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Clinical Management of Gastric Neuroendocrine Tumors

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Gastric neuroendocrine tumors (GNETs, also known as gastric carcinoids) are rare form of hormone-secreting neoplasms that present with varied clinical syndromes. There are four types of GNETs based on size, proliferation, localization, differentiation, and hormone production. Type I GNET is related to autoimmune atrophic gastritis and hypergastrinemia. Type II GNETs are related to multiple endocrine neoplasia (MEN)-1, Zollinger-Ellison syndrome and hypergastrinemia. Type 3 GNETs are not associated with any background pathology, and type 4 GNETs are poorly differentiated tumors. The most useful diagnostic and prognostic marker for gastrointestinal NETs is plasma chromogranin A (CgA) levels. Endoscopic ultrasound is the method of choice to determine tumor size and depth of infiltration. For optimal management, the type, biology, and stage of the tumor must be considered. Here, we provide a comprehensive and up-to-date review of GNETs.

Key Words: Gastric neuroendocrine tumors, Chromogranin A, Multiple endocrine neoplasia, Autoimmune atrophic gastritis

INTRODUCTION

Gastric neuroendocrine tumors (GNETs, also known as gastric carcinoids) are rare, but they are increasing in incidence owing to the increased frequency of upper gastrointestinal endoscopy screening. They are generally slow-growing and secrete various peptides and neuroamines, some of which cause clinical symptoms. There are four types of GNETs based on size, proliferation, localization, differentiation, and hormone production. Type 1 GNETs are associated with autoimmune atrophic gastritis and hypergastrinemia, and type 2 with multiple endocrine neoplasia 1 (MEN-1, Zollinger-Ellison syndrome, and hypergastrinemia). Sporadic type 3 GNETs are not associated with any background pathology, and type 4 GNETs are poorly differentiated tumors. Clinical awareness of the protean and intermittent symptoms of GNETs (e.g., sweating, flushing, diarrhea, and bronchospasms) is critical for timely diagnosis; however, the classical carcinoid syndrome is relatively uncommon. Because of new epidemiological data, the management of GNETs warrants review. Here, we provide a comprehensive and up-to-date review of GNETs.

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DIAGNOSIS

The diagnostic work-up starts with gastroscopy. Endoscopically, GNETs present as polypoid lesions or, more frequently, as smooth and rounded submucosal lesions and may appear yellow or red in color. A depression can sometimes be seen at the center of the tumor. The use of high-resolution magnifying endoscopy (ME) and narrow band imaging (NBI) might be helpful for the endoscopic diagnosis of GNETs. Endoscopic ultrasonography (EUS) is useful for judging GNET invasion depth. GNETs are commonly seen in the second (deeper mucosa) or third (submucosa) echo layer and have a hypoechoic intramural structure. In type 1 and type 2 gastric NET disease, the specificity of EUS for T stage is greater than 90%.[1] EUS-guided FNA can be employed to define the borders of the lesion and obtain tissue for histological verification. Biopsies must be stained for chromogranin A and synaptophysin, and a mitotic count as well as a Ki-67 index assessment should be carried out. Abdominal ultrasound (or abdominal computed tomography [CT]) is recommended to search for liver metastases in type 1 and type 2 gastric NETs. Abdominal and thoracic CT scans are recommended for both type 3 and type 4 gastric NETs. Laboratory testing may be performed for specific hormones. Routinely, serum gastrin and serum

chromogranin A must be determined. If hypergastrinemia and a hyperacidic stomach (basal acid output >10 mmol/h or gastric pH<2) are found, a secretin stimulation test should be performed to establish the presence of ZES. In contrast to normal gastrin values found in type 3 NET disease, serum gastrin levels are high in type 1 and type 2 gastric NETs. Carcinoid syndrome only rarely occurs with gastric NETs. If symptoms of the carcinoid syndrome are present, the 24-hour urine accumulation is tested for 5-hydroxylindoleacetic acid (5-HIAA), and in rare patients determination of histamine metabolites or 5-hydroxytryphophan may be needed.

CLASSIFICATION

1. Type 1

Type 1 GNETs account for approximately 80% of all GNETs. They are associated with achlorhydria and hypergastrinemia, which occur in patients with chronic atrophic gastritis, and are generally present (77% of cases) as multifocal polypoid mucosal protrusions (<10 mm) in the corpus and/or fundus of the stomach. Underlying causes include elevated gastrin levels and consequent growth of enterochromaffin-like (ECL) cells resulting in dysplasia. Type 1 GNETs are characteristically minimally invasive with 27% limited to the mucosa, 64% invading to the mucosa and/or submucosa only, and 9% invading the muscularis propria only.[2] ECL cells secreting serotonin or somatostatin can be identified both immunohistologically and ultrastructurally. In addition to synaptophysin and chromogranin A, ECL cells express vesicular monoamine transporter 2 (VMAT2) and often alpha-human chorionic gonadotrophin (alpha HCG).[3] There are no reports of clinical hypersecretion syndromes in patients with type I GNETs or deaths resulting from type 1 GNETs.

2. Type 2

Type 2 GNETs are associated with MEN-1 and, to a lesser extent, Zollinger-Ellison syndrome. They express VMAT2, chromogranin A, and synaptophysin and are thought to originate from ECL cells, as are type 1 GNETs, with the ECL cells undergoing varying degrees of hyperplasia during tumor development.[4] Unlike type 1 GNETs, type 2 GNETs have both chief and parietal hyperplastic cells in the mucosa of the gastric body. Type 2 GNETs usually present after 15-20 years of MEN-1/Zollinger-Ellison syndrome rather than at the beginning. Morphologically, they are similar to type I lesions and usually 1-2 cm in size. Infiltrative growth and metastatic spread is more prevalent in type 2 GNETs than type 1 GNETs (10-30%).

3. Type 3

Type 3 GNETs are sporadic neoplasms not associated with any other stomach disease, hypergastrinemia, or ECL hyperplasia. They present as solitary polypoid tumors in any part of the stomach. Histologically, they exhibit a solid and trabecular growth pattern, and their proliferation rate often exceeds the 2% cutoff level of type 1 and 2 GNETs. In most instances, they consist of VMAT2-positive ECL cells. Most type 3 GNETs are larger than 10 mm (70%) at the time of diagnosis and usually metastatic at presentation (75%), with spread to the regional lymph nodes and the liver. Mortality is approximately 50%.

4. Type 4

Poorly differentiated neuroendocrine carcinomas of the stomach are nowadays classified as type 4 GNETs; they were not been any part of the original classification by Rindi et al.[3], which focused on gastric carcinoids. Type 4 neuroendocrine cancers are rare solitary carcinomas. When diagnosed, they are often ulcerated and they have already grown to a considerable size (50-70 mm in diameter). Histologically, they show a solid pattern reminiscent of small-cell or large-cell neuroendocrine lung carcinomas. There are numerous mitoses and angioinvasion. The tumor cells usually express synaptophysin, rarely express chromogranin A, and do not express VMAT2 or hormones. Most type 4 GNETs are diagnosed at an advanced stage and grow aggressively; half of the patients die of the disease within 12 months.

The four types of GNETs are described in Table 1.

PROGNOSIS FACTORS

1. Grading Proposal

It is generally accepted that no histological grading system effectively predicts the behavior of well-differentiated endocrine tumors. It was therefore decided to introduce a grading system that could help sort well-differentiated GNETs into G1 and G2 categories. As a working hypothesis, we proposed applying to foregut NETs a modified version of the grading system adopted by the World Health Organization for endocrine tumors of the lung, but exclusively referring to proliferative status (Table 2). Three tumor categories were identified: G1, <2 mitoses per 2 mm^2 (10 high-power fields, 40× magnification) and/or Ki-67 index ≤2%; G2, 2-20 mitoses per 2 mm^2 and/or Ki-67 index between 3 and 20%; and G3 ≥21 mitoses per 2 mm^2 and Ki-67 index >20%

Table 1. Classification and general features of the four types of gastric neuroendocrine tumors (GNETS)

	GNET (gastric carcinoid)			
	Type 1	Type 2	Type 3	Type 4 (Poorly differentiated neuroendocrine gastric cancer)
Relative frequency	70–80%	5–6%	14–25%	6–8%
Features	Often small (<10 mm) and multiple	Often small (<10 mm) and multiple	Solitary, often >20 mm	Solitary, often exulcerated, >20 mm
Associated conditions	CAG	MEN-1/ZES*	No	No
Histology	Well differentiated G1	Well differentiated G1	Well differentiated G1/G2	Poorly differentiated, G3
Serum gastrin	Very high or high	Very high or high	Normal	Mostly normal
Gastric pH	Anacidic	Hyperacidic	Normal	Mostly normal
Metastases	<10%	10–30%	50–100%	80–100%
Tumor-related deaths	No	<10%	25–30%	>50%

CAG, chronic atrophic gastritis; MEN-1, multiple endocrine neoplasia type 1; ZES, Zollinger-Ellison-syndrome
*ZES associated with MEN-1
†G1 and G2 indicate a well-differentiated tumor; G3 indicates a poorly differentiated. Ki-67 index: G1, 0–2%; G2, 3–20%; G3 >20%.

2. Chromogranin A

Chromogranin A is the most widely used diagnostic and prognostic marker for endocrine tumors. The increasing frequency of patients diagnosed with NETs emphasizes the necessity of relevant and reliable diagnostic assays based on clinical chemistry. A promising approach for future chromogranin A measurements is processing-independent analysis (PIA). PIA is used to measure levels of chromogranin A with increased diagnostic sensitivity, while simultaneously and easily estimating tumor burden.

Table 2. Grading proposal for neuroendocrine tumors

Grade	Mitotic count (10 HPFs)*	Ki-67 index (%)†
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

HPFs, high-power fields
*An HPFs is 2 mm^2, and at least 40 fields at 40× magnification were evaluated in areas with the highest density of mitotic figures.
†Determined using an MIB1 antibody. Approximately 2,000 tumor cells were evaluated in areas with the highest nuclear labeling.

MANAGEMENT

There are several treatment options for patients with gastric carcinoid tumors. The primary treatment for patients with GNETs should be curative surgery. Patients may receive one or more treatments such as surgery, minimally invasive therapy, hormone therapy, chemotherapy, and radiolabeled therapy. Treatment options for type 1 and 2 GNETs ≤2 cm include endoscopic mucosal resection, if feasible, with biopsy of the tumor and adjacent mucosa, and observation.[5] Endoscopic surveillance is recommended every 6-12 months, and radiologic tests based on clinical condition can be performed during the first 3 years. If there is no recurrence during the first 3 years, follow-up endoscopy and a radiologic examination can be performed at 1-year intervals. However, local resection or gastrectomy is recommended if the tumor invades behind the submucosa, margins are positive after endoscopic mucosal resection, or multiple tumors >1 cm or regional lymph node metastasis is observed. Several other treatment modalities are also available for the management of advanced NETs; these include administration of a somatostatin analog, peptide receptor radionuclide therapy, targeted therapies (everolimus and sunitinib), and chemotherapy. These treatments are summarized in Fig. 1.

1. Type 1 or Type 2 Gastric NETs Without Risk Factors for Metastatic Disease

Type 1 or 2 gastric NETs that are 1 cm in size or smaller, and without risk factors such as muscular wall infiltration, increased proliferation (>2%), and/or angioinvasion, can either be managed conservatively with regular surveillance or removed endoscopically. For type 1 or 2 tumors, of size 10 mmor smaller, with fewer than six nodules, and without the above mentioned risk factors, endoscopic removal is also recom-

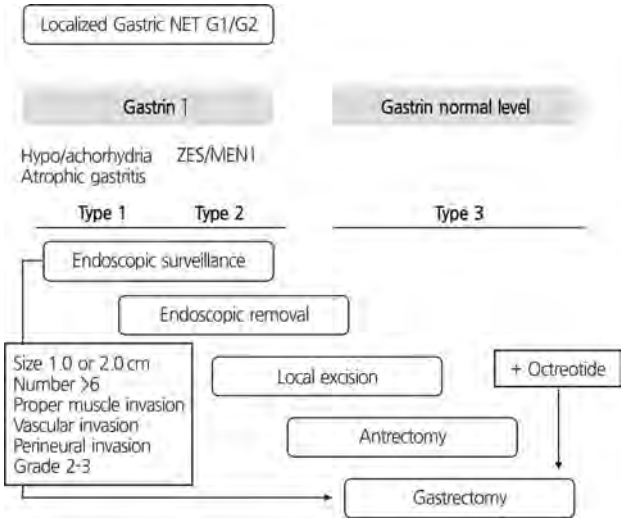

Fig. 1. Therapeutic methods for the management of gastric neuroendocrine tumors
NET, neuroendocrine tumor; MEN-1, multiple endocrine neoplasia type 1; ZES, Zollinger-Ellison-syndrome

mended.[6] Surveillance by gastroscopy is repeated at 1- or 2-year intervals.

2. Type 1 or Type 2 Gastric NETs 10-20 mm in Size

Various aspects of the treatment of type 1 or 2 gastric NETs that are 10-20 mm in size are a matter of debate. Whereas, most commonly, these carcinoids are resected endoscopically and followed thereafter by histological and endoscopic surveillance at 1- or 2-year intervals,[7] some authors have recommended different surgical strategies NETs 10-20 mm in size. Up to 3-6% of patients with type 1 gastric NET disease may develop second gastric adenocarcinoma.[2] Thus, in the setting of chronic atrophic gastritis, multiple biopsies should be taken. If infiltration of the muscular wall, angioinvasion, G2 grading (Ki-67 index >2%), or lymph node involvement are detected during follow-up, surgical therapy of the NET disease is indicated and interdisciplinary discussion is needed.

3. Type 1 or Type 2 Gastric NETs with Risk Factors (for Metastatic Disease)

In most countries, surgery is recommended for any gastric NETs greater than 20-30 mm in diameter.[7] Even small (<20 mm) type 1 or type 2 gastric NETs must be considered for surgery if they become angioinvasive, infiltrate the muscular wall, show G2 grading, or have metastasized. Treatment recommendations for type 2 gastric NETs can only be based on case reports and small case series. Management of the gastric NETs in these patients presents two particular problems: the carcinoid tumors are invariably multiple and the patient's hypergastrinemia cannot be easily reversed surgically. Because the hypergastrinemia is due to ectopic secretion from the gastrinoma, an antrectomy will not be effective.[8] If surgery is envisaged, total gastrectomy is preferred to partial gastrectomy

4. Type 3 Gastric NETs

Solitary type 3 gastric NETs should be managed surgically.[8] Only small (<10 mm), well differentiated (G1) type 3 gastric NETs may be treated conservatively by endoscopic mucosectomy. Because of the generally favorable tumor biology, surgery and/or local ablation should be considered even in metastatic carcinoid disease.

5. Poorly Differentiated Neuroendocrine Carcinomas of the Stomach

If the disease is locally limited, oncological surgical resection is indicated. In the case of systemic disease, cytostatic therapy as used for small-cell lung cancer is generally advised. Whether the poorly differentiated neuroendocrine cancer is node-positive or node-negative does not matter for systemic therapy. Liver involvement can occur even in the absence of locoregional lymph node metastases.[9]

6. Medical Therapy of Carcinoid Syndrome or ZES

Even though the carcinoid syndrome is characteristically atypical, long-acting somatostatin analogues are the drugs of choice, and if they fail alpha-interferon could be considered. Because of their better tolerability, depot preparations of somatostatin analogues (e.g. octreotide, lanreotide) are preferred to alpha-interferon. PPIs are the medical treatment of choice for ZES.[10] Patients with sporadic ZES disease should be managed surgically.

CONCLUSION

GNETs encompass indolent tumors to metastatic malignancies. The treatment of patients with GNETs has evolved and will continue to change new therapeutic options. Various treatment options have been incorporated into clinical practice. Radiologists in collaboration with oncologists, surgeons, and pathologists should adopt a multidisciplinary therapeutic approach that includes use of imaging and clinicopathologic data for optimized, focused care of patients with GNETs. In the future, highly sensitive biomarkers will be developed, and along with molecular imaging, they will become the cornerstones in the management of NETs.

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