layer; however, GP sometimes extends beyond the submucosa and metastasizes to the lymph nodes and the liver (1). Death is reported to occur after the progression of the disease (2).

The GP tumor is histologically composed of three tissue types: endocrine cells, ganglion cells, and spindle cells. Many theories have been proposed with respect to the histogenesis of GP, but there is currently no satisfactory explanation. To date, GP of the duodenal major papilla has been reported in a large number of cases, whereas that of the minor papilla is quite rare. We herein describe the case of a patient with a GP protruding from the minor papilla who was suc-cessfully treated by laparotomic window surgery (3).

Case Report

A 71-year-old man was referred to Shizuoka Cancer Center Hospital for the investigation of a duodenal polyp that was detected during upper gastrointestinal endoscopy, which was performed for a health check. The patient had no specific symptoms. The histology of a forceps biopsy specimen taken at the previous hospital showed only a normal duodenal mucosa with Brunner glands. He had a smoking habit (20 cigarettes per day) and a history of hypertension, but no history of obvious melena or abdominal pain. With regard to his family history, his father had duodenal cancer and his mother had lung cancer. The laboratory data on admission demonstrated mild renal dysfunction [BUN, 21.0 mg/dL (normal range, 6-20 mg/dL); creatinine, 1.09 mg/dL (normal range, 0.61-1.04 mg/dL)] and an increased level of serum urinary acid [9.8 mg/dL (normal range, 3.7-7.0 mg/dL)]. The serum levels of various hormones (gastrin, insulin, and

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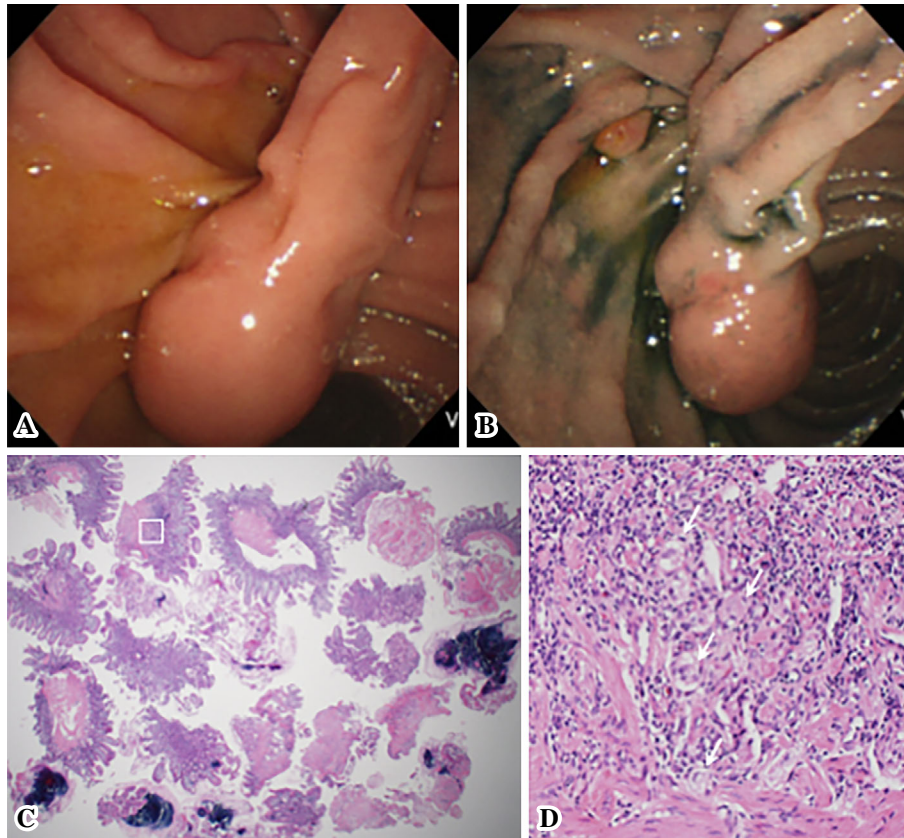
Figure 1. An endoscopic view of the duodenal tumor. An upward directed view showing a submucosal tumor with a smooth surface and a long stalk (A). An overhead view after spraying with indigo carmine shows the major papilla at the anal side of the stalk root (B). Forceps boring biopsies of the tumor, which were performed 22 times (C) [Hematoxylin and Eosin (H&E) staining, ×12.5], demonstrated a very small number of ganglion-like cells infiltration (D) [H&E staining, ×200; corresponding to the white square in (C)].
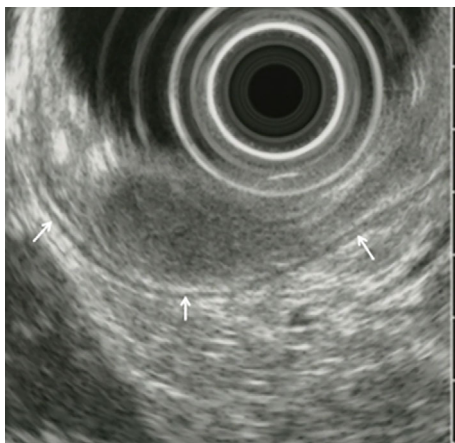

Figure 2. Endoscopic ultrasonography (EUS) showing a homogeneously low-echoic duodenal polyp of 17 mm in size, and the intact muscular propria of the duodenum (arrows).

vasoactive intestinal peptide) and tumor markers [carcinoembryonic antigen (CEA): 1.6 ng/mL (normal: ≤5.0 ng/mL), cancer antigen (CA) 19-9: ≤2.0 U/mL (normal: ≤37 U/mL), neuron-specific enolase (NSE): 7.1 ng/mL (normal: ≤10 ng/mL), and pro-gastrin-releasing peptide (proGRP): 46.1 pg/mL (normal: <70 pg/mL)] were within the normal ranges.

Duodenoscopy demonstrated a pedunculated tumor with a smooth surface, at the duodenal minor papilla (Fig. 1A and B). The histological examination of multiple boring biopsies (Fig. 1C and D) of the tumor showed the infiltration of ganglion-like cells, which were positive for chromogranin-A and synaptophysin. Endoscopic ultrasonography demonstrated that a tumor of 17 mm in size located within the submucosa with a homogeneously low echoic interior (Fig. 2). Enhanced computed tomography (CT) and magnetic resonance image (MRI) (Fig. 3A-C) demonstrated the marginal enhancement of the tumor, but no metastasis. Diffusion-weighted MRI showed a high-intensity signal within the tumor (Fig. 3D). Magnetic resonance cholangiopancreatography was normal, but the Santorini's duct was not visible. ^{18}F-fluolodeoxyglucose positron emission tomography (FDG-PET) indicated no abnormal uptake in the duodenum, but the tumor was positive at the pulmonary apex area (SUV max: 3.70) (Fig. 4), which suggested malignancy. Transbronchial needle aspiration cytology and brushing cytology were performed from the left B1 branch, and revealed clusters of adenocarcinoma cells. The duodenal biopsy findings indicated that the duodenal tumor was a well-
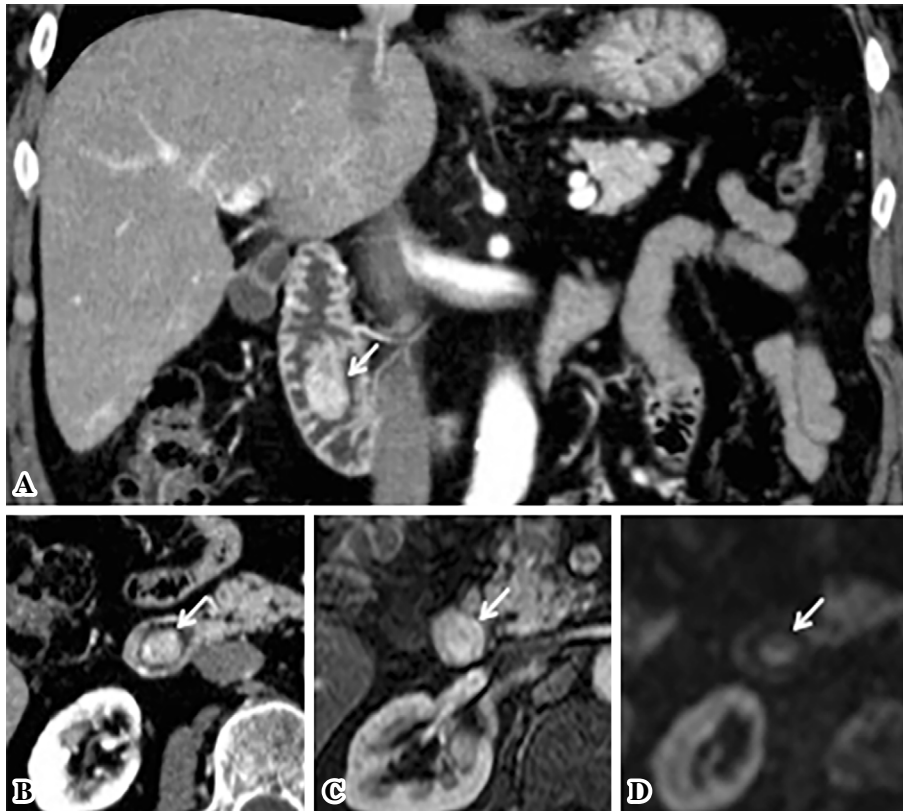
Figure 3. Cross-section images. A high vascular tumor protruding into the duodenal lumen, as depicted by enhanced computed tomography (CT) (A: coronal view, B: horizontal view) and by enhanced magnetic resonance imaging (MRI) (C). Diffusion-weighted MRI showing a high-intensity signal at the tumor (D). White arrows indicate the tumor.
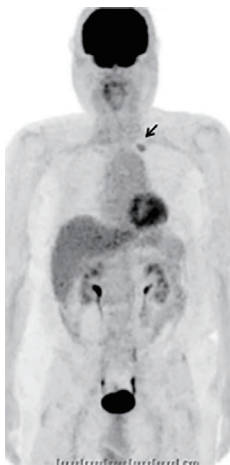

Figure 4. ^{18}F-fluolodeoxyglucose positron emission tomography (FDG-PET) showing the abnormal uptake of FDG at the apex area of the left lung.

differentiated neuroendocrine tumor (a so-called carcinoid) or a GP; hence, the lung cancer was treated first as it was a more life-threatening disease. Upper segmentectomy of the left lung was performed prior to the resection of the duodenal tumor. A surgical specimen showed a well-differentiated adenocarcinoma with a mixed bronchial-alveolar carcinoma subtype of 20 mm in size, without lymph node metastasis (0/10).

Three months after the diagnosis of the minor papilla tumor, the patient underwent laparotomic duodenal polypectomy. The tumor at the duodenal papilla was either carcinoid tumor or GP, both of which have shown the potential to metastasize to the lymph nodes, even in cases involving small tumors (1, 4, 5). Thus, regional lymph node dissection was also added. The macroscopic examination of the surgical specimen showed a whitish-yellow, well-demarcated tumor with erosion, probably corresponding to the biopsy site (Fig. 5A). The histological examination of the duodenal tumor showed a GP of 18 mm in size, which consisted of three neoplastic components: endocrine cells, spindle cells and ganglion-like cells (Fig. 5B-F). This tumor was limited to within the submucosa, the surgical margin was negative and no lymph node metastasis was detected (0/4). Immuno-histochemistry revealed that all of the tissue types in the tumor were positive for synaptophysin and NSE (Table 1). The Ki-67 labeling index of the tumor was 1.1% (number of counted cells: >1,000). The patient underwent follow-up examinations at six-month intervals. He is currently in good health today, with no evidence of recurrence at 67 months.

Discussion

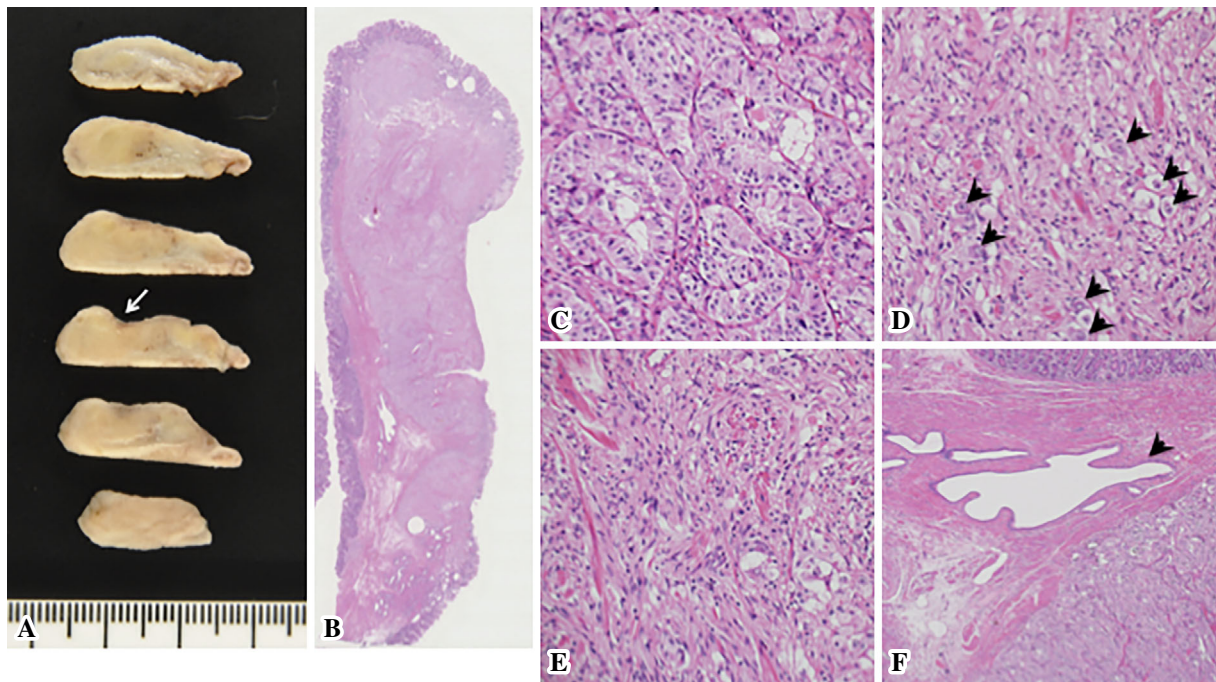GP is a rare tumor, which is mostly recognized in the

Figure 5. The histology of the resected duodenal tumor. A macroscopic view of the thin-sliced polyp demonstrating a whitish-yellow, well-demarcated tumor with an erosive area probably corresponding to the biopsy site (white arrow) (A). A loupe view of the polyp (B) [Hematoxylin and Eosin (H&E) staining]. A magnified view of the tumor histology showing three components: endocrine cells (C), ganglion cells (arrowheads) (D) and spindle cells (E) (H&E staining, ×200). Santorini's duct running alongside the endocrine tumor component (arrowhead) (F) (H&E staining, ×40).

Table 1. Immunohistochemical Findings for Each of Three Types of Tumor Component.

	Endocrine cell	Spindle cell	Ganglion-like cell
Neuron specific enolase	(++)	(++)	(++)
Synaptophysin	(++)	(+-++)	(+-++)
S-100	(+)	(++)	(+)
Chromogranin A	(+)	(-)	(-)
Somatostatin	(++)	(-)	(+)
Pancreatic polypeptide	(++)	(-)	(+)

(++): diffusely positive, (+-++): heterogeneously positive, (+): weakly and/or focally positive, (-): negative

duodenum. It rarely develops in other organs, including the esophagus, mediastinum (6), thymus (7), lung (8), and ovary (9). According to a search of the PubMed database, 45 cases of the duodenal GP have been reported during the last decade (2007-2016) (Table 2) (2, 3, 10-48). This tumor frequently develops in middle-aged and elderly individuals (mean, 51.2 years; range, 16-92 years) and predominantly affects men (27 men vs. 18 women). The major symptoms at the onset of disease were abdominal pain and melena. GP often develops in the 2nd and 3rd portions of the duodenum, especially at the major papilla of Vater (1), and usually appears as a pedunculated or polypoid, submucosal tumor, with a mean size of 26.5 mm (range, 10-50 mm) (Table 2).

GP has generally been regarded as a neuroendocrine tumor that produces a variety of hormones (1). It has been hypothesized that a hamartoma-like mechanism is involved in the development of GP from misplaced embryonic pancre-

atic tissue (1, 49, 50). Although there are only two reported cases of a GP of the duodenal minor papilla (11, 51), this theory can be compatible with the viewpoint of its favored location, as the endocrine cell micronest and (ectopic) pancreatic tissue are often recognized within the minor papilla (52). However, the high incidence in the duodenum and not the pancreas suggests that some other factors remain to be elucidated (e.g., digestive or chemical stimuli such as pancreatic juice and/or bile exposure).

A preoperative diagnosis of GP is generally difficult due to its rarity and because various other submucosal tumors, including neuroendocrine tumors, gastrointestinal stromal tumors (GISTs), smooth muscle tumors, lipomas, aberrant pancreas, Brunner gland's hyperplasia, cysts, and lymphoma, also develop in the duodenum. In addition, the reported diagnostic rate of forceps biopsy specimens is only 11% (1). In our case, the biopsy performed in the previous hospital

Table 2. **Reported Cases of Ganglyocytic Paraganglioma of the Duodenum (2007-2016, n=45).**

No.	ref.	Age	Sex	Symptom at onset	Location	Size (mm)	Macroscopic-type	Depth	LN	Treatment	Status, Follow-up period (mth)
1	10	51	M	fatigue, dyspnea	MPV	14	polypoid mass	N.A	(-)	ER	NED, 14
2	11	66	M	epigastralgia, vomitting	minor papilla	20	SMT	SM	(-)	ER	NED, 24
3	12	53	M	no symptom	2nd portion	13	pedunculated SMT	SM	N.A	ER	N.A
4	13	75	F	melena, anemia	2nd portion	40	pedunculated tumor	N.A	(-)	LapTDTR	NED, 24
5	14	38	F	abdominal pain	near MPV	15	polypoid	MP	(+)	ER → PPPD	N.A
6	15	48	M	abdominal pain	2nd portion	35	subepithelial tumor	N.A	N.A	local excision	N.A
7	16	67	M	no symptom	MPV	15	ball-like lesion	N.A	N.A	LTDR	N.A
8	17	17	F	abdominal pain, weight loss	2nd~3rd portion	N.A	mass	SS	(+)	PPPD	N.A
9	18	60s	M	no symptom	anal of MPV	25	polypoid SMT	SM	N.A	PD	NED, 12
10	19	70	F	abdominal pain	near MPV	19	polypoid mass	N.A	N.A	ER → LTDR	NED, 48
11	20	56	F	melena	MPV	25	SMT	MP	(-)	PPPD	NED, 16
12	21	61	M	epigastralgia, melena	MPV	30	lobulated SMT	MP	(+)	PPPD	NED, 6
13	22	52	M	vomitting	3rd portion	35	SMT	MP	(-)	LTDR	N.A
14	23	62	F	abdominal pain	MPV	20	polypoid mass	SM	(-)	laparotomy	NED, 12
15	24	61	M	abdominal pain, weight loss	2nd portion	15	submucosal nodule	N.A	(+)	PPPD	NED, 12
16	25	33	F	abdominal pain, vomitting	MPV	39	polypoid mass	N.A	N.A	local excision	NED, 12
17	26	16	M	melena, dyspnea	MPV	35	polypoid	MP	(+)	PPPD	NED, 36
18	27	20	F	melena, anemia	2nd portion	50	polypoid mass	MP	(-)	PPPD	NED, 11
19	28	52	F	N.A	near minor papilla	10	nodular mass	MP	(+)	PD	alive*, 27
20	29	53	M	abdominal pain, vomitting	MPV	25	SMT	N.A	(-)	LTDR	N.A$
21	30	51	F	melena, anemia	MPV	25	polypoid mass	SS	(+)	PD	NED, 96
22	31	54	F	no symptom	near MPV	15	SMT	N.A	N.A	LTDR	NED, 30
23	32	16	M	abdominal pain, weight loss	3rd portion	25	pedunculated SMT	SM	(-)	LTDR	NED, 15
24	33	67	M	melena, anemia	2nd portion	30	submucosal nodule	SM	(-)	local excision	NED, 15
25	34	57	M	abdominal pain, vomitting	MPV	30	mass	N.A	(+)	laparotomy	alive*, 8
26	35	56	F	abdominal pain, weight loss	near MPV	18	mass	N.A	(+)	PPPD	N.A
27	36	32	M	melena	2nd portion	23	SMT	SM	N.A	LTDR	N.A
28	37	92	F	jaundice	near MPV	20	SMT	SM	(-)	ER	N.A
29	38	72	F	weight loss	near MPV	37	polypoid mass	SM	(-)	local excision	NED, 17
30	2	47	M	abdominal pain	near MPV	30	mass	pancreas	(+)	PD	dead, 13#
31	39	56	F	dyspepsia	near MPV	29	subepithelial tumor	N.A	N.A	ER	NED, 6
32	"	56	F	anemia	2nd portion	50	lobulated mass	N.A	N.A	ER → LTDR	NED, 30
33	"	46	F	no symptom	MPV	N.A	enlarged papilla	N.A	N.A	ER	NED, 23
34	"	70	M	no symptom	2nd portion	20	subepithelial tumor	N.A	(-)	ER	NED, 12
35	3	50	M	abdominal pain	MPV	30	mass	SM	N.A	LTDR	NED, 36
36	40	47	M	abdominal pain	MPV	40	polypoid	pancreas	(+)	PD	NED, 24
37	41	48	M	melena, weight loss	4th portion	40	polypoid	SM	N.A	SD	NED, 24
38	42	48	M	no symptom	2nd portion	15	subepithelial tumor	SM	N.A	ER	N.A
39	43	41	F	abdominal pain	MPV	20	polypoid	SM	(-)	ER	NED, 6
40	44	38	M	hematochezia, anemia	2nd portion	15	polypoid	SM	(-)	local excision	NED, 12
41	45	70	M	no symptom	MPV	23	SMT	SM	(-)	LTDR	N.A
42	46	50	M	melena	3rd portion	25	SMT	MP	(-)	LTDR	N.A
43	47	42	M	melena, dizziness	3rd portion	30	polypoid	SM	N.A	local excision	not followed
44	"	49	M	abdominal pain	MPV	40	mass	pancreas	(+)	PD	NED, 36
45	48	45	M	abdominal pain, melena	MPV	15	mass (pedunculated)	SM	(+)	LTDR	alive, 3**

F: female, M: male, LN: lymph node metastasis, MPV: major papilla Vater, ER: endoscopic resection, PD: pancreaticoduodenectomy, PPPD: pylorus-preserving pancreaticoduodenectomy, NED: no evidence of disease, SMT: submucosal tumor, SM: submucosa, MP: muscular propria, SS: subserosa, LapTDR: laparoscopic transduodenal resection, LTDR: laparotomic transduodenal resection, SD: segmental duodenectomy, *alive with liver metastasis, **alive with regional lymph node recurrence, $accompanied with esophageal adenocarcinoma, #died of disease with metastasis to the pelvis and liver

was not diagnostic, and our biopsy demonstrated only a small number of infiltrating ganglion-like cells, despite the fact that we performed repeated sampling 22 times (Fig. 1C and D). Hence, when only a spindle cell component is obtained, it may be diagnosed as a GIST, while it might be diagnosed as a neuroendocrine tumor when only an endocrine cell component is found. The EUS findings are important for the differential diagnosis as well as for determining the extent of the tumor. The difference in tumor size can be subtle between cases with (29.8 mm) and without (23.5 mm) lymph node metastasis. Nevertheless, the ratio of lymph node metastasis differs significantly in tumors that are located within the submucosa (2.4%, 1/42) and those that extend beyond the submucosa (16.7%, 11/66)(p< 0.05) (1). A preoperative EUS examination is therefore critical for deciding suitable treatment.

Our treatment of an 18-mm neuroendocrine tumor or a tumor that is located at the minor papilla is to perform an open transduodenal resection with regional lymph node dissection, as this operation results in a good prognosis. As mentioned above, a small size is not a definitive factor for predicting lymph node metastasis. According to a summary by Park et al. (5), up to 36% (8/22) of tumors of ≤2 cm in size had lymph node metastasis. Even in cases of carcinoid tumors, a small size does not guarantee that there will be no metastasis (4). Although the overall survival after tumor resection is favorable (1, 5), progressive disease with recurrence and tumor-associated death have been reported for this tumor (2, 14, 53). Hence, in our case, despite the tumor's small size, the EUS finding of the tumor extent (within the submucosa) and the absence of regional lymph node swelling (as determined by preoperative CT), we selected a laparotomic transduodenal operation, which enabled us to perform a local tumor resection as well as regional lymph node dissection. If the tumor had appeared to extend beyond the submucosa or if lymph node metastasis was suspected, we would have selected pancreatoduodenectomy.

In conclusion, GP should be listed as a differential diagnosis of duodenal submucosal tumors, especially tumors with a pedunculated shape. GP often develops at the major Vater and rarely at the minor papilla. Surgical resection must be carefully performed, while keeping the risk of

lymph node metastasis in mind.

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

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