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ORIGINAL ARTICLE

Periampullary Gangliocytic Paraganglioma

Ching-Shu Chiang[1] · Bor-Uei Shyr[1] · Shih-Chin Chen[1] · Yi-Ming Shyr[1] · Shin-E Wang[1]

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Abstract

Background Gangliocytic paraganglioma (GP) is rare and difficult to be differentiated from other periampullary neoplasms. The clinical characteristics and optimal treatment of periampullary GPs have not been clarified.

Methods The data pool for the analysis comprised of cases of periampullary GP encountered in our institution and sporadic cases reported in the English literature.

Results A total of 117 cases with periampullary GP were studied, including 2 from our institute, and among them, duodenal GP was the most common (53.0%). GP size ranged from 0.7 to 19.0 cm, with a median of 2.2 cm. The most common presenting symptom for overall periampullary GPs was epigastric pain in 49.5% cases, followed by gastrointestinal bleeding in 35.4% cases. Most (84.1%) of the periampullary GPs were benign, whereas 15.9% were malignant. Metastasis was noted in 26.3% of periampullary GPs, with 14.5% showing lymph node metastasis and 1.8% showing liver metastasis. Of the periampullary GP cases included, 30.1% were treated with pancreaticoduodenectomy, 40.6% with local excision, and 17.7% with endoscopic resection.

Conclusions Periampullary GP should be considered as a tumor with malignant potential. Endoscopic resection is the treatment of choice for most of the duodenal GPs, whereas pancreaticoduodenectomy is recommended for GPs with possible malignancy, such as large size, with submucosal invasion, or pancreatic GP.

Keywords Gangliocytic paraganglioma · Gastrointestinal bleeding · Periampullary

Introduction

Gangliocytic paraganglioma (GP) is an extremely rare neoplasm originating in the hindgut, predominantly arising in the second part of the duodenum, with rare local recurrence or metastasis to regional lymph nodes.[1–4] GP was first reported as duodenal ganglioneuroma by Dahl et al.[5] in 1957. Based on the features this tumor has in common with both paraganglioma and ganglioneuroma, the term "gangliocytic paraganglioma" was coined by Kepes and Zacharias[6] in 1971. This tumor could often be misdiagnosed as grade 1 (G1) neuroendocrine tumor (NET). However, patients with GP usually have a better prognosis than those with NET. Thus, it is important to differentiate GP from NET.[7]

Accurate diagnosis using small biopsy specimens obtained from an endoscopic procedure or before surgical intervention has been reported to be extremely difficult.[2,8] The key to diagnosis is to identify the characteristic histological picture, which typically consists of triphasic cellular components, i.e., the neuroendocrine component (paraganglioma-like or carcinoid-like), ganglion cell component (ganglion cell-like), and spindle cell component with Schwannian differentiation.[1–4,9–11] Many theories have been proposed with respect to the histogenesis of GP. Some authors have reported that GP is a hamartoma developing in misplaced embryonic pancreatic tissue. Despite these investigations, the origin of GP remains unclear.[1,9,12]

GP is often mistaken for other periampullary neoplasms, such as adenoma and gastrointestinal stromal tumor (GIST) because of its rarity. The purposes of this study were to present our clinical experience with periampullary GPs and to analyze an expanded sample size by adding cases from the literature to our pool of study cases. Thus, an attempt was made to clarify the characteristics, clinical presentations, and management of periampullary GPs. This research method can provide an up-to-date key to decipher the periampullary GPs that have never been studied together before in literature.

✉ Shin-E Wang
sewang0408@gmail.com

[1] Division of General Surgery, Department of Surgery, Taipei Veterans General Hospital, National Yang Ming University, 201 Section 2 Shipai Road, Taipei 112, Taiwan

Materials and Methods

A brief description was made for each case of GP encountered at our institute between 2010 and 2017. Individualized data of GP cases from the periampullary region described in English literature were extracted and added to our database to determine the characteristics of periampullary GP and expand the study sample size for a more complete analysis. Two methods were utilized to search for relevant cases in the literature. First, a computerized search was performed on the PubMed electronic database, covering data from 1971 to 2017 to identify the relevant articles in English pertaining to periampullary GP in the literature. The following keywords were used for the PubMed search: gangliocytic paraganglioma, periampullary, duodenal, ampullary, pancreatic and common bile duct (CBD). Second, the reference lists of PubMed-selected periampullary GP articles were screened systematically for additional studies of interest. A total of 83 related articles were selected for the study.[1–4,6–83] Cases without individualized data and duplicate cases reported in literature were excluded from the analysis. The data pool from the related literature and our patients' cases was analyzed to determine the characteristics of periampullary GP including demographics, tumor size, diagnostic methods, presenting symptoms, pathology, metastasis, treatment modality, and outcomes. These data were also used to make comparisons between periampullary GP groups including duodenal, ampullary, pancreatic, and distal CBD GP.

Statistical analyses were carried out using Statistical Product and Service Solutions (SPSS) version 21.0 software (SPSS Inc., IBM, Armonk, NY, USA). Continuous data were presented as median and mean ± standard deviation, and frequencies were presented as appropriate to the type of the data. The mean values of continuous variables were compared with a two-tailed Student's t test or one-way analysis of variance (ANOVA). Non-parametric statistical tests were used if the variables did not follow normal distribution. Categorical variables were presented as numbers and percentages and were compared using Pearson's χ^2 test or Fisher's exact test contingency tables. For all analyses, a P value < 0.050 was considered statistically significant.

Results

A total of 117 cases with periampullary GP were studied, including 62 (53.0%) cases of duodenal GP, 33 (28.2%) cases of ampullary GP, 16 (13.7%) cases of pancreatic GP, and 2 (1.7%) cases of distal CBD GP. Two cases were from our institute. The first patient from our institute was a 58-year-old female presenting with no symptom, but a polypoid lesion was incidentally found along the posterior wall of the duodenum on endoscopy during a physical examination. Endoscopic ultrasound showed a submucosal tumor, suggestive of gastrointestinal stroma tumor or lipoma. Endoscopic biopsy showed chronic inflammation. Magnetic resonance imaging revealed a polypoid lesion about 2 cm in size along the posterior wall of the junction of the first and second portions of the duodenum, without local invasion or regional lymphadenopathy. Dynamic study showed strong arterial enhancement, indicating hypervascularity of the tumor (Fig. 1). Transduodenal local resection was performed without any complication. The resected surgical specimen showed a submucosal, gray to white mass, 2.8 × 2.6 × 1.3 cm, with mucosal ulceration. Microscopic examination revealed a picture of gangliocytic paraganglioma, with three components: (1) a neuroendocrine component with eosinophilic or amphophilic cytoplasm and uniform ovoid nuclei arranged in ribbons, solid nests, or pseudoglandular structures; (2) a spindle cell component with fascicles and strongly positive for S-100 stains; and (3) a ganglion cell component with pale nuclei and prominent nucleoli. The patient survived for 9 years without any evidence of recurrence. Our second patient, a 41-year-old female, presented with tarry stool for 2 weeks. The endoscopy revealed a protruding ampullary tumor with ulceration and bleeding (Fig. 2), and biopsy was reported to be tubular adenoma. Pancreaticoduodenectomy revealed a pedunculated, polypoid gray tumor, 1.5 × 0.8 cm at the ampulla of Vater. The pathology showed a picture of gangliocytic paraganglioma with a triphasic pattern consisting of neuroendocrine cells, spindle cells, and ganglion cells. The patient survived for 1 year without recurrence.

Table 1 lists the pooled data for demographics and clinical presentations of periampullary GP. There was no sex predilection for the periampullary GP, with 49.6% cases being male and 50.4% being female among all patients. The median age for the overall periampullary GP was 56 years, ranging from 15 to 92 years. The size of the GP ranged from 0.7 to 19.0 cm with a median of 2.2 cm for overall GP. There was a significant difference in size among the periampullary GPs, with a median of 2.2 cm for duodenal GP, 2.0 cm for ampullary GP, 4.0 cm for pancreatic GP, and 15.0 cm for distal CBD GP, $P < 0.001$. The most common presenting symptom for the overall periampullary GPs was epigastric pain in 49.5%, followed by gastrointestinal bleeding in 35.4%, and no symptom in 20.2%. Gastrointestinal bleeding was more common in duodenal (43.9%) and ampullary GP (37.5%) than in pancreatic GP (6.3%) and distal CBD (0%), $P = 0.031$. Obstructive jaundice was noted in 8.1% of the overall periampullary GPs, with 1.8% in duodenal GP, 25.0% GP, 0% pancreatic GP, and 50% distal CBD GP, $P < 0.001$.

Endoscopy (77.3%) was the most commonly tool used for diagnosis of periampullary GP (Table 2). Most (84.1%) of the periampullary GP were benign, whereas 18 (15.9%) cases were malignant among all the cases, with 8 (12.9%) cases of duodenal GP, 6 (18.2%) of ampullary GP, 3 (18.8%) of

Fig. 1 Magnetic resonance imaging (MRI) reveals a polypoid lesion about 2 cm along the posterior wall of the junction of the first and second portions of the duodenum without local invasion or regional lymphadenopathy. **a** True fast imaging with steady-state precession (TrueFISP) coronary MRI showed a well-circumscribed polypoid mass. **b** Fat sat T1-weighted imaging (T1WI). **c** Pre-contrast T1WI MRI. **d** Contrasted T1WI MRI showing strong arterial enhancement, indicating hypervascularity of the tumor

pancreatic head PG, and 1 (50%) of distal CBD. There is no predilection for the location of malignant GP, with 16.7% being malignant vs. 13.7% being benign GPs in the pancreatic head ($P = 0.7180$). The size of the malignant GP was not significantly different from that of benign GP, with a median of 2.7 cm vs. 2.1 and a mean of 3.9 ± 3.5 vs. 2.9 ± 2.4, $P = 0.124$. Metastasis was noted in 26.3% of the overall cases, with 14.5% cases showing lymph node metastasis and 1.8% showing liver metastasis. Among all the cases of periampullary GP, 30.1% were treated with pancreaticoduodenectomy, 40.6% with local excision, and 17.7% with endoscopic resection. Most (62.9%) of the duodenal GP underwent local excision, whereas 48.5% ampullary GPs and 56.3% pancreatic head GPs underwent pancreaticoduodenectomy, $P < 0.001$. Survival time was available for analysis only in 13 cases of malignant periampullary GP. The median survival time was 12 months (5–96 months) among patients with periampullary GP, 10 months (6–30 months) for those with duodenal GP, 30 months (5–96 months) for those with ampullary GP, and 24 months (12–36 months) for those with pancreatic head GP. Accumulative 1-year, 3-year, and 5-year survival was 100%, 83.3%, and 55.6% respectively among patients with periampullary GP. One-year survival was 100% for patients with duodenal GP, ampullary GP, and pancreatic head GP.

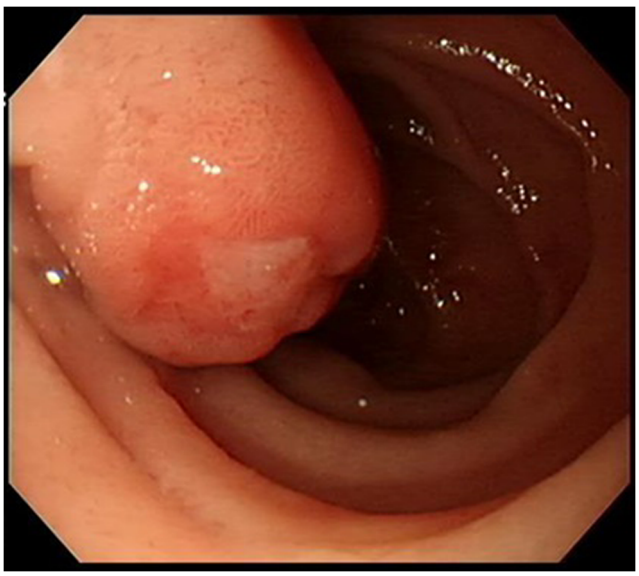

Fig. 2 Endoscopic finding of a protruding ampullary tumor, about 2 cm, with ulceration

Discussion

GP can be listed in the differential diagnosis of periampullary tumors, especially those that are pedunculated polypoid tumor as was seen in the 2 cases from our institute.[12,59] Among the periampullary GPs, duodenal GP was the most common (53.0%), followed by ampullary GP (28.2%), pancreatic GP (13.7%), and distal CBD GP (1.7%) according to this study. In addition, GP can be found in other organs, such as the respiratory system, low-level spinal cord, jejunum, esophagus, and appendix.[2] Extremely rare cases of GP in the stomach, ileum, mediastinum, and thymus have also been reported.[2,13,15] However, periampullary GP is seldom recognized preoperatively because it is rare. The diagnosis using biopsy specimens has been considered extremely difficult. The diagnostic rate reported using a biopsy before surgical intervention was only 11–16.7% (10/60) in the literature,[2,3,12] and GP could be misdiagnosed as gastrointestinal stromal tumor, neuroendocrine tumors, smooth

Table 1 Demographics and clinical presentations of periampullary gangliocytic paraganglioma (GP)

	Total GP	Duodenal GP	Ampullary GP	Pancreatic head GP	Distal CBD GP	*P* value
Cases	113	62 (53.0%)	33 (28.2%)	16 (13.7%)	2 (1.7%)	
Sex						0.167
Male	56 (49.6%)	32 (51.6%)	19 (57.6%)	5 (31.3%)	0	
Female	57 (50.4%)	30 (48.4%)	14 (42.4%)	11 (68.8%)	2 (100%)	
Age (y/o)						0.062
Median (range)	56 (15–92)	56 (16–74)	56 (15–92)	57 (19–85)	30 (28–32)	
Mean ± SD	55.0 ± 14.3	54.3 ± 13.0	57.0 ± 15.1	57.0 ± 15.8	30.0 ± 2.8	
Size (cm)	*n* = 103	*n* = 59	*n* = 29	*n* = 14	*n* = 1	< 0.001
Median (range)	2.2 (0.7–19.0)	2.2 (1.0–10.0)	2.0 (0.7–6.0)	4.0 (1.5–19.0)	15.0 (15.0–15.0)	
Mean ± SD	3.0 ± 2.6	2.8 ± 1.6	2.1 ± 1.1	5.2 ± 4.5	15.0	
Duration of symptom (month)	*n* = 49	*n* = 16	*n* = 16	*n* = 6	*n* = 2	0.641
Median (range)	3.0 (0.0–84.0)	3.0 (0.0–84.0)	1.5 (0.0–84.0)	2.5 (0.7–12.0)	1.9 (0.8–3.0)	
Mean ± SD	11.5 ± 19.0	13.6 ± 19.6	12.1 ± 22.1	4.1 ± 4.1	1.9 ± 1.6	
Symptom	*n* = 99	*n* = 57	*n* = 24	*n* = 16	*n* = 2	
No symptom	20 (20.2%)	11 (19.3%)	5 (20.8%)	4 (25.0%)	0	0.857
Epigastric pain	49 (49.5%)	27 (47.4%)	12 (50.0%)	9 (56.3%)	1 (50.0%)	0.941
Gastrointestinal bleeding	35 (35.4%)	25 (43.9%)	9 (37.5%)	1 (6.3%)	0	0.031
Epigastric fullness	1 (1.0%)	1 (1.8%)	0	0	0	0.863
Back pain	5 (5.1%)	2 (3.5%)	2 (8.3%)	1 (6.3%)	0	0.807
Body weight loss	7 (7.1%)	5 (8.8%)	1 (4.2%)	0	1 (50.0%)	0.061
Nausea/vomiting	9 (9.1%)	3 (5.3%)	5 (20.8%)	1 (6.3%)	0	0.147
Jaundice	8 (8.1%)	1 (1.8%)	6 (25.0%)	0	1 (50.0%)	< 0.001
Diarrhea	1 (1.0%)	0	0	1 (6.3%)	0	0.155
Fever	1 (1.0%)	0	0	1 (6.3%)	1 (50.0%)	0.941

N/A, not available; *AFP*, alpha-fetoprotein; *CA 19-9*, carbohydrate antigen 19-9; *CEA*, carcinoembryonic antigen

muscle tumor, ganglioneuroma, paraganglioma, carcinoid, periampullary adenoma, aberrant pancreas, Brunner gland's hyperplasia, and lymphoma.[2,3,12]

Periampullary GP occurs most commonly in the sixth decade of life, but can be seen from 15 to 92 years of age, and has no sex predilection. The median size of periampullary GPs is 2.2 cm, ranging from 0.7 to 19.0 cm. GPs of the pancreatic head (4.0 cm) are larger than those of the duodenum (2.2 cm) and the ampulla of Vater (2.0 cm). About one-fifth of the periampullary GPs present with no symptom. When present, the most common symptom for duodena and ampullary GPs is gastrointestinal bleeding, due to the ulcerated mucosa, whereas pancreatic head GPs often present with epigastric pain. GP appears as a solid and homogeneous submucosal tumor on endoscopic ultrasound, and has strong arterial enhancement on computed tomography scan and magnetic resonance images, indicating an extremely hypervascular mass. All these features could be indicative of a prospective diagnosis.[10,51]

Histologically, GPs are composed of three morphologically distinct cell components: (1) an epithelioid cell component, which is arranged in nests and gland-like structures with granular eosinophilic cytoplasm and round to oval-shaped nucleus with an inconspicuous nucleolus, and often misdiagnosed as grade 1 neuroendocrine tumor; (2) a spindle cell component, formed as slender fascicles wrapping around nests of epithelioid cells with an elongated and plump nucleus, including an attenuated eosinophilic cytoplasm without marked atypia; and (3) a ganglion cell component.[2,3,7,12,25] In this study, although most (84.1%) of the periampullary GPs were benign histologically, 16.3% presented with metastasis, 14.5% to the lymph node and 1.8% to the liver. GP should be considered as a tumor with malignant potential, rather than benign.[25] There are no known histopathologic differences between cases with or without lymph node metastasis.[14] Some authors reported that tumor size (larger than 2 cm), young age, and submucosal invasion of the tumor could be risk factors for lymph node metastasis.[1,2,8,14,15] Compared with the duodenal GPs, the pancreatic GP is claimed to be larger and have a higher incidence of metastasis, suggesting a greater potential for malignancy.[13] This is in accordance with the findings of this study. Therefore, the primary origin of GP might be also an important prognostic factor. Consequently, due to lack of validated predictive markers for malignancy and possible aggressive behavior of the tumor, long-term follow-up is recommended.[3,10,14,25]

Table 2 Pathology and treatment for periampullary gangliocytic paraganglioma (GP)

	Total GP	Duodenal GP	Ampullary GP	Pancreatic head GP	Distal CBD GP	*P* value
Diagnostic method	*n* = 88	*n* = 44	*n* = 25	*n* = 13	*n* = 2	N/A
Endoscopy	68 (77.3%)	40 (90.9%)	23 (92.0%)	4 (30.8%)	1 (50.0%)	
CT	57 (64.8%)	28 (63.6%)	15 (60.0%)	13 (100%)	1 (50.0%)	
MRI	16 (18.2%)	7 (15.9%)	7 (28.0%)	2 (15.4%)	0	
Sonography	14 (15.9%)	2 (4.5)	3 (12.0%)	9 (69.2%)	0	
EUS	26 (29.5%)	4 (9.1%)	9 (36.0%)	2 (15.4%)	0	
Other	18 (20.5%)	15 (34.1%)	2 (8.0%)	4 (30.8%)	0	
Pathology	*n* = 113	*n* = 62	*n* = 33	*n* = 16	*n* = 2	0.498
Benign	95 (84.1%)	54 (87.1%)	27 (81.8%)	13 (81.3%)	1 (50.0%)	
Malignant	18 (15.9%)	8 (12.9%)	6 (18.2%)	3 (18.8%)	1 (50.0%)	
Metastasis	*n* = 110	*n* = 60	*n* = 32	*n* = 16	*n* = 2	< 0.001
No	92 (83.6%)	52 (86.7%)	26 (81.3%)	13 (81.3%)	1 (50.0%)	
LN	16 (14.5%)	8 (13.3%)	5 (15.6%)	3 (18.8%)	0	
Liver	2 (1.8%)	0	1 (3.1%)	0	1 (50.0%)	
Treatment	*n* = 113	*n* = 62	*n* = 33	*n* = 16	*n* = 2	< 0.001
Pancreaticoduodenectomy	34 (30.1%)	9 (14.5%)	16 (48.5%)	9 (56.3%)	0	
Local excision	52 (46.0%)	39 (62.9%)	7 (21.2%)	5 (31.3%)	1 (50.0%)	
Endoscopic resection	20 (17.7%)	11 (17.7%)	9 (27.3%)	0	0	
Other	7 (6.2%)	3 (4.8%)	1 (3.0%)	2 (12.5%)	1 (50.0%)	
Survival outcomes for malignant GP	*n* = 13	*n* = 5	*n* = 6	*n* = 2	*n* = 0	
Median (range)	12 (5–96)	10 (6–30)	30 (5–96)	24 (12–36)	N/A	
Mean ± SD	25.5 ± 26.3	13.6 ± 9.5	35.8 ± 35.6	14.0 (24.0–17.0)	N/A	
1-year survival	100%	100%	100%	100%	N/A	
3-year survival	83.3%	50%	66.7%	N/A	N/A	
5-year survival	55.6%	N/A	N/A	N/A	N/A	

CT, computed tomography; *MRI*, magnetic resonance imaging; *EUS*, endoscopic ultrasound; *LN*, lymph node; *N/A*, not available

A consensus has not been reached on the standard of management of GP because of its rarity. In cases of duodenal GPs that show local disease without evidence of metastasis on preoperative imaging, endoscopic resection is the treatment of choice.[2,8–11,18] In the case of GPs with possible malignancy such as large tumor size (more than 2 cm), submucosal extent, or pancreatic origin, a more radical approach such as pancreaticoduodenectomy would be a judicious option.[2,8,13,15] The use of chemotherapy and radiation is questionable.[15]

The prognosis of GP has been claimed to be favorable, even better than grade 1 neuroendocrine tumor.[7] In this study, the 1-year, 3-year, and 5-year survival for overall malignant periampullary GPs is 100%, 83.3%, and 55.6% respectively. However, a larger sample size is needed to reach a solid conclusion regarding the prognosis of malignant GPs.

Conclusion

Duodenal GP is the most common among the periampullary GPs. Periampullary GP should be considered as a tumor with malignant potential, because metastasis could occur in some cases, although most of them are benign histologically. Endoscopic resection is the treatment of choice for the duodenal GP without evidence of metastasis, whereas pancreaticoduodenectomy is recommended for those with features suggestive of malignancy such as large tumor size, submucosal extent, or pancreatic GP.

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