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The Biological Relevance of Gastric Neuroendocrine Tumors

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Gastric neuroendocrine tumors were originally thought to have a low incidence (three percent). Since endoscopic diagnostic procedures have become clinical routine, they are now found more frequently (relative incidence up to 41 percent). In recent years, classifications have been developed that attempt to consider the biological relevance of these tumors. Four types of gastric neuroendocrine tumor may be distinguished: Type 1 gastric neuroendocrine tumor is most common. It is associated with chronic atrophic fundus gastritis, hypergastrinemia and often with pernicious anemia. Usually it is multicentric and smaller than one cm, does not produce any symptoms and has an excellent prognosis. Type 2 gastric neuroendocrine tumor is second in frequency. It has no association with other diseases, is solitary and has no predilection for a particular localization. It may be larger than 1 cm, produce a carcinoid syndrome or Zollinger-Ellison syndrome and have a metastasis rate of up to 30 percent. Type 3 gastric neuroendocrine tumor is rare and always associated with Zollinger-Ellison syndrome and multiple endocrine neoplasia type I. It occurs as multiple lesions in the gastric body fundus and has a lower metastatic rate than type 2 gastric neuroendocrine tumor. Type 4 gastric neuroendocrine tumor corresponds to a small-cell carcinoma.

INTRODUCTION

The incidence of gastric carcinoids, here collectively termed neuroendocrine (NE)[b] tumors of the stomach [1], was thought to be low [2, 3], not exceeding three percent of all gastrointestinal neuroendocrine tumors. Recent reports, however, have challenged this figure and suggested that the true incidence of gastric neuroendocrine tumors (GNET) ranges between 11 percent and 41 percent [4-6]. These rising figures probably do not represent a true increase in incidence, but rather indicate that the rate of occurrence was underestimated in former times, because the small GNETs associated with chronic atrophic corpus gastritis (CAG) were scarcely detected in the pre-endoscopic era.

The fact that GNETs are quite frequently encountered by the active endoscopist raises the question as to their biology and clinical significance. During recent years, the available information has increased rapidly, culminating in detailed accounts that have led to a better understanding of these lesions. As a consequence, new classifications that take their biology and prognosis into account have been developed [1, 7-9]. Based on this work, GNETs can be divided into four types, which we shall describe in more detail below.

CLASSIFICATION

Type 1 gastric neuroendocrine tumors

Type 1 GNET is the most frequent neuroendocrine tumor in the stomach, with a relative incidence between 51 percent and 88 percent [8, 10] (Table 1). This tumor is associated with

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[b]*Abbreviations:* NE, neuroendocrine; GNET, gastric neuroendocrine tumor; CAG, chronic atrophic corpus gastritis; ECL, enterochromaffin-like; MEN-1, multiple endocrine neoplasia syndrome, type 1; ZES, Zollinger-Ellison syndrome.

fundic CAG, which is usually of autoimmune nature, occurs predominantly in women and in some 20 percent of cases is combined with pernicious anemia [10]. If only patients with pernicious anemia are considered, GNETs may be found in five to 10 percent of the patients [4, 11]. Because of the disappearance of HCl-producing cells in the fundic mucosa of the stomach, there is sustained hypergastrinemia. Gastrin, however, is trophic for the ECL cells of the fundic mucosa [12-16], leading to their numerical increase (hyperplasia) and promoting their eventual clonal proliferation (tumor). Tumor development is usually multicentric and very slow, resulting in multiple small tumors (< 1 cm), which are restricted to the mucosa and submucosa. Tumors that are larger than 1 cm and invade vessels and/or the muscular wall of the stomach are extremely rare. Metastasis to the regional lymph nodes or liver is therefore the exception [8, 10]. This implies that type 1 GNET can be controlled by endoscopic surgery and have an excellent prognosis. Interestingly, regression of ECL-cell gastric carcinoids has been reported in patients with pernicious anemia after elimination of hypergastrinemia by antrectomy [17]. The tumors, which consist mainly of histamine-producing ECL cells (with some scattered serotonin and somatostatin cells), remain non-functioning, probably because they are well differentiated and very small. The ECL cells of the tumors and the cells of the precursor lesions consistently express the alpha-subunit of human chorionic gonadotropin [18].

Type 2 gastric neuroendocrine tumors

Second in frequency to type 1 GNET are well-differentiated NE tumors that arise sporadically in the gastric mucosa (Table 2). They may occur anywhere in the stomach and are not associated with CAG or any other specific disease. Their potential to metastasize is obviously greater than that of type 1 GNET [8, 10, 11]. If they are larger than 2 cm or show angioinvasion and deep muscle invasion, regional lymph node metastases can be expected in 60 percent of the cases and liver metastases in 80 percent [8]. Patients in whom metastasis has occurred have a mean survival of about four years. Histologically, the tumors usually show a trabecular pattern, and immunocytochemically they stain for neuroendocrine markers [8, 10] and for biogenic amines and peptides such as serotonin, histamine, glucagon, pancreatic polypeptide and others [19, 20]. Serotonin or histamine-positive tumors with metastasis to the liver (about 20 to 25 percent of all type 2 gastric NE tumors) produce either a classical carcinoid syndrome (due to the systemic effects of serotonin) or an atypical carcinoid syndrome (due to the effects of histamine [21, 22]).

Among the sporadic GNETs, there are a few that produce gastrin. A survey of the literature revealed eight of these tumors that were immunocytochemically verified and another seven tumors without detailed morphologic description (Table 3). These gastric gastrinomas may be differentiated from the remaining GNETs, not only because of their gastrin production, but also because of their peculiar localization. All but three of the immunocytochemically identified gastrin-producing GNETs arose in the antropyloric region.

Type 3 gastric neuroendocrine tumors

Type 3 GNETs are those that arise against the background of the inherited syndrome of multiple endocrine neoplasia type 1 (MEN-1) presenting with the Zollinger-Ellison syndrome (ZES) (Table 4). In this condition, the gastrinoma responsible for the ZES and hypergastrinemia is usually found in the duodenum [33, 34]. In addition to hypertrophic gastropathy, hypergastrinemia causes ECL cell hyperplasia in the oxyntic mucosa. ECL tumors may also occur in addition to ECL cell hyperplasia, but the tumors are thought to be promoted by the genetic changes underlying MEN-1 since similar tumors have never been observed in association with sporadic ZES [8], apart from one doubtful case [35]. The MEN-1/ZES associated tumors are usually small (mean 0.5 cm; range 0.1-1.6 cm) but

Table 1. Features of Type 1 GNET.

Relative incidence	51-88 percent
Association with other diseases	Chronic atrophic fundus gastritis Pernicious anemia
Hypergastrinemia	Present
Site	Gastric body fundus
Precursor lesions	Present
Occurrence	Multiple
Size	< 1 cm (95 percent)
Hormonal syndrome	No
Metastasis	3-8 percent nodal 1-4 percent hepatic

Table 2. Features of Type 2 GNET.

Relative incidence	12-18 percent
Association with other diseases	No
Hypergastrinemia	Absent
Site	Gastric body fundus (90 percent) Gastric antrum (10 percent)
Precursor lesions	Absent
Occurrence	Solitary (85 percent)
Size	> 1 cm (25 percent)
Hormonal syndrome	Carcinoid syndrome (7 percent) ZES (very rare)
Metastasis	26 percent nodal 17 percent hepatic

Table 3: Gastrin-producing GNETs.

Author	Number of patients	ZES	Site
Royston et al. 1972 [23]	1	Yes	Antropyloric
Larsson et al. 1973 [24]	1	Yes	Antropyloric
Soule et al. 1976 [25]	1	Yes	Antropyloric
Berger et al. 1978 [26]	1	Yes	Antropyloric
Russo et al. 1980 [27]	1	No	Antral-fundic
Thompson et al. 1985 [28]	1	Yes	Antral
Rindi et al. 1993 [8]	1	Yes	Antropyloric
Ahlmann et al. 1994 [11]	1	No	Antral
Mignon et al. 1986 [29]*	2	Yes	Gastric
Norton et al. 1986 [30]*	3	Yes	Near pylorus
Vogel et al. 1987 [31]*	1	Yes	Lesser curvature
Kaplan et al. 1990 [32]*	1	Yes	Antrum

*Tumors without immunocytochemical analysis and detailed descriptions.

Table 4. Features of Type 3 GNET.

Relative incidence	0-13 percent
Association with other diseases	ZES and MEN 1
Hypergastrinemia	Absent
Site	Gastric body fundus
Precursor lesions	Present
Occurrence	Multiple
Hormonal syndrome	No
Metastasis	20 percent nodal

Table 5. Features of Type 4 GNET.

Relative incidence	1-16 percent
Association with other diseases	No
Hypergastrinemia	No
Site	No predilection
Precursor lesions	Absent
Occurrence	Solitary
Hormonal syndrome	No
Metastasis	> 90 percent

may occasionally become large [36] or involve the oxyntic mucosa diffusely [37]. Metastasis to the regional lymph nodes has been observed in a few tumors [8, 36], all of them large.

Type 4 gastric neuroendocrine tumors

This GNET is characterized by its poor differentiation (Table 5). Histologically, the tumor is composed of medium-sized, rather than small cells, showing high proliferation activity. At the time of diagnosis, most of the tumors are already advanced. Their prognosis is therefore poor, with three quarters of the patients dying within one year of diagnosis due to extensive metastatic disease [8, 10, 38-42].

CONCLUSION

The GNETs show a broad functional and biological spectrum, which makes a division into different types necessary. The classification outlined in this paper considers the morphology and function of the tumors and their association with other diseases. On this basis four types can be distinguished, each with its own clinical relevance.

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