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EDITORIAL

Sporadic versus hereditary gastrinomas of the duodenum and pancreas: Distinct clinico-pathological and epidemiological features

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Abstract

Gastrinomas are defined as gastrin secreting tumors that are associated with Zollinger-Ellison syndrome (ZES). ZES is characterized by elevated fasting gastrin serum levels, positive secretin stimulation test and clinical symptoms such as recurrent peptic ulcer disease, gastroesophageal reflux disease and occasional diarrhea. Genetically, nonhereditary (sporadic) gastrinomas are distinguished from hereditary gastrinomas, which are associated with multiple endocrine neoplasia type 1 (MEN1) syndrome. In general, duodenal gastrinomas are small and solitary if they are sporadic and multiple as well as hereditary. The sporadic gastrinomas occur in the duodenum or in the pancreas while the hereditary gastrinomas almost all occur in the duodenum. Our series of 77 sporadic duodenal neuroendocrine tumors (NETs) includes 18 patients (23.4%) with gastrinomas and ZES. Of 535 sporadic NETs in the pancreas collected from the NET archives of the departments of pathology in Zürich, Switzerland, and Kiel, Germany, 24 patients (4.5%) suffered from sporadic pancreatic gastrinomas and ZES. These NETs have to be distinguished from tumors with immunohistochemical positivity for gastrin but without evidence of ZES. An additional 19 patients suffered from MEN1 and ZES. These patients showed exclusively duodenal gastrinomas, but not pancreatic gastrinomas. The prognosis of sporadic and MEN1-associated duodenal gastrinomas is better than that of pancreatic gastrinomas, since they progress slowly to liver metastasis. In summary, sporadic and MEN1-associated gastrinomas in the duodenum and pancreas show different clinico-pathological and genetic features. The incidence of sporadic duodenal gastrin-producing tumors is increasing, possibly due to optimized diagnostic procedures. In contrast, pancreatic MEN1-associated gastrinomas seem to be extremely rare. A considerable subset of tumors with immunohistochemical expression of gastrin but without evidence of ZES should be designated as functionally inactive NETs expressing gastrin, but not as gastrinomas.

Key words: Endocrine tumor; Gastrinoma; Multiple endocrine neoplasia type 1; Precursor lesion; Zollinger-Ellison syndrome

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INTRODUCTION

Gastrinomas are defined as gastrin-producing tumors that are associated with Zollinger-Ellison syndrome (ZES) due to inappropriate gastrin secretion. ZES is characterized by elevated fasting gastrin serum levels, positive gastrin secretin stimulation test and clinical symptoms such as recurrent peptic ulcer disease, gastroesophageal reflux disease and occasional diarrhea[1,2].

The first cases of ZES were described in 1955[3].

One patient, a 36-year-old woman with severe recurrent ulcer disease and a family history strongly suggestive of multiple endocrine neoplasia type 1 (MEN1) background, was found to have several endocrine tumors, including microadenomas, in the pancreas. This case report already illustrates many of the issues that are still encountered in the diagnosis of gastrinoma. A closer look at the report by Zollinger and Ellison, on the basis of our current knowledge on gastrinomas, reveals that they were most likely dealing with a MEN1 patient. What is the reason for this assumption? Zollinger and Ellison described multiple endocrine tumors in the pancreas, which they thought were the cause of the ulcer syndrome, since their removal by a Whipple resection cured the patient. However, today we know that multiple gastrinomas virtually do not exist in the pancreas, but virtually always occur in the duodenum in the setting of MEN1. In this hereditary syndrome duodenal tumors producing gastrin are tiny and usually associated with multiple pancreatic tumors that do not produce gastrin, but may be large. In 1955, it was not possible to prove that the tumors produced gastrin. Firstly, gastrin still has to be isolated[4,5], and secondly, immunohistochemistry for gastrin has not yet been invented. Therefore, it is a quite likely assumption that Drs. Zollinger and Ellison's patient suffered from a recurrent ulcer disease in the setting of MEN1 syndrome and had multiple small gastrinomas in the duodenum, which were removed together with non-gastrin producing endocrine tumors in the pancreas. While the tumors in the pancreas were easily noticed and described, the duodenal minigastrinomas probably escaped detection.

This review focuses on the clinical setting and morphological aspects of sporadic and MEN1-associated duodenal and pancreatic gastrinomas. In addition, the results of an analysis of epidemiology of sporadic and MEN1-associated duodenal and pancreatic gastrinomas in a large series of duodenal and pancreatic neuroendocrine tumors (NETs) from the Swiss and German NET archives are presented.

CLINICAL SETTING OF GASTRINOMAS

Between 60% and 75% of patients with ZES are found to have an isolated duodenal or pancreatic gastrinoma (sporadic ZES). In the remaining patients ZES is part of MEN1 syndrome and these patients usually exhibit multiple duodenal gastrinomas (hereditary gastrinoma)[6-8]. The term pseudo-ZES (also called ZES type 1, as opposed to ZES type 2 caused by a gastrinoma) is coined for a syndrome with symptoms similar to ZES that appears to be caused by antral G-cell hyperfunction and hyperplasia[9,10]. The fact that this syndrome has no longer been described in recent years raises questions of whether it exists at all. In rare cases the syndrome of recurrent and intractable peptic ulceration may be found in association with a pancreatic endocrine tumor that does not produce and secrete gastrin[11]. The factor causing peptic ulceration in these patients has yet to be identified[12].

Among the gastroenteropancreatic neuroendocrine tumors associated with hormonal syndrome, gastrinomas are second only in incidence to insulinomas and are malignant in more than 60% of the cases. These tumors are classified as low grade malignant neoplasms, i.e. well differentiated neuroendocrine carcinomas. The peak incidence of gastrinomas lies between 40 and 50 years, children (5-15 years of age) are rarely affected[1].

SPORADIC GASTRINOMA

Sporadic gastrinomas occur either in the pancreas or in the duodenum and are apparently solitary tumors. In the past, approximately 70%-80% of these gastrinomas were thought to occur in the pancreas, particularly in its head. Currently, gastrinomas are more frequently found in the duodenum.

In general, gastrinomas represent the only type of endocrinologically active duodenal NETs, while all other types of duodenal NET (i.e. functionally inactive NETs expressing somatostatin, serotonin or gastrin, gangliocytic paraganglioma and poorly differentiated neuroendocrine carcinomas) are found to be endocrinologically silent. The reason for the increasing incidence of sporadic duodenal gastrinomas and endocrinologically silent inactive gastrin-producing NETs may be that many of these small NETs were overlooked but their large periduodenal/peripancreatic lymph node metastases were noted and recorded as primary gastrinoma in the pancreas or as primary lymph node gastrinoma in the past (details are shown below).

Sporadic duodenal gastrinomas usually arise from the first part of the duodenum and are located in the submucosa. They are most often less than 1 cm in diameter[13-16] (Figure 1A and 1B). Despite this small size metastases to regional lymph nodes are already found in 60% to 80% of the patients at the time of diagnosis[13]. It seems that periduodenal and peripancreatic lymph node metastases may grow faster than their duodenal primary tumors and thus may form large tumors that are easily recognized, in contrast to the duodenal primary tumors. It has therefore been suggested that the so-called peripancreatic and periduodenal lymph node gastrinomas that were described in the past may in fact be metastases of duodenal microgastrinomas that are overlooked during diagnostic work-up and surgery, rather than true primary tumors[17-19]. Apart from lymph node metastases, duodenal gastrinomas may metastasize to the liver, but only in a small percentage of cases (about 10%) and only many years after the manifestation of the disease[13]. Thus the10-year survival rate of 84% has been reported in patients with duodenal gastrinomas[20,21]. Fast growing and metastasizing duodenal gastrinomas are rare.

Histologically, duodenal gastrinomas are often submucosal tumors that infiltrate the mucosa and may also infiltrate the muscular layer if they are larger than 1 cm in diameter. They most often show a trabecular or pseudoglandular pattern. Their proliferative activity is usually between 2% and 10% (Figure 2). Some of the tumors may show angioinvasion. Their prognostic classification is outlined in detail in Table 1. Immunocytochemically, gastrin can be detected in all tumors[7,22]. Many duodenal gastrinomas are multihormonal and additionally contain single somatostatin or serotonin

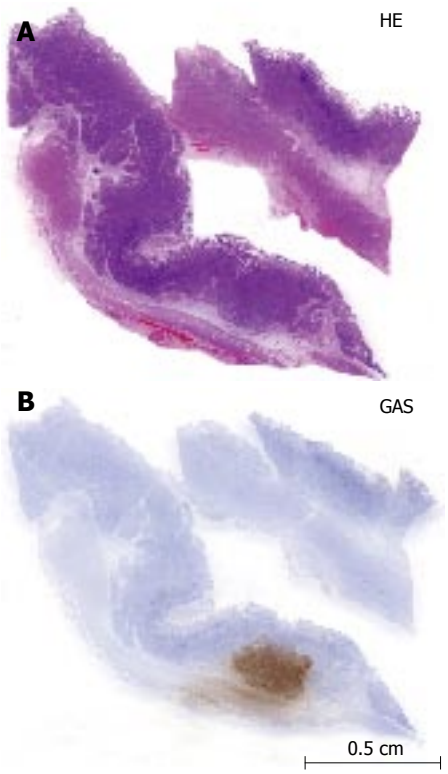

Figure 1 Overview of sporadic gastrinomas less than 3 mm in size within the submucosa stained with hematoxylin and eosin (**A**) and gastrin (**B**).

expressing cells in addition to gastrin cells.

Sporadic gastrinomas in the pancreas usually have a diameter of 2 cm or more (Figure 3). It has been reported that they occur more frequently in the head of the pancreas[13]. However, in our series they were found in all parts of the organ.

Metastasis of sporadic pancreatic gastrinomas to regional lymph nodes is found in approximately 60% of patients at the time of diagnosis[23], and liver metastases occur more frequently (10%-20%) than duodenal gastrinoma liver metastasis[17,18,23]. Thus the 10-year survival rate is worse in patients with pancreatic gastrinomas (57%) than in patients with duodenal gastrinomas (84%)[20,21]. In rare cases, bone metastases may develop in the terminal phase of a metastasized gastrinoma.

Histologically, pancreatic gastrinomas are similar to duodenal gastrinomas, but may have a higher proliferation and angioinvasion rate. Table 1 shows their prognostic assessment. Immunocytochemically, gastrin can be detected in almost all tumors[7,22]. Approximately 50% of gastrinomas are multihormonal and contain PP, glucagon and/or insulin in addition to gastrin.

Islet hyperplasia and nesidioblastosis have repeatedly been described in the non-neoplastic pancreas of patients with gastrinomas, but these findings cannot be confirmed by morphometry[24]. Recently, however, morphometrically defined PP-cell hyperplasia has been described in the ventrally derived region of the pancreatic head[25]. It has not been definitely established whether hypergastrinemia can influence these changes. In the stomach mucosa, however, sustained hypergastrinemia induces parietal cell hyperplasia with thickened mucosal folds and gastric acid hypersecretion. In addition, the number of enterochromaffin-like (ECL) cells is increased

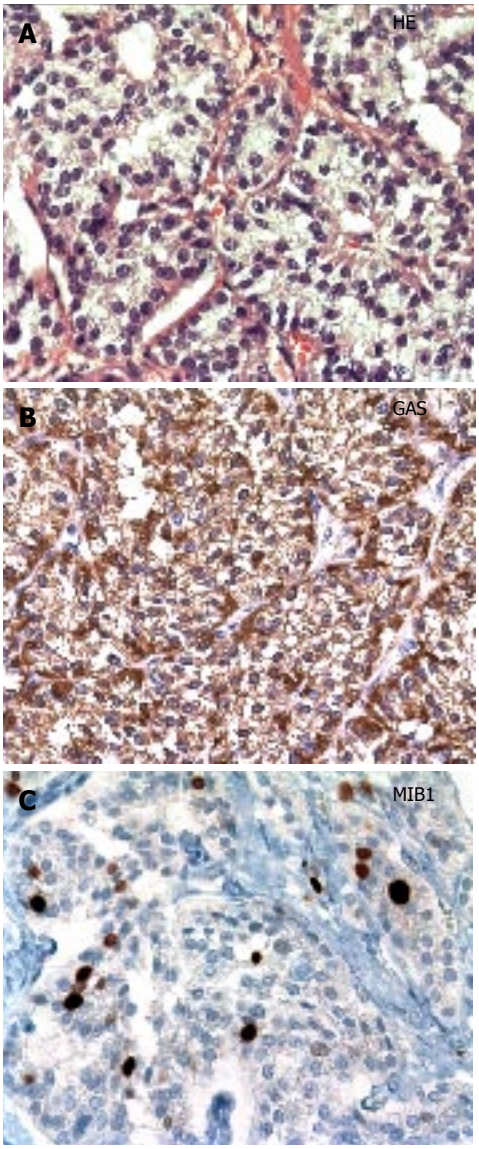

Figure 2 Morphology of sporadic duodenal gastrinoma stained with HE showing a trabecular and glandular growth pattern (**A**); strong immunoreactivity for gastrin (**B**), and expression of the nuclear proliferation antigen MIB1 in more than 2% of NET cells (**C**).

in the fundal mucosa[26-28]. ECL cell tumors in the fundus of the stomach, which are a well-known complication in patients suffering from pernicious anemia due to chronic type A gastritis, appear to be very uncommon in patients with sporadic ZES[7]. They have, however, been reported in patients with ZES and MEN1. In these instances they probably represent another neoplastic manifestation of MEN1 syndrome (see below) rather than merely the result of a trophic effect of gastrin[26,29].

MEN1-ASSOCIATED GASTRINOMAS

Approximately 25%-33% of patients with gastrinomas develop these tumors in the setting of MEN1. Almost all these gastrinomas reside in the duodenum[30]. They are usually smaller than 1 cm in diameter and multicentric, arising from multifocal hyperplastic gastrin cell proliferations[31] (Figures 4 and 5). Histologically,

Table 1 Classification of neuroendocrine tumors of the pancreas (WHO classification 2004)[41]

1 Well-differentiated neuroendocrine tumor
- Benign: confined to pancreas, < 2 cm in size, nonangioinvasive, ⩽ 2 mitoses/HPF and ⩽ 2% Ki-67-positive cells
  - Functioning: insulinoma
  - Nonfunctioning
- Benign or low grade malignant (uncertain malignant potential): confined to pancreas, ⩾ 2 cm in size, > 2 mitoses/HPF, > 2% Ki-67-positive cells, or angioinvasive
  - Functioning: gastrinoma, insulinoma, VIPoma, glucagonoma, somatostatinoma, or ectopic hormonal syndrome
  - Nonfunctioning

2 Well-differentiated neuroendocrine carcinoma
- Low grade malignant: invasion of adjacent organs and/or metastases
  - Functioning: gastrinoma, insulinoma, glucagonoma, VIPoma, somatostatinoma or ectopic hormonal syndrome
  - Nonfunctioning

3 Poorly-differentiated neuroendocrine carcinoma
- High grade malignant

Table 2 Classification of neuroendocrine tumors of the duodenum and upper jejunum

1 Well-differentiated neuroendocrine tumor
- Benign: nonfunctioning, confined to mucosa-submucosa, nonangioinvasive, ⩽ 1 cm in size
  - Gastrin-producing tumor (upper part of the duodenum)
  - Serotonin-producing tumor
  - Gangliocytic paraganglioma (any size and extension, periampullary)
- Benign or low grade malignant (uncertain malignant potential): confined to mucosa-submucosa, with or without angioinvasion, or > 1 cm in size
  - Functioning gastrin-producing tumor (gastrinoma), sporadic or MEN-1 associated
  - Nonfunctioning somatostatin-producing tumor (ampullary region) with or without neurofibromatosis type 1
  - Nonfunctioning serotonin-producing tumor

2 Well-differentiated neuroendocrine carcinoma
- Low grade malignant: invasion of the muscularis propria and beyond or metastases
  - Functioning gastrin-producing carcinoma (gastrinoma), sporadic or MEN-1 associated
  - Nonfunctioning somatostatin-producing carcinoma (ampullary region) with or without neurofibromatosis type 1
  - Nonfunctioning or functioning carcinoma (with carcinoid syndrome)
  - Malignant gangliocytic paraganglioma

3 Poorly-differentiated neuroendocrine carcinoma
- High grade malignant

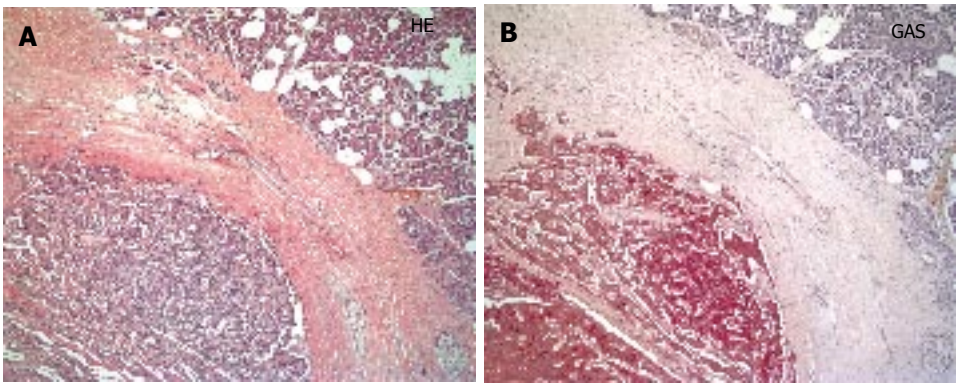

Figure 3 Overview of sporadic pancreatic gastrinoma surrounded by thickened collagen in the vicinity of normal pancreatic parenchyma stained with hematoxylin and eosin (**A**) and gastrin (**B**).

they show trabecular and pseudoglandular patterns and immunohistochemically they express gastrin and occasionally also somatostatin. Because of their small size they are (like sporadic duodenal gastrinomas) difficult to detect. Pancreatic gastrinomas associated with MEN1 are very rare[6,32], although the pancreas of these patients usually contains multiple endocrine micro- and macrotumors[33]. These tumors, however, virtually never produce significant amounts of gastrin[6,32]. The metastatic and biological behavior of duodenal MEN1-associated gastrinomas is similar to that of sporadic counterparts (Table 2).

EXTRADUODENAL AND EXTRAPANCREATIC GASTRINOMAS

Unusual sites of gastrinomas are the stomach[34], jejunum[35,36], biliary tract, liver[37] and kidney[38]. Ovarian or pancreatic mucinous cystic tumors that contain a sufficient number of active endocrine cells with gastrin production

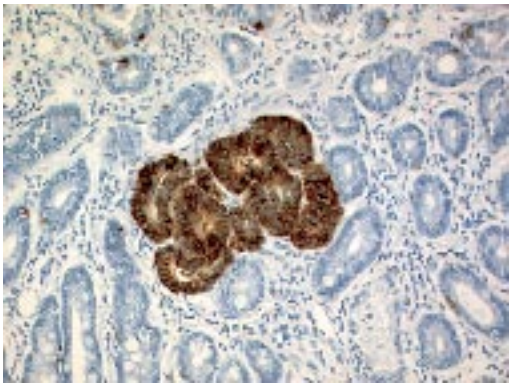

Figure 4 Circumscribed linear and nodular hyperplasia of gastrin cells within the Brunner's glands in a patient with MEN1.

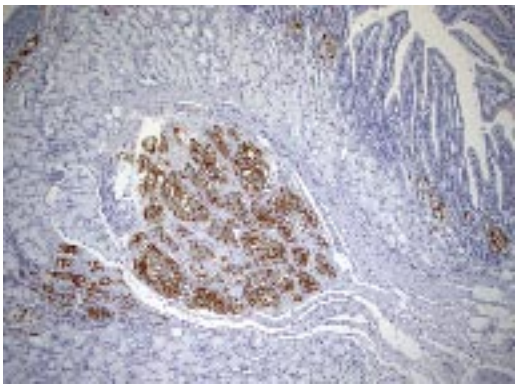

Figure 5 Tiny MEN1-associated duodenal gastrinoma within the submucosa revealing a diameter of less than 1 mm.

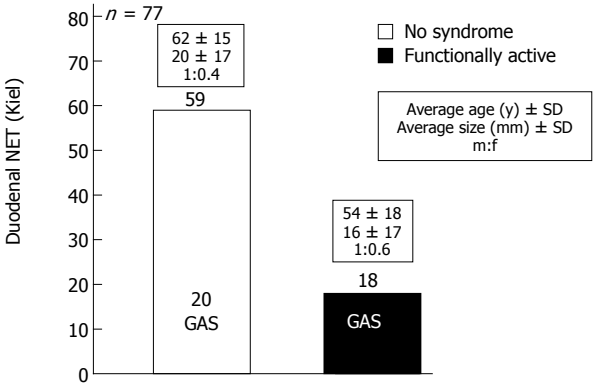

Figure 6 Duodenal NETs in the Kiel tumor archive. Fifty-nine (76.6%) out of the 77 NETs were endocrinologically not active, 20 of them expressed gastrin. These were not associated with ZES. All the functionally active NETs (18; 23.4%) were immunohistochemically positive for gastrin and showed a ZES.

may also cause ZES, but are uncommon[39-41].

PERSONAL OBSERVATIONS

In our series of sporadic duodenal NETs collected from 1975 to 2006, duodenal gastrin producing tumors account for 49.4% (38) of 77 sporadic NETs (Figure 6). Surprisingly, only 47.4% (18) of the gastrin-immunoreactive sporadic NETs show an association

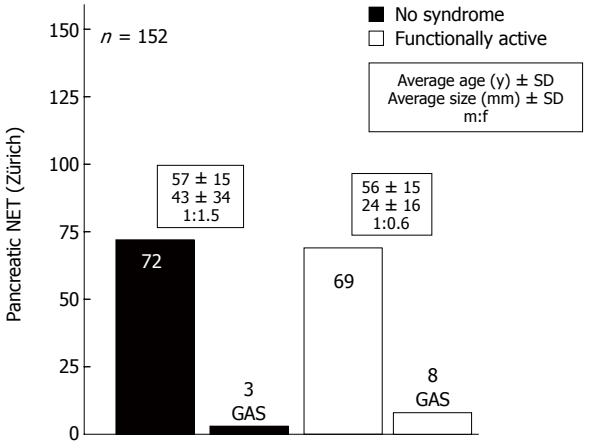

Figure 7 Pancreatic NETs in the Zürich tumor archives. Seventy-five (49.3%) out of the 152 pancreatic NETs were endocrinologically not active, of which 3 expressed gastrin. These 3 gastrin-expressing NETs were not associated with ZES. Eight of the 77 functionally active NETs were immunohistochemically positive for gastrin and associated with ZES.

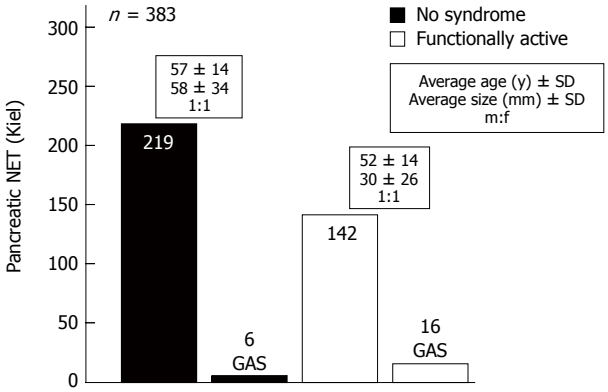

Figure 8 Pancreatic NETs in the Kiel tumor archives. Two hundred and twenty-five (58.7%) out of the 383 pancreatic NETs were endocrinologically not active. These gastrin-expressing NET were not associated with ZES. Sixteen of the 158 functionally active NETs were immunohistochemically positive for gastrin and showed a ZES.

with ZES (Figure 6). The reason for the lack of ZES in a considerable subset of patients with gastrin-expressing tumors remains to be analyzed in detail. Whether these gastrin producing tumors in the duodenum are similar in behavior to the duodenal gastrinomas remains unknown. However, it seems that they may have a different biology. Terminologically, these NETs with immunohistochemical expression of gastrin but without evidence of ZES should be designated as functionally inactive NETs expressing gastrin, but not as gastrinomas.

In two large series of sporadic pancreatic NETs from Kiel (n = 383) and Zürich (n = 152) pancreatic gastrinomas were found to be rare tumors, accounting for 4.2% (Kiel) and 5.3% (Zürich) of all collected sporadic tumors, respectively. Similar to duodenal tumors an additional 1.6 % (Kiel) and 2.0% (Zürich) of sporadic gastrin-expressing tumors were not associated with ZES and were therefore designated as functionally inactive pancreatic NETs producing gastrin (Figures 7 and 8).

It was reported that 19 (59.4%) of 32 patients with MEN1 showed ZES. The source of ZES in these patients

is duodenal rather than pancreatic gastrinomas. Most of these exhibit multifocal duodenal gastrinomas and lymph node metastases[31,33].

CONCLUSION

The preferred site of gastrinomas is the duodenum rather than the pancreas. Despite the small size of duodenal gastrinomas they may show the same rate of metastasis at the time of diagnosis as pancreatic gastrinomas, which are usually larger in size. However, the survival rate of patients with pancreatic gastrinomas is lower than that of patients with duodenal gastrinomas. MEN1- associated gastrinomas are virtually all localized in the duodenum. They are usually multiple. They probably arise from multifocal precursor lesions, i.e. diffuse gastrin cell proliferations that are lacking in sporadic duodenal gastrinomas. Biologically, the behavior of MEN1-associated gastrinomas is similar to that of sporadic duodenal gastrinomas. Gastrin expressing tumors both in the duodenum and in the pancreas without evidence of ZES should be designated as functionally inactive NETs producing gastrin, but not as gastrinomas. The reasons for the lack of hormonal symptoms in gastrin expressing NETs still need to be analyzed in detail.

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