Treatment and management of duodenal gangliocytic paraganglioma: A case report

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Abstract. Gangliocytic paraganglioma (GP) is a rare neuroendocrine tumor primarily found in the duodenum, most commonly in the second and third sections of the duodenum. Diagnosis of GP is based on its distinctive histopathological characteristics, which include three types of tumor cells in varying proportions: i) Epithelioid, ii) spindle-like and iii) ganglion-shaped cells. The distribution of the three tumor cell components varies from case to case and a patient may be easily misdiagnosed if one of the components is predominant. Endoscopic submucosal dissection (ESD) or surgical resection is the ideal treatment for duodenal GP (DGP); however, biotherapy, nuclide therapy, chemotherapy, targeted therapy and immunotherapy can be selected individually for patients with postoperative recurrence, metastasis or not suitable for surgery. In the present study, a male patient with DGP experienced recurrence after ESD surgery, and so received octreotide (Novartis; 30 mg/28 days) for 12 consecutive cycles. The patient had no further symptoms of gastrointestinal bleeding and no new lesions or metastases were observed after 47 months of follow-up.

Introduction

Gangliocytic paraganglioma (GP) is a markedly rare neuroendocrine tumor (NET) that was initially identified by Dahl *et al* (1) in 1957. In total, >260 cases of GP have been documented thus far worldwide. GP can arise at any age. The median age at onset is 51.2 years and a greater number of patients are male, with a male-to-female ratio of 157:104 (2). The majority of documented cases were from the second and third sections of the duodenum, particularly the duodenal ampulla around the abdomen (3), The size of GP around the ampulla ranges from 0.7 to 19.0 cm, with a median size of ~2.2 cm (4). A few cases were detected elsewhere, including the esophagus, mediastinum, pericardium, thymus and lung (5-7). GP consists of varying proportions of three types of tumor cells: i) Epithelioid, ii) ganglion-shaped and iii) spindle-like cells, and is identified by distinct histopathological and immunohistochemical markers (8). The proportion of the three tumor cell components varies from case to case and misdiagnosis is common when one cell component dominates in an individual. Duodenal GP (DGP) is typically considered a benign tumor; however, there is a certain risk of malignancy associated with it (9).

The present study describes the diagnosis and treatment of a case of DGP that reappeared after endoscopic resection, in an effort to improve the current understanding of this disease and to provide a reference for future clinical work.

Case report

The patient was a 39-year-old male with no previous underlying disease, a heavy oily and spicy diet, a history of smoking (10 cigarettes per day) and no history of alcohol intake. The patient was admitted to the Second Affiliated Hospital of Xuzhou Medical University (Xuzhou, China) in March 2020 with black stools for 3 days. The patient had tarry stools, accompanied by dizziness, palpitation and weakness of the limbs. The patient vomited coffee-colored stomach contents, fainted once and regained consciousness within a short period of time. Physical examination revealed acute anemia, a soft belly with no pressure or rebound pain and no abdominal mass.

After admission, hemoglobin was found to be 54.2 g/l (normal, 150-175 g/l), with no abnormalities in coagulation, liver or renal function, or tumor indicators. An enhanced computed tomography (CT) scan of the whole abdomen revealed a soft tissue mass, measuring ~2.7x2.4 cm, with a modest increase upon enhanced scanning (Fig. 1A). During the hospitalisation, the patient continuously vomited brilliant red blood, destooled dark red blood, and appeared to be in hemorrhagic shock; hemoglobin gradually decreased to 40 g/l. At 2-days post-admission, an emergency gastroscopy revealed a large irregular bulge in the duodenal papilla. The surface mucosa was smooth, the papillary opening was not clearly visible and an ulcer and a red thrombus head with limited

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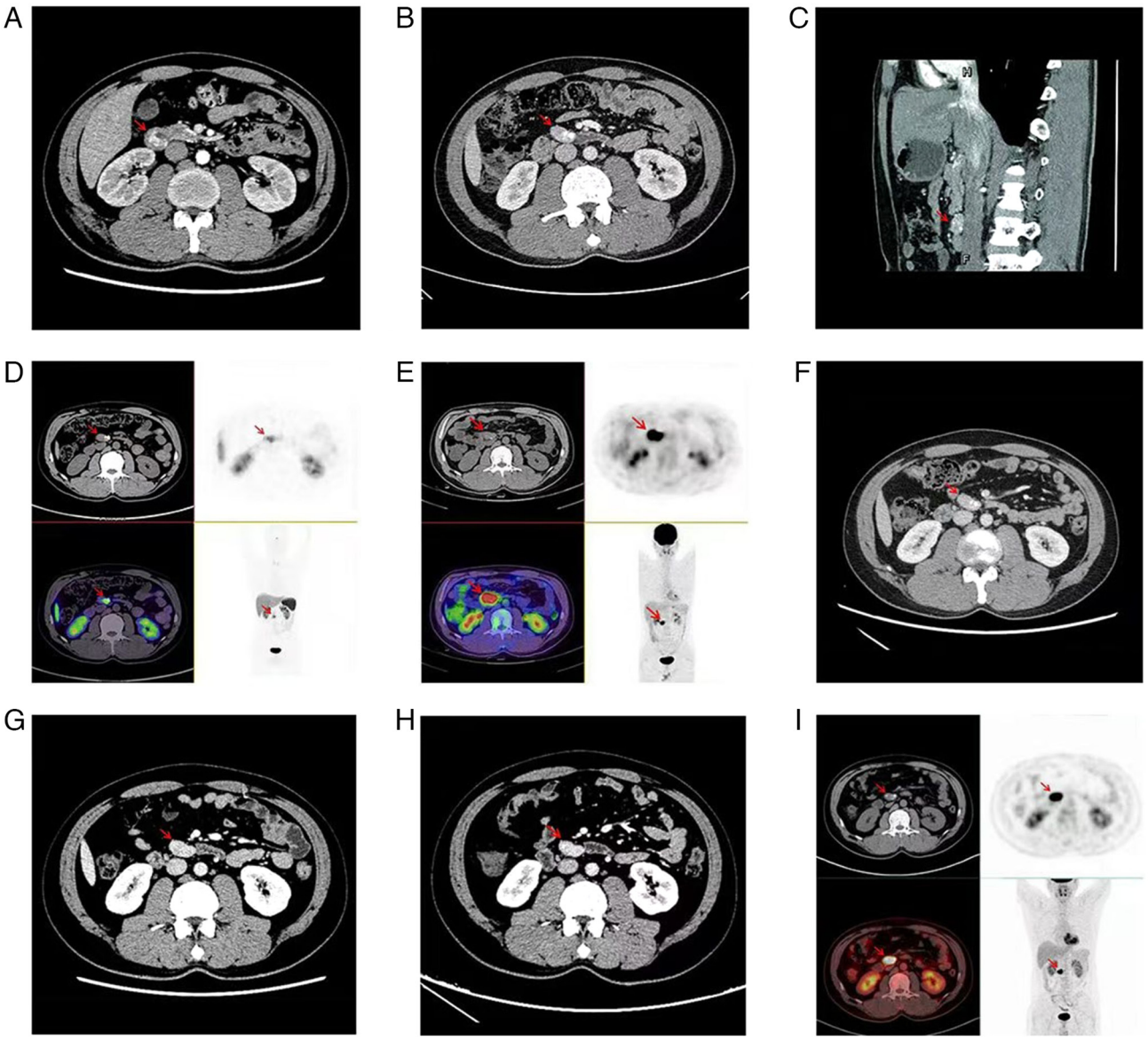


Figure 1. Imaging results of the duodenal mass corresponding to the present case report. (A) Abdominal enhanced CT (March 2020) showing a modest enhancement on enhanced scanning and a soft tissue mass in the descending section of the duodenum ~2.7x2.4 cm in size (arrow). (B) Transverse plane and (C) Sagittal plane abdominal enhanced CT (June 2020) showing a mass of 2.8x1.9 cm in the horizontal section of the duodenum, which could be a recurrence of duodenal gangliocytic paraganglioma (arrows). (D) ^{68}Ga-Dotatate and (E) ^{18}F-FDG PET-CT (June 2020) revealed a focus of considerably increased FDG uptake of ~2.9x1.9 cm in size (arrows). Punctate calcification was observed inside, as well as elevated ^{68}Ga uptake above the horizontal section of the retroperitoneal duodenum, suggesting possible metastasis or recurrence. (F-H) Abdominal enhanced CT on (F) September 2020, (G) February 2021 and (H) February 2024 revealed that the masse's size was hardly altered compared with the previous scan (arrows), and the enhancement scan showed limited enhancement. (I) PET-CT on February 2024 revealed a nodule with enhanced FDG metabolism, measuring ~2.9x1.8 cm and located above the duodenum (arrows). CT, computed tomography; PET, positron emission tomography; FDG, fluorodeoxyglucose.

bleeding were visible on the surface. A titanium clip was attached to stop the bleeding (Fig. 2A and B). After 8 days of endoscopic haemostasis, the patient's vital signs were stable, and the bleeding was temporarily controlled. The duodenoscope and endoscopic ultrasound revealed that the titanium clip had slipped off. The duodenal papilla was large, with the white submucosal tumour barely visible and bile outflowing from the papilla opening. Ultrasonography indicated that the lesion was hypoechoic, with well-defined borders and a generally uniform texture (Fig. 2C and D). Endoscopic treatment was advised in the case of DGP.

A gastroenterologist suggested performing a major surgery to remove the tumor. Following careful consideration, the patient and his family requested endoscopic treatment for the tumor. On March 20, 2020, endoscopic resection of a duodenal papilloma was performed. The operation revealed a 2.7x2.5-cm firm and smooth protrusion in the descending portion of the duodenum. The root of the tumor was ligated with a snare, and most of the tumor was mucous membrane. Electrocoagulation resection was performed in stages and pulsatile haemorrhage was discovered in a blood artery beneath the mucosa soon after cutting. To halt the bleeding, electrocoagulation forceps were used and peripheral blood vessels were treated. The procedure was successful. The wound was found to be smooth and free of tumour residue, and it was rinsed to ensure that there were no vascular residues or perforations on the surface.

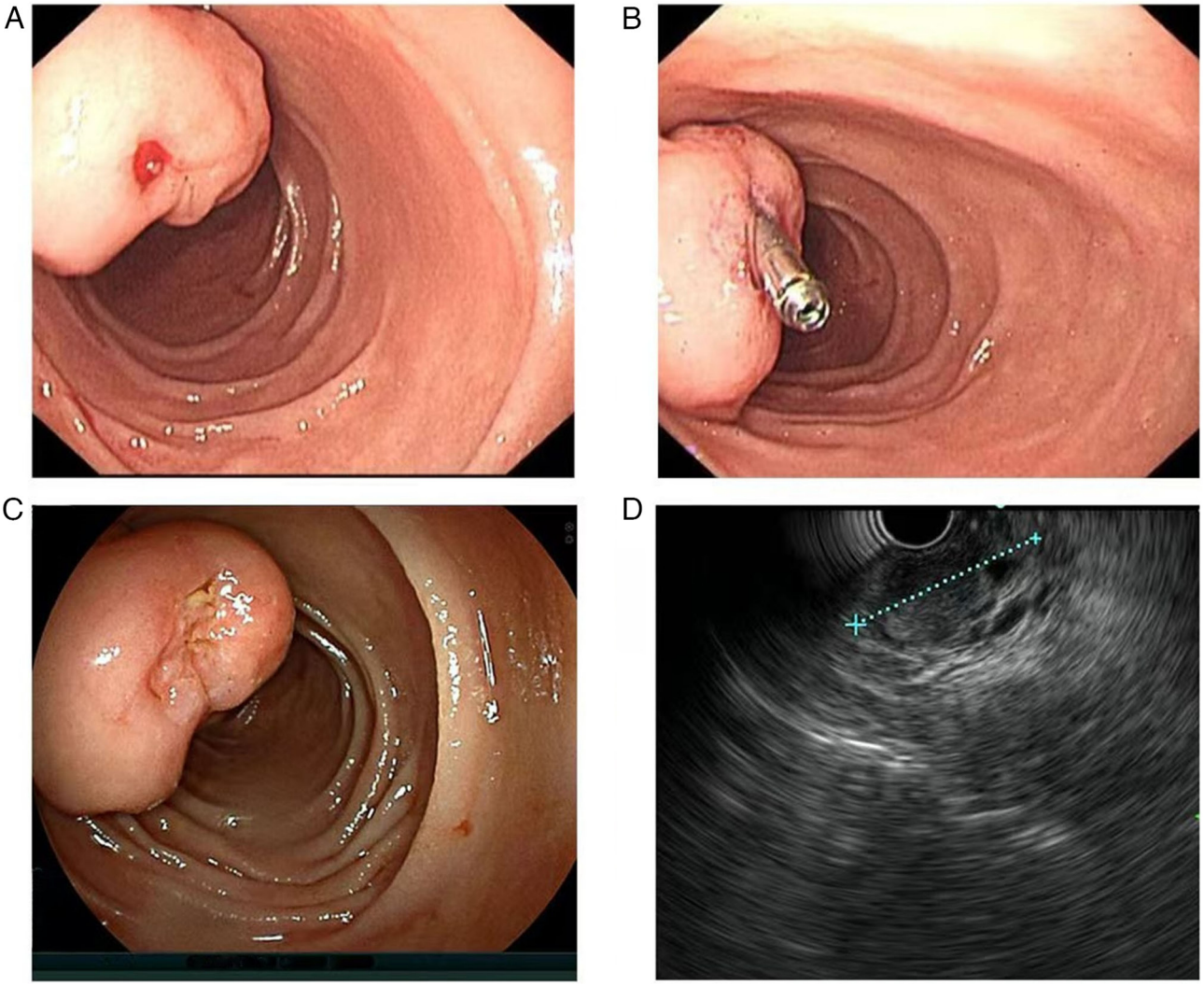


Figure 2. Duodenoscopic and ultrasonographic endoscopy of the duodenal mass. During duodenoscopy, (A) a large irregular protrusion of ~2.7x2.5 cm was observed in the duodenal papilla. It included a smooth mucosa surface, an ulcer and a red thrombus head with some hemorrhage. (B) A titanium clip was used to seal the bleeding site. (C) After 8 days of endoscopic haemostasis, the clip slipped off, leaving the duodenal papilla with submucosal prominence and surface erosion. (D) On ultrasound, the lesion appeared to be hypoechoic, with clearly defined borders and a generally uniform texture.

The patient made a full recovery and was released 10 days after the surgery.

Regarding the findings of the histopathological analyses (duodenum), which were performed according to standard procedures, tumor tissue was found in the mucous membrane, mucous membrane muscular and submucous membrane layers (Fig. 3A). The tumor was a single piece of grayish-white nodular tissue that measured ~2.7x2.4x1.9 cm. The tumor tissue was composed of three different types of cells, namely epithelioid, ganglion-shaped and spindle-like cells. The majority of the tumour cells were arranged in nests; the cells were oval, with abundant and light-stained cytoplasm and oval nuclei, and nuclear mitotic figures were difficult to discern. There were visible short spindle cells arranged in sheets or bundles and nodule-like cells dispersed throughout the area (Fig. 3B-D).

Immunohistochemical staining was performed according to the standard percedures (10). Regarding the immunohistochemical findings, the tumor cells expressed somatostatin receptor (SSTR)2(+) (cat. no. 704011; 1:1,000 dilution), the epithelioid cells exhibited the following characteristics: Synaptophysin(+) (Syn; cat. no. MA5-14532; 1:1,000 dilution) (Fig. 3E), chromogranin A(+) (CgA; cat. no. MA1-25038; 1:100 dilution), CD56(+) (cat. no. MA5-11563; 1:500 dilution) (Fig. 3G), cytokeratin(+) (CK; cat. no. MA5-32118; 1:500 dilution), melan-A(+) (cat. no. MA5-14168; 1:200 dilution) and epithelial membrane antigen(-) (EMA; cat. no. MA5-11202; 1:100 dilution). The spindle-like cells showed the following characteristics: S100(+) (cat. no. MA5-12969; 1:100 dilution) (Fig. 3F), neurofilament dispersed(+) (NF; cat. no. PA5-78668; 1:500 dilution) and partly CD34(+) (cat. no. MA1-10202; 1:100 dilution). The ganglion-shaped cells exhibited the following characteristics: NF(+) (Fig. 3H), <2% Ki-67(+) (cat. no. MA5-14520; 1:200 dilution), HMB45(-) (cat. no. MA5-13232; 1:80 dilution), desmin(-) (cat. no. MA5-13259; 1:100 dilution), smooth muscle actin(-) (SMA; cat. no. 14-9760-82; 1:500 dilution), gastrointestinal stromal tumor 1(-) (Dog-1; cat. no. MA5-16358; 1:100 dilution) and CD117 (cat. no. MA5-15894; 1:500 dilution) (all Thermo Fisher Scientific, Inc.). DGP was considered when combining the

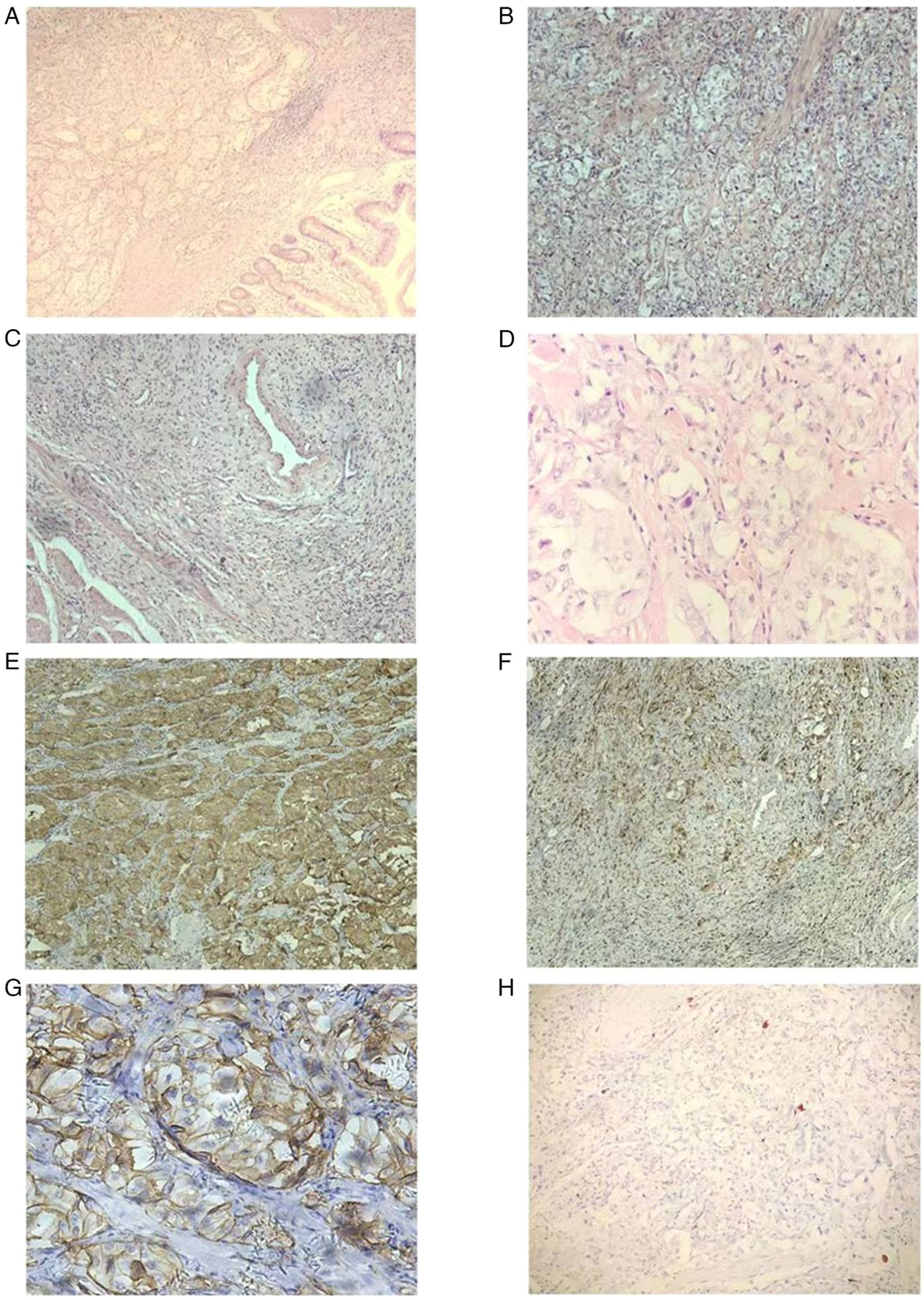


Figure 3. Histopathological and immunohistochemical characteristics of the duodenal gangliocytic paraganglioma. (A) The tumor was dispersed throughout the submucosa, mucosal muscle layer and mucosal layer. The tumor consisted of (B) epithelioid cells, (C) spindle-like cells and (D) distributed nodal ganglion-shaped cells (H&E staining; magnification, x100). (E) Epithelioid cells were positive for synaptophysin (magnification, x100). (F) Spindle-like cells were positive for S100 (magnification, x100). (G) Epithelioid cells were positive for CD56 (magnification, x200). (H) Ganglion-shaped cells were focal positive for neurofilament (magnification, x100). H&E, hematoxylin and eosin.

morphological findings revealed by hematoxylin and eosin staining with the immunohistochemical findings.

In June 2020, the patient was examined by an abdominal enhanced CT scan, which revealed a mass of ~2.9x1.9 cm in the horizontal segment of the duodenum, and a nodular cell paraganglioma recurrence was considered (Fig. 1B and C). The next day, ^{68}Ga-Dotatate (Target Molecule Corp.) and ^{18}F-FDG (Target Molecule Corp.) positron emission tomography (PET)-CT were further performed for refinement to evaluate metastasis or recurrence, which also identified a retroperitoneal duodenal nodule above the horizontal portion; there was positive growth inhibitory receptor imaging and considerably active glucose metabolism (Fig. 1D and E). It was suggested that the patient may undergo endoscopic, radical surgical or biological treatments. After consideration, the patient requested biotherapy and received octreotide (Novartis Corp.) at 30 mg/28 days for 12 consecutive cycles. After 47 months of postoperative follow-up, the patient did not have any further symptoms of gastrointestinal bleeding and was re-examined in September 2020, February 2021 and February 2024, with hemoglobin and gastrointestinal tumor markers within the normal ranges. The lesions at the horizontal duodenum appeared to be unremarkable compared with the previous imaging changes and no new lesions or metastases were observed (Fig. 1F-I).

Discussion

GP is now classified as composite gangliocytoma/neuroma and neuroendocrine tumor according to the 2022 World Health Organization (WHO) Classification of Neuroendocrine Neoplasms (11,12). NETs frequently overexpress SSTRs, particularly of type 2 (13). ^{68}Ga-Dotatate is a selective SSTR-2 PET tracer with a strong affinity for SSTR-2-expressing NETs; thus, it is recommended as the imaging modality of choice for the early diagnosis of GP (14). The final diagnosis of GP is based on its distinct histopathological features, which include a mixture of three cell types, namely epithelioid, spindle-like and ganglion-shaped, in varying proportions (8). Epithelioid cells in GPs are similar to those that compose paragangliomas and/or carcinoid tumors, with polygonal cells, abundant cytoplasm, ovoid nuclei, indistinct nucleoli and dense core granules visible on electron microscopy, and are arranged in dense nests and trabeculae. Epithelioid cells are mainly positively immunoreactive for Syn, neuron-specific enolase (NSE), CgA, CD56, growth inhibitors and pancreatic polypeptide (PP) (15). Spindle-like cells show a neurofibromatous structure with elongated nuclei in bundles surrounding nests of epithelioid cells and ganglion-shaped cells, and are mainly positive for S100 and NSE (16). Ganglion-shaped cells are spread singly or in nests amid epithelioid and spindle-like cells, with infrequent mitotic cell divisions and no evident anisotropy or necrosis. They proliferate in a manner similar to that of ganglioneuromas, with big nuclei containing large quantities of eosinophilic cytoplasm. Ganglion-shaped cells show positive reactivity for Syn, NSE and CD56 (17).

The tumor proliferation index or Ki-67 is used clinically to assess tumor cell division and proliferation activities. The higher the value, the greater the proliferation activity of tumor cells (18). In the present study, positive expression of Ki-67 was <2%, indicating that tumor cell proliferation activity was weak and prognosis was good. The proportion of the three tumor cell components varies from case to case and misdiagnosis is common when one cell component dominates in an individual.

GP is notably rare and typically appears clinically in the second and third sections of the duodenum, particularly in the area surrounding the duodenal jugular abdomen (3), although it can also be present in the biliary tract, pancreas, esophagus, stomach, jejunum, cecum, thymus, mediastinum, lungs, bladder and other areas of the body (5-7,19-22). GP can arise at any age. It has been recorded in patients aged 15 to 92 years. The median age at onset is 51.2 years and the majority of them are males, with a male-to-female ratio of 157:104 (2). Previous research also indicated that there was no gender difference in terms of occurrence of GP and the size of GP around the ampulla ranges from 0.7 to 19.0 cm, with a median size of ~2.2 cm (4). The 2019 WHO Classification of Tumors of the Digestive System (5th edition) (23) indicated that GP was a NET with a fair prognosis that is not likely to experience recurrence or metastasis; however, there is still a risk of malignancy. The 1-, 3- and 5-year survival rates of GP around the duodenal jugular abdomen were reported to be 100, 83.3 and 55.6%, respectively, according to a study by Chiang *et al* (4). An increasing number of case reports of GP with distant metastasis, recurrence and lymph node metastasis have been published (9,24). The most common type of metastasis is lymph node metastasis, followed by liver, lung, bone and other organ metastases. Li *et al* (25) reported a case of lethal GP with multifocal metastasis. The present study reports a case of DGP with short-term recurrence. No lymph node or distant metastases were identified during 4 years of follow-up.

The primary factor influencing the clinical presentation of GP is the tumor growth site. While gastrointestinal bleeding, abdominal pain, anemia, diarrhea, wasting and other symptoms are typical of DGP, a few patients may experience biliary obstruction symptoms (26) or even no symptoms at all that are unintentionally identified during physical examination. The main clinical manifestations of DGP reported in the present study were black stool and anemia, which could easily be misdiagnosed as other digestive diseases.

GP is uncommon in clinical practice and clinicians have limited knowledge of this condition. GP is formed by the combination of epithelioid, spindle-like and ganglion-shaped cells in different ratios. It is usually dominated by epithelioid and spindle-like cells, with ganglion-shaped cells dispersed throughout. In clinical practice, it is easy to cause missed diagnosis and misinterpretation when a sample is acquired incompletely or a specific cell component is prominent.

It is necessary to differentiate this condition from the following illnesses when epithelioid cells predominate over GP: i) NET grade 1 (NET G1): In 2022, the WHO classified NET into G1, G2 and G3 according to their mitotic count or Ki67 index. The diagnostic criteria for NET include: G1, <2 mitoses/2 mm^2 and/or Ki67 <3%; G2, 2-20 mitoses/2 mm^2 and/or Ki67 3-20%; and G3, >20 mitoses/2 mm^2 and/or Ki67 >20% (11). NET G1 is a carcinoid that accounts for 50% of all gastrointestinal and pancreatic NETs. Clinical symptoms include abdominal discomfort, abdominal pain, black stool, weight loss and other symptoms. Tumor cells can be arranged in an island-like, trabecular or adenoid pattern on pathology.

Immunohistochemistry shows that Syn, CgA, NSE, carcinoembryonic antigen (CEA), CD56 and Ki-67 are all positively expressed, similar to GP. However, GP epithelioid cells were previously reported to be positive for PP and progesterone receptor, while NET G1 are negative for these, which is helpful to differentiate them (2); and ii) poorly-differentiated adenocarcinoma: When GP epithelioid cells exhibit invasive proliferation, they must be distinguished from poorly-differentiated adenocarcinoma. The immunophenotype of GP epithelioid cells is often positive in Syn and CgA expression, while negative for EMA and CEA expression, whereas the immunophenotype of poorly differentiated adenocarcinoma cells is simple in composition and apparent in atypia.

When GP is dominated by spindle-like cells, it should be distinguished from the following diseases: i) Gastrointestinal stromal tumor (GIST), which is a type of gastrointestinal mesenchymal tumor that often affects the stomach and small intestine. It is more frequent in middle and old age, and there are no evident clinical signs in the early stage. Patients with mid- and late-stage GIST may experience gastrointestinal bleeding, abdominal pain, abdominal mass, anemia, emaciation and other symptoms (27). The pathology of GIST is mainly composed of spindle and/or epithelioid cells, which may be mistaken for GP dominated by spindle-like cells. The immunohistochemistry of GIST is characterized by CD117 (c-KIT), CD34 and DOG-1 expression, but negative Syn and S100 expression, whereas GP often shows positive SSTR2 and Syn expression but negative CD117, CD34 and DOG-1 expression (28). In the present study, the expression of SSTR2 and Syn in DGP was positive, while CD117 and DOG-1 were negative. Accordingly, the difference in immunohistochemical phenotype is helpful to distinguish DGP from GIST; and ii) gastrointestinal leiomyoma, which is a benign tumor caused by aberrant smooth muscle hyperplasia that typically develops in the esophagus and colon, but rarely in the stomach or small intestine. In total, 90% of tumors are solitary, round or oval, with no genuine envelope, clear boundary, hard, smooth surface and core ulcer development. Histologically, the tumor cells are organized in a cross bundle, with no or limited mitogenic signals and limited malignant signs. Leiomyoma has a positive SMA and desmin immunohistochemical phenotype, but exhibits negative S100, CD117 and DOG-1 expression (29). In the present case report, the tumor was positive for S100 but negative for SMA and desmin. As a result, S100, SMA and desmin can help to distinguish between gastrointestinal leiomyoma and GP. Furthermore, the characteristics in terms of expression of CD117, DOG-1, CD34, SMA and desmin allow to distinguish GIST from leiomyoma.

GP should also be distinguished from ganglioneuroma (GNs) when it is dominated by ganglion-shaped cells. GN is a benign tumor that develops from the neural crest of the sympathetic nervous system and is common in young patients. Histopathologically, GNS is composed of ganglion-shaped cells and nerve fibers, with the fundamental distinction from GP being the absence of epithelioid cells (30). Thus, identifying epithelioid cells is key to distinguishing between GP and GNS.

At present, there are no defined diagnostic or therapeutic standards for GP; thus, local or radical resection is the primary treatment for GP in clinical practice. Endoscopic submucosal dissection (ESD) offers advantages such as reduced surgical trauma, less bleeding, shorter surgical time and faster recuperation compared to surgical operation. ESD has become the recommended treatment technique for DGP when the tumor diameter is <2.0 cm and if the tumor is restricted to the mucosal or submucosal layers, with no local invasion or distant metastases (31), and a study has relaxed the tumor diameter to 3.0 cm (32). In a systematic review by Okubo (33), 27 individuals with GP who received endoscopic treatment had positive outcomes. When GP is >2.0 cm in diameter, it infiltrates into the intrinsic muscle layer, and if it has no local invasion or distant metastases, it can be removed locally using laparoscopic or open surgery (34,35). Cathcart *et al* (36) coupled duodenoscopy with laparoscopy and employed laparoscopy with endoscopic-assisted localization to completely resect the DGP and adjacent duodenal wall, resulting in a successful outcome and safe discharge from the hospital 10 days later. When infiltrative growth is detected with vascular and lymph node invasion or distant metastasis, pancreaticoduodenectomy and local lymph node dissection are advised as palliative surgical treatments (24).

GP is a type of NET; thus, the pharmacological treatment options for NETs are also useful for GP, including biotherapy, nuclide therapy, targeted therapy, chemotherapy and immunotherapy. Biotherapy is recommended for individuals with Ki-67 <10%, which includes long-acting somatostatin analogues (SSAs) and interferon (IFN)-α. IFN-α is less frequently utilized in clinical settings and is mostly used for refractory functional NETs. The most widely used long-acting SSAs exert antiproliferative/antitumor effects via the SSTR2 (37,38), including octretide, lanreotide and pasireotide, among which octreotide is mainly used for gastrointestinal NETs, while lanreotide is also used for pancreatic NETs. According to Nesti *et al* (39), the progression-free overall survival (PFS) of patients with NET in the octreotide group was noticeably higher than that of patients in the placebo group. Lanotide significantly extended the PFS of patients with gastroenteropancreatic (GEP)-NET (40). According to a study by Caplin *et al* (41), patients with advanced enteropancreatic NETs who were in the lanreotide group had a significantly higher PFS than patients in the control group. In addition, patients in the lanreotide group experienced a significantly lower incidence of treatment-related adverse events, as well as an overall decrease in adverse events. In the present study, after surgical recurrence, the patient, who exhibited Ki67 <2%, received biotherapy with octreotide, and, during routine follow-up assessment, no metastasis was observed in the lesion. Currently, NETs can be treated with nuclear therapy as a second or third line of treatment. Lutetium-177 (^{177}Lu) is a commonly used radioactive nucleotide that frequently binds to somatostatin analogues to form ^{177}Lu-dotatate, which targets SSTR-positive NETs, inducing DNA breaks in tumor cells, leading to apoptosis (42). In September 2017 and January 2018, ^{177}Lu-dotatate was licensed in Europe and the US, respectively, for the treatment of SSTR-positive GEP NETs (43). In a phase III clinical trial, patients with advanced mid-gut NETs treated with ^{177}Lu-Dotatate in conjunction with long-acting octreotide exhibited a significant improvement in PFS compared to those treated with high-dose long-acting octreotide alone (44). Chemotherapy is the first line of treatment for patients

with high-grade (G3) NETs and has an antitumor effect by preventing tumor cells from entering the mitotic cycle. It is not usually utilized for patients in the G1 or G2 stages of cancer (45), including alkylating agents (cisplatin, temozolomide), topoisomerase inhibitors (etoposide) and thymidylate synthase inhibitors (capecitabine). Molecularly targeted drugs are divided into two categories, namely i) mammalian target of rapamycin inhibitors, with the most representative drug being everolimus; and ii) tyrosine kinase inhibitors, including sunitinib and sofantinib (46). Everolimus plus temozolomide may be the first-line treatment for metastatic high-grade GEP NETs, according to a prospective multicenter phase II trial (47). Immunotherapy drugs include programmed cell death protein 1 inhibitors, such as pabolizumab, and programmed cell death ligand 1 inhibitors, such as dovalizumab (48). The efficacy of single immune checkpoint inhibitors in the treatment of advanced neuroendocrine neoplasms is limited. At present, dual immune checkpoint therapy or a combination of other drugs is typically employed to treat them. In a non-randomized controlled multicohort phase II clinical trial, tremelimumab in combination with durvalumab demonstrated good antitumor effectiveness and safety in GEP and lung NETs (49). The selection of initial and post-progression treatment options for GEP NETs must be evaluated in various aspects according to the tumor's SSTR expression, stage, primary characteristic, hormonal status and other characteristics. When the tumor is SSTR (-), chemotherapy and targeted drugs are recommended for patients with stage G1 to G2; when the tumor is SSTR (+), long-acting SSAs are first recommended for patients. Systemic chemotherapy is recommended for patients with G3 stage tumors independently of SSTR expression by the tumor (50).

In conclusion, DGP is a clinically atypical NET, which lacks specific clinical manifestations. The diagnosis of DGP is primarily based on its distinct histopathological manifestations, which dictate the treatment modality based on the tumor's size, depth of infiltration and metastasis. In our opinion, for gastrointestinal tumors, when the preoperative diagnosis is unknown, endoscopic local excision can be selected first to maximize the guarantee of negative margins and reduce the risk of secondary surgery, and, if the pathology exists in the presence of positive margins and plexus nerve invasion, additional surgical treatment may be performed. In the present case, the tumor originated from the mucosal layer and the depth of infiltration was shallow, therefore ESD therapy was used to totally remove the tumor. The patient required further biological therapy after the tumor recurred following surgery. There was no lymph node metastases or distant metastasis discovered during the ~4-year follow-up period. GP is a low-grade cancer with a low risk of metastasis and a favorable prognosis. ESD or surgical resection is preferred, and for patients with postoperative recurrence, metastasis or those unsuitable for surgery, biotherapy, nuclear therapy, chemotherapy, targeted therapy and immunotherapy can be selected independently based on factors including hormone receptor expression and tumor grading.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NX and LHS made substantial contributions to the conception or design of the work, and confirm the authenticity of all the raw data. SMZ, HL and LFL gathered, analyzed and interpreted the data. NX, LHS and SMZ wrote the original manuscript, and reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Second Affiliated Hospital of Xuzhou Medical University (approval no. 2024031205).

Patient consent for publication

Written informed consent was obtained from the patient for the publication of the present case report and the accompanying associated images.

Competing interests

The authors declare that they have no competing interests.

References

1. Dahl EV, Waugh JM and Dahlin DC: Gastrointestinal ganglioneuromas; brief review with report of a duodenal ganglioneuroma. Am J Pathol 33: 953-965, 1957.
2. Okubo Y, Yoshioka E, Suzuki M, Washimi K, Kawachi K, Kameda Y and Yokose T: Diagnosis, pathological findings, and clinical management of gangliocytic paraganglioma: A systematic review. Front Oncol 8: 291, 2018.
3. Matsubayashi H, Ishiwatari H, Matsui T, Fujie S, Uesaka K, Sugiura T, Okamura Y, Yamamoto Y, Ashida R, Ito T, *et al*: Gangliocytic paraganglioma of the minor papilla of the duodenum. Intern Med 56: 1029-1035, 2017.
4. Chiang CS, Shyr BU, Chen SC, Shyr YM and Wang SE: Periampullary gangliocytic paraganglioma. J Gastrointest Surg 23: 2247-2254, 2019.
5. Weinrach DM, Wang KL, Blum MG, Yeldandi AV and Laskin WB: Multifocal presentation of gangliocytic paraganglioma in the mediastinum and esophagus. Hum Pathol 35: 1288-1291, 2004.
6. Palacio D, Jo N, Del Pilar Gutierrez M, Shponka V and Betancourt S: Multimodality imaging appearance of intrapericardial paragangliomas. Clin Radiol 77: 952-959, 2022.
7. Naso JR, Wang D, Romero AO, Leclair T, Smit P, Boland JM, Folpe AL and Bois MC: Pulmonary gangliocytic paraganglioma: An under-recognized mimic of carcinoid tumor. Hum Pathol 146: 23-27, 2024.
8. Mete O, Asa SL, Gill AJ, Kimura N, de Krijger RR and Tischler A: Overview of the 2022 WHO classification of paragangliomas and pheochromocytomas. Endocr Pathol 33: 90-114, 2022.
9. Park HK and Han HS: Duodenal gangliocytic paraganglioma with lymph node metastasis. Arch Pathol Lab Med 140: 94-98, 2016.
10. Ramos-Vara JA: Principles and methods of immunohistochemistry. Methods Mol Biol 1641: 115-128, 2017.

11. Rindi G, Mete O, Uccella S, Basturk O, La Rosa S, Brosens LAA, Ezzat S, de Herder WW, Klimstra DS, Papotti M and Asa SL: Overview of the 2022 WHO classification of neuroendocrine neoplasms. Endocr Pathol 33: 115-154, 2022.
12. Helderman NC, Suerink M, Kilinç G, van den Berg JG, Nielsen M and Tesselaar MET: Relation between WHO classification and location- and functionality-based classifications of neuroendocrine neoplasms of the digestive tract. Neuroendocrinology 114: 120-133, 2024.
13. Oronsky B, Ma PC, Morgensztern D and Carter CA: Nothing but NET: A review of neuroendocrine tumors and carcinomas. Neoplasia 19: 991-1002, 2017.
14. Sanli Y, Garg I, Kandathil A, Kendi T, Zanetti MJB, Kuyumcu S and Subramaniam RM: Neuroendocrine tumor diagnosis and management: ^{68}Ga-DOTATATE PET/CT. AJR Am J Roentgenol 211: 267-277, 2018.
15. Li J, Wang LP and Zhu PS: Is gangliocytic paraganglioma designated as a subtype of composite paragangliomas and originated from pancreas islet? A case report and review of literature. Front Endocrinol (Lausanne) 13: 847632, 2022.
16. Wang B, Zou Y, Zhang H, Xu L, Jiang X and Sun K: Duodenal gangliocytic paraganglioma: Report of two cases and review of literature. Int J Clin Exp Pathol 8: 9752-9759, 2015.
17. Furihata M, Sonobe H, Iwata J, Ido E, Ohtsuki Y and Ohnishi S: Immunohistochemical characterization of a case of duodenal gangliocytic paraganglioma. Pathol Int 46: 610-613, 1996.
18. Rubisz P, Ciebiera M, Hirnle L, Zgliczyńska M, Łoziński T, Dzięgiel P and Kobierzycki C: The usefulness of immunohistochemistry in the differential diagnosis of lesions originating from the myometrium. Int J Mol Sci 20: 1136, 2019.
19. Harries K, Nunn T, Shah V, Richards D and Manson JM: First reported case of esophageal paraganglioma. A review of the literature of gastrointestinal tract paraganglioma including gangliocytic paraganglioma. Dis Esophagus 17: 191-195, 2004.
20. Nonaka K, Matsuda Y, Okaniwa A, Kasajima A, Sasano H and Arai T: Pancreatic gangliocytic paraganglioma harboring lymph node metastasis: A case report and literature review. Diagn Pathol 12: 57, 2017.
21. Seo G, Park J, Lee E, Han J, Kim D, Kim D, Park J, Kwag M and Jung S: Gangliocytic paraganglioma of the gastrointestinal tract: A case report of cecal origin. Curr Med Imaging 18: 95-98, 2022.
22. Usuda H and Emura I: Composite paraganglioma-ganglioneuroma of the urinary bladder. Pathol Int 55: 596-601, 2005.
23. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F and Cree IA; WHO Classification of Tumours Editorial Board: The 2019 WHO classification of tumours of the digestive system. Histopathology 76: 182-188, 2020.
24. Choi H, Choi JW, Ryu DH, Park S, Kim MJ, Yoo KC and Woo CG: Ampullary gangliocytic paraganglioma with lymph node metastasis: A case report with literature review. Medicine (Baltimore) 101: e29138, 2022.
25. Li B, Li Y, Tian XY, Luo BN and Li Z: Malignant gangliocytic paraganglioma of the duodenum with distant metastases and a lethal course. World J Gastroenterol 20: 15454-15461, 2014.
26. Sharma S, Gaspar BL, Kumar P, Yadav TD and Vasishta RK: Gangliocytic paraganglioma with atypical immunohistochemical features presenting as extrahepatic biliary obstruction. Int J Surg Pathol 23: 561-566, 2015.
27. Serrano C, Martin-Broto J, Asencio-Pascual JM, Lopez-Guerrero JA, Rubio-Casadevall J, Bague S, Garcia-Del-Muro X, Fernandez-Hernandez JA, Herrero L, Lopez-Pousa A, *et al*: 2023 GEIS guidelines for gastrointestinal stromal tumors. Ther Adv Med Oncol 15: 17588359231192388, 2023.
28. Munteanu A, Patrascu S, Bordu S, Laskou S, Surlin V and Radu P: Clinical and morphological characteristics of gastrointestinal stromal tumor. Chirurgia (Bucur) 118: 618-623, 2023.
29. Virani N, Pang J and Lew M: Cytologic and immunohistochemical evaluation of low-grade spindle cell lesions of the gastrointestinal tract. Arch Pathol Lab Med 140: 1038-1044, 2016.
30. Goldberg JL, Tong J and McGrath LB Jr: Spinal ganglioneuroma. World Neurosurg 162: 15-16, 2022.
31. Barret M, Rahmi G, van Huyen JP, Landi B, Cellier C and Berger A: Duodenal gangliocytic paraganglioma with lymph node metastasis and an 8-year follow-up: A case report. Eur J Gastroenterol Hepatol 24: 90-94, 2012.
32. Hernandez AG, Lanuza ED, Matias AC, Huertas RP, Rodriguez KM, Perez PG and Mompean FO: Large gangliocytic paraganglioma of the duodenum: A rare entity. World J Gastrointest Surg 7: 170-173, 2015.
33. Okubo Y: Gangliocytic paraganglioma: An overview and future perspective. World J Clin Oncol 10: 300-302, 2019.
34. Zhang Z, Tu Z, Lv Z, Luo Y and Yuan J: Case report: Totally laparoscopic resection of retroperitoneal paraganglioma masquerading as a duodenal gastrointestinal stromal tumor. Front Surg 8: 586503, 2021.
35. Moriyama H, Asai K, Watanabe R, Nagata T, Futawatari N, Enomoto T, Nagao S, Watanabe M, Oharazeki T and Saida Y: Laparoscopic tumor resection for asymptomatic paraganglioma-a case study. Gan To Kagaku Ryoho 50: 1924-1927, 2023 (In Japanese).
36. Cathcart SJ, Sasson AR, Kozel JA, Oliveto JM and Ly QP: Duodenal gangliocytic paraganglioma with lymph node metastases: A case report and comparative review of 31 cases. World J Clin Cases 5: 222-233, 2017.
37. Lamberts SW, Hofland LJ and Nobels FR: Neuroendocrine tumor markers. Front Neuroendocrinol 22: 309-339, 2001.
38. Stueven AK, Kayser A, Wetz C, Amthauer H, Wree A, Tacke F, Wiedenmann B, Roderburg C and Jann H: Somatostatin analogues in the treatment of neuroendocrine tumors: Past, present and future. Int J Mol Sci 20: 3049, 2019.
39. Nesti C, Bräutigam K, Benavent M, Bernal L, Boharoon H, Botling J, Bouroumeau A, Brcic I, Brunner M, Cadiot G, *et al*: Hemicolectomy versus appendectomy for patients with appendiceal neuroendocrine tumours 1-2 cm in size: A retrospective, Europe-wide, pooled cohort study. Lancet Oncol 24: 187-194, 2023.
40. Saif MW: Lanreotide for the treatment of gastroenteropancreatic neuroendocrine tumors. Expert Opin Pharmacother 17: 443-456, 2016.
41. Caplin ME, Pavel M, Phan AT, Ćwikła JB, Sedláčková E, Thanh XT, Wolin EM and Ruszniewski P; CLARINET Investigators: Lanreotide autogel/depot in advanced enteropancreatic neuroendocrine tumours: Final results of the CLARINET open-label extension study. Endocrine 71: 502-513, 2021.
42. Becx MN, Minczeles NS, Brabander T, de Herder WW, Nonnekens J and Hofland J: A clinical guide to peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE in neuroendocrine tumor patients. Cancers (Basel) 14: 5792, 2022.
43. Mittra ES: Neuroendocrine tumor therapy: ^{177}Lu-DOTATATE. AJR Am J Roentgenol 211: 278-285, 2018.
44. Strosberg JR, Caplin ME, Kunz PL, Ruszniewski PB, Bodei L, Hendifar A, Mittra E, Wolin EM, Yao JC, Pavel ME, *et al*: ^{177}Lu-Dotatate plus long-acting octreotide versus high-dose long-acting octreotide in patients with midgut neuroendocrine tumours (NETTER-1): Final overall survival and long-term safety results from an open-label, randomised, controlled, phase 3 trial. Lancet Oncol 22: 1752-1763, 2021.
45. Chan DL and Singh S: Current chemotherapy use in neuroendocrine tumors. Endocrinol Metab Clin North Am 47: 603-614, 2018.
46. Hijioka S, Morizane C, Ikeda M, Ishii H, Okusaka T and Furuse J: Current status of medical treatment for gastroenteropancreatic neuroendocrine neoplasms and future perspectives. Jpn J Clin Oncol 51: 1185-1196, 2021.
47. Morken S, Langer SW, Sundlöv A, Vestermark LW, Ladekarl M, Hjortland GO, Svensson JB, Tabaksblat EM, Haslerud TM, Assmus J, *et al*: Phase II study of everolimus and temozolomide as first-line treatment in metastatic high-grade gastroenteropancreatic neuroendocrine neoplasms. Br J Cancer 129: 1930-1939, 2023.
48. Ooki A, Osumi H, Fukuda K and Yamaguchi K: Potent molecular-targeted therapies for gastro-entero-pancreatic neuroendocrine carcinoma. Cancer Metastasis Rev 42: 1021-1054, 2023.
49. Capdevila J, Hernando J, Teule A, Lopez C, Garcia-Carbonero R, Benavent M, Custodio A, Garcia-Alvarez A, Cubillo A, Alonso V, *et al*: Durvalumab plus tremelimumab for the treatment of advanced neuroendocrine neoplasms of gastroenteropancreatic and lung origin. Nat Commun 14: 2973, 2023.
50. Del Rivero J, Perez K, Kennedy EB, Mittra ES, Vijayvergia N, Arshad J, Basu S, Chauhan A, Dasari AN, Bellizzi AM, *et al*: Systemic therapy for tumor control in metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: ASCO guideline. J Clin Oncol 41: 5049-5067, 2023.

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