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Sporadic duodenal macrogastrinoma: a rare case report

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Gastrinomas are rare neuroendocrine tumors characterized by the secretion of gastrin, which causes hyperchlorhydria, thereby producing the Zollinger-Ellison syndrome. In most cases this syndrome manifests as severe peptic ulcer disease. We are presenting an extremely rare clinical case of sporadic duodenal macrogastrinoma. The patient underwent investigation due to six-year history of epigastric pain, heartburn and episodic diarrhea. Endoscopy, endosonoscopy and histologic examination of biopsy specimens indicated the presence of duodenal gastrinoma with no signs of peptic ulcers. Pyloroduodenal segment including 3.5 cm macrogastrinoma was resected. This case is unique as duodenal gastrinomas are usually very small, up to 1 cm. During the follow up period we observed slowly decreasing hypergastrinemia. Somatostatin receptor scintigraphy, CT and upper GI endoscopy were performed to reveal the reasons, though did not find any abnormalities. 8 months of follow-up did not reveal any progression of the disease. The etiology of slowly decreasing hypergastrinemia remains unclear, controversial and is under investigation.

Key words: gastrinoma, duodenal macrogastrinoma, Zollinger-Ellison syndrome

INTRODUCTION

Gastrinoma is a neuroendocrine tumor characterized by the secretion of gastrin, which causes hyperchlorhydria, thereby producing the Zollinger-Ellison syndrome (ZES) (1). This syndrome manifests as severe peptic ulcer disease in 70–90% of the cases (2, 3). The true incidence and prevalence of ZES are unknown. It was estimated that the incidence ranged from 0.1 to 1% of patients with peptic ulcer disease (4, 5). With current assays for serum gastrin, numbers of patients who are diagnosed with the ZES are increasing (4, 6).

Gastrinomas can be sporadic or associated with multiple endocrine neoplasia type 1 (MEN

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1) (7–9). 70% of sporadic gastrinomas form in the duodenum. They are usually very small and difficult to locate (4). Duodenal macrogastrinomas are extremely rare. The present article describes the patient with a 3.5 cm size sporadic duodenal macrogastrinoma, who had six-year history of heartburn, episodic diarrhea and no peptic ulcer disease.

MATERIALS AND METHODS

A 67-year-old male was admitted to the hospital in July 2011 with a six-year history of faintness, mild postprandial epigastric pain, heartburn and episodic diarrhea, but no weight loss.

Endoscopy did not show any abnormal changes in the oesophagus and stomach, but revealed a 30 mm submucosal tumor with ulcerated mucosa in the posterior wall of the duodenal bulb. We detected a 28 by 30 mm in diameter tumor of irregular echogeneity (relative sign of malignancy), similar to a gastrointestinal stromal tumor (Fig. 1). There were no signs of enlarged lymph nodes. Biopsies had been performed from the ulcerated surface of the tumor. Histologic examination of biopsy specimens indicated the presence of neuroendocrine tumor producing gastrin.

On admission to our hospital, general physical examination was unremarkable. Routine haematology was: WBC 6.88 (normal 4.0–9.0 *10e9/l), Neu 4.29 (normal 2.0–6.93 *10e9/l), RBC 4.13 (normal 4.5–5.5 *10e12/l), Hg 118 (normal 135–160 g/l), Hct 0.369 (normal 0.40–0.48 l/l), Plt 254 (normal 180–320 *10e9/l). Preoperative routine biochemistry tests were normal. Serum gastrin concentration was 1 225 pmol per liter (2 450 pg per milliliter); normal, 6.2–54.8 pmol per liter (12.4–109.6 pg per milliliter). A contrast-enhanced computed tomography (CT) of the abdomen delineated a hypervascularized tumor of the duodenal bulb 38 by 35 by 33 mm in diameter, obstructing almost all lumen (Fig. 2). Small regional

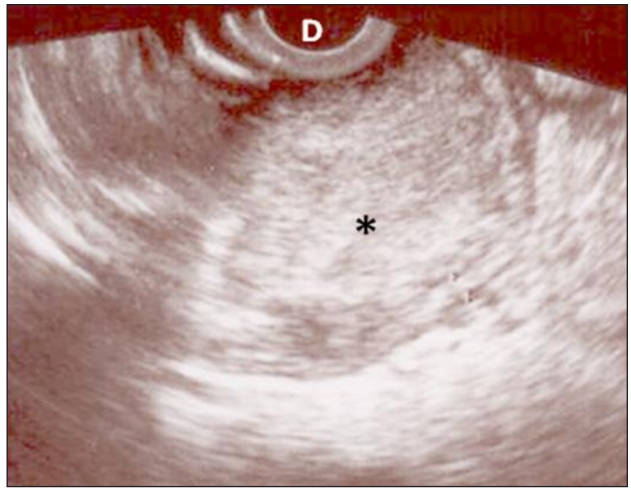

Fig. 1. Endosonographic image of the gastrinoma seen as 28 by 30 mm size tumor of irregular echogeneity (asterisk), located within the submucosal layer of the duodenal bulb (D)

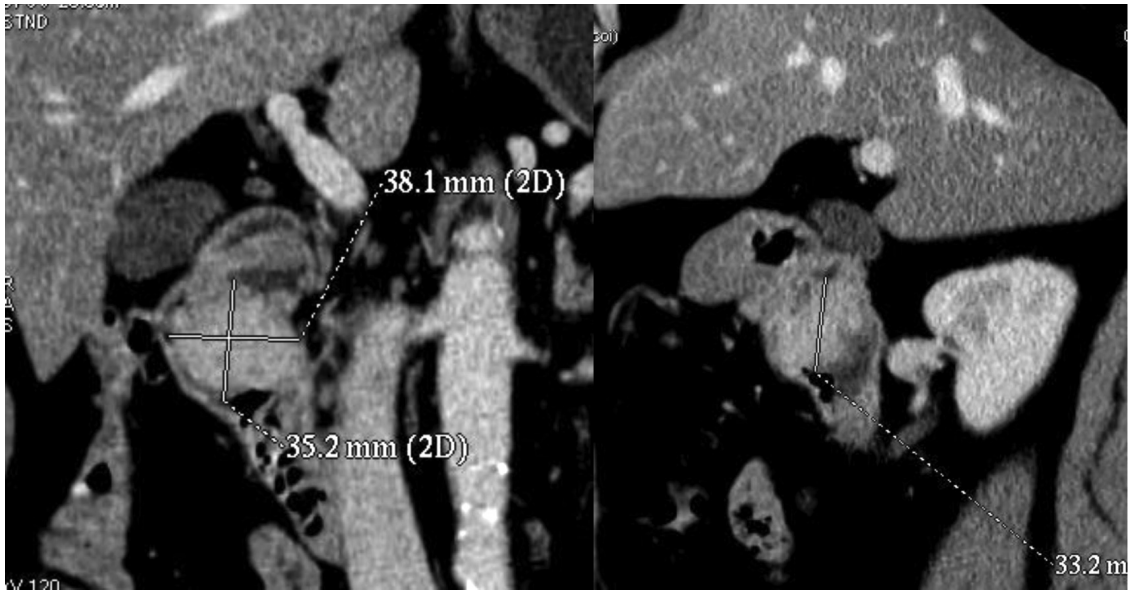

Fig. 2. CT reconstructed pictures in coronal and sagittal planes: hypervascularized tumor of the duodenal bulb 38 by 35 by 33 mm in diameter, obstructing almost all lumen

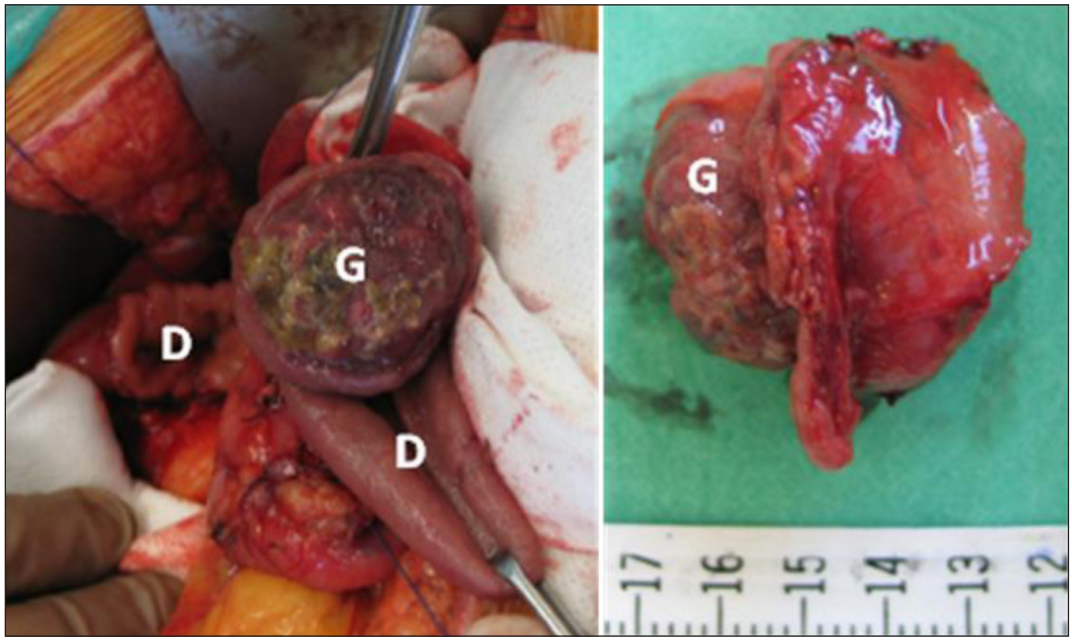

Fig. 3. Operative photograph showing duodenal gastrinoma 3.5 cm in diameter. D – duodenum, G – gastrinoma

nonspecific lymph nodes up to 6 by 4 mm, hepatosteatosis and small cysts of right kidney were also shown. At laparotomy a juxtapyloric (immediately distal to the pylorus) gastrinoma 3.5 cm in diameter was found. There were no metastases or enlarged lymph nodes noted, the pancreas and other viscera including the liver were grossly normal. The Kocher manoeuvre was performed and a 4 cm pyloroduodenal segment including gastrinoma was resected (Fig. 3). Pathological analysis of the mass revealed a 3 by 3 by 3.5 cm size tumor with at least 0.5 cm clear resection margin. The tumor infiltrated mucosal and submucosal layers. There was no angioinvasion. Histologic examination showed a predominantly trabecular growth pattern with good vascularization. The tumor cells had rather uniform nuclei, eosinophilic and fine granular cytoplasm. Mitoses were rare: less than 1 in 10 high power fields. Immunohistologic analyses revealed the expression of chromogranin A, synaptophysin and gastrin in the absolute majority of tumor cells. Ki-67 index was less than 1%. There was no expression of somatostatin, serotonin, glucagon, insulin. These features confirmed the lesion to be a well-differentiated neuroendocrine tumor pT2G1 (10) and the grossly elevated fasting serum gastrin (1 225 pmol/l) was corroborative of gastrinoma as the final diagnosis. The patient had an uneventful recovery and was discharged on the 8th postoperative day in good condition. He has been on regular reviews thereafter. On the 50th day after the operation, the serum gastrin level was 1 119 pmol/l. Other gastrinomas or metastases were considered and a somatostatin-receptor scintigraphy was requested. Abdominal scintigraphy did not reveal any accumulation of the radioligand and no local or metastasic lesions were identified. On the 115th postoperative day, the serum gastrin concentration decreased to 477 pmol per liter (Fig. 4). Repeated CT scanning and upper endoscopy revealed no abnormalities. At 8-month follow-up, the patient has mild intermittent dyspepsia symptoms and is kept under further observation.

DISCUSSION

Our patient resembles patients from the literature in many clinical features (sex, symptoms, tumor location), though there are some pronounced differences in a number of clinical, laboratory, and tumor features (higher age, absence of peptic ulcers, large tumor size, high fasting serum gastrin (FSG) level and its slow decrease after the operation).

ZES is diagnosed between the ages of 20 and 60 in 90% of the cases, although it may occur in children and the elderly (11). Our patient is a 67-year-

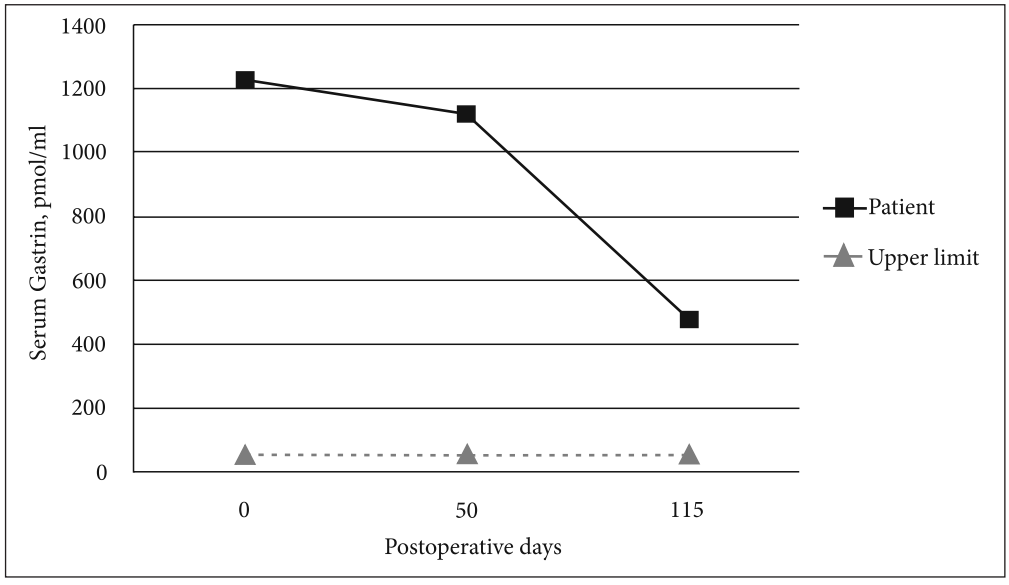

Fig. 4. Serum gastrin concentration before and after excision of the gastrinoma. The broken line indicates the upper limit of normal values for serum gastrin concentration. To convert values for serum gastrin to picograms per milliliter, multiply by 2

old man. The male to female ratio ranges between 1.5 : 1 and 2 : 1 (2).

Large series in the literature report that gastrinomas can be either sporadic (70–80% of the cases) or associated with MEN 1 (20–30%) (7–9). In sporadic gastrinoma patients, only 2% are correctly diagnosed at initial presentation (11). There was a long delay (6 years) in diagnosis in this case as well as reported in larger studies (5–7 years) (2). The clinical presentation is not specific for gastrinoma and there is overlap of symptoms associated with this illness and other more common gastrointestinal conditions (Table) (8). Similar to almost all series of ZES patients, pain was the most prominent feature and diarrhea, heartburn were also pronounced symptoms in this case (2, 8). 70–90% of the patients develop peptic ulcers (2, 3), however, endoscopy did not reveal ulcers in our patient and he had not been taking antacids.

Duodenoscopy showed a submucosal tumor in the duodenal bulb. More than 80% of gastrinomas are localized in the anatomic area known as the gastrinoma triangle (11, 12) (Fig. 5). 70% of gastrinomas form in the duodenum, the rest arise in the pancreas or less often in lymph nodes adjacent to

Table. Symptoms in patients with Zollinger-Ellison syndrome (8)

Symptom	Frequency, %
Abdominal pain	75
Diarrhea	73
Abdominal pain + Diarrhea	55
Heartburn	44
Nausea	33
Vomiting	25
Bleeding	25
Abdominal pain + Bleeding	20
Weight loss	17
Duodenal or pyloric scarring	10
Esophageal stricture	4
Perforation	4

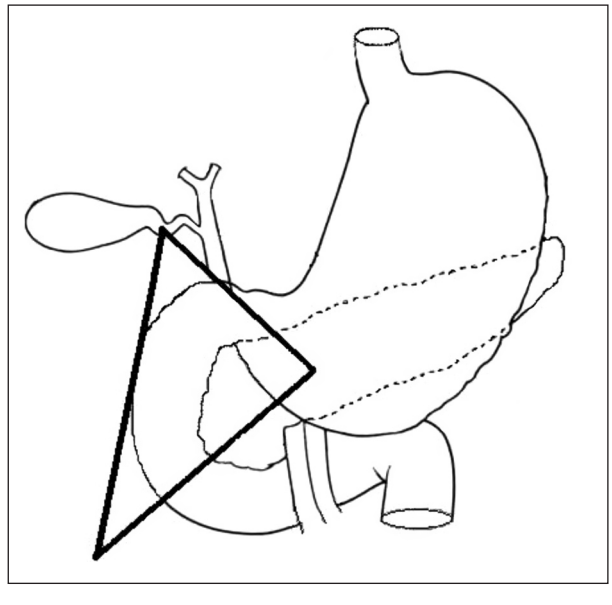

Fig. 5. The gastrinoma triangle

the pancreas (4, 13, 14). Ectopic gastrinomas have been described in stomach, bones, ovaries, liver, bile ducts (15–18). In sporadic gastrinoma duodenal primaries are usually in the first and second portion of the duodenum but in some cases may be in the third and fourth portion (19).

Duodenal gastrinomas tend to be small: usually they are up to 1 cm and difficult to locate (4, 19). Here the case of 3.5 cm size sporadic duodenal macrogastrinoma in the typical location (the first part of duodenum) has been represented by us. We performed literature search and found very few cases about duodenal macrogastrinomas (20). This suggests they are very rare worldwide. To our knowledge, it is the first such case in our country.

Most reports suggest that the diagnosis of ZES can be established in patients with gastrin levels greater than 1 000 pg/ml (500 pmol/l) (11). Interestingly, we found preoperative gastrin level to be severely high (21, 22) – greater than 22-fold upper limit (1 225 pmol/l (2 450 pg/ml)). Some studies observed gastrin levels greater than 10,000 pg/ml, but extremely high gastrin values (>100 times the normal value) are very rare in ZES (2). Studies suggest that there is no correlation between gastrin levels and the patient age, gender, race, disease duration, prior medical treatment, symptoms, however, there is a relationship between the gastrin level and tumor size, extent of disease (2, 11). Higher levels are more likely with larger tumor size and with metastatic disease (2, 4).

Surgical treatment is preferred as it has been clearly shown that nonsurgical patients develop liver metastases faster and die more frequently of this disease or some other causes (23, 24). Interestingly, some studies have shown there is no difference in overall survival among operated and non-operated patients (23). Larger studies recommend to perform lymph node excision, however, lymph node metastases have not been shown to adversely effect survival after resection with curative intent (25). It has been reported that both R0 (normal postoperative gastrin) or R1 resection (postoperative hypergastrinemia with no measurable residual disease) improved disease-specific survival in ZES whereas R2 resection (gross residual disease) did not improve disease-specific survival (11, 26). Furthermore, lymph node excision is associated with higher incidence of intraoperative and postoperative complications. We performed duodenal resection without lymph node excision, since there were no signs of metastases in lymph nodes or other organs, tumor was partially obstructing the lumen of the duodenum, our patient was older than an average patient with gastrinoma.

During the follow up period we observed slowly decreasing hypergastrinemia (Fig. 4). The etiology could be: other gastrinoma, lymph node involvement, metastases or hypertrophy of antral cells producing gastrin. The majority of sporadic gastrinomas are solitary, however, 20% of patients may have multiple duodenal gastrinomas or concurrent duodenal and pancreatic gastrinomas (9, 27, 28). Thompson and colleagues reported microadenomas of the duodenum as a common cause for persistent hypergastrinemia after surgery (29, 30). We performed somatostatin receptor scintigraphy, CT and upper GI endoscopy to reveal the reasons of slowly decreasing hypergastrinemia, though did not find any abnormalities. According to some studies, although somatostatin receptor scintigraphy has greater sensitivity (58%) than all other conventional studies (ultrasonography, CT, MRI, angiography) combined, it is unable to detect one third of all lesions found at surgery (11, 31). Furthermore, the localization of the tumor in the duodenum results in a sensitivity of scintigraphy of only 32%, whereas in the pancreas and other primary sites it is 90%, while half of the gastrinoma primary lesions are located in the duodenum (25, 32, 33). Besides, tumor size plays an important role: while gastrinomas larger than 2 cm are detected in 96% of the cases, the sensitivity of scintigraphy decreases to 30% when tumor is smaller than 1.1 cm (31, 32). What is more, somatostatin receptors are usually expressed in 80–100% of gastrinomas (11, 34), however, immunohistologic analyses in our case revealed no expression of somatostatin receptors. The available literature shows a good correlation between somatostatin receptor expression and in vivo detection by scintigraphy. Consequently, the potential use of radiolabeled somatostatin for management and possible use of long-acting somatostatin analogs for treatment in this case are doubtful.

What concerns the prognosis in our case, even if eugastrinemia has not been reached, it has been shown that surgical resection of all gross disease increases the disease-specific survival and decreases

the development of distant metastatic disease (11). Hepatic metastases most importantly influence long-term survival, whereas prevalence of lymph node metastases does not indicate premature death in patients with sporadic gastrinomas (9, 24, 35). It confirms the conclusions of authors who suggested TNM elements of gastrinoma staging in 1995 and found this staging to be highly reliable in predicting disease specific survival (26, 36). Lymph node involvement was not identified as a predictor of poor survival or disease progression. The most important variables in staging were tumor size and the presence or absence of metastases to the liver or other distant sites (26). According to this staging system, gastrinoma was T4 in our case. Other series report that poor prognostic factors in addition to liver metastases include: inadequate control gastric acid hypersecretion, presence of lymph node metastases, female gender, absence of MEN1, markedly increased fasting gastrin levels, presence of a large primary tumor (>3 cm), a pancreatic primary gastrinoma, histological features including Ki-67 index >2 (1, 37).

CONCLUSIONS

We have presented a case of a very rare 3.5 cm size sporadic duodenal macrogastrinoma with typical tumor location and some symptoms, but no peptic ulcer disease. Large tumor size is a poor prognostic factor, however, 8 months of follow-up did not reveal progression of the disease. The etiology of slowly decreasing hypergastrinemia remains unclear, controversial and is under investigation.

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SPORADINĖ DVYLIKAPIRŠTĖS ŽARNOS MAKROGASTRINOMA: RETAS KLINIKINIS ATVEJIS

Santrauka

Gastrinoma yra retas neuroendokrininis navikas, produkuojantis gastriną, kuris padidina druskos rūgšties sekreciją skrandyje ir sukelia Zollinger-Ellison sindromą. Šis sindromas dažniausiai pasireiškia sunkiai gyjančiomis viršutinės virškinamojo trakto dalies opomis. Pristatome labai retą dvylikapirštės žarnos sporadinės makrogastrinomos klinikinį atvejį. Pacientas buvo tiriamas dėl šešerius metus trukusio diskomforto viršutinėje pilvo dalyje, rėmens, protarpinio viduriavimo. Endoskopiškai, endosonoskopiškai ir histologiškai nustatyta dvylikapirštės žarnos gastrinoma. Jokių peptinės opos požymių nebuvo. Operacijos metu buvo pašalintas prievarčio ir dvylikapirštės žarnos segmentas su 3,5 cm dydžio makrogastrinoma. Šis atvejis unikalus, kadangi gastrinomos dažniausiai būna labai mažos – nuo kelių milimetrų iki 1 cm. Pooperaciniu periodu stebėta lėtai mažėjanti hipergastrinemija. Jos priežasčiai nustatyti atlikta somatostatino receptorių scintigrafija, kompiuterinė tomografija, endoskopinis tyrimas, tačiau patologijos nerasta. Aštuntą mėnesį po operacijos ligos progresavimo požymių neatsirado. Lėtai mažėjančios hipergastrinemijos etiologija išlieka kontroversiška, neaiški ir toliau tiriama.

Raktažodžiai: gastrinoma, dvylikapirštės žarnos makrogastrinoma, Zollinger-Ellison sindromas