REVIEW

Endoscopic diagnosis and management of type I neuroendocrine tumors

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Abstract

Type I gastric neuroendocrine tumors (TI-GNETs) are related to chronic atrophic gastritis with hypergastrinemia and enterochromaffin-like cell hyperplasia. The incidence of TI-GNETs has significantly increased, with the great majority being TI-GNETs. TI-GNETs present as small (< 10 mm) and multiple lesions endoscopically and are generally limited to the mucosa or submucosa. Narrow band imaging and high resolution magnification endoscopy may be helpful for the endoscopic diagnosis of TI-GNETs. TI-GNETs are usually histologically classified by World Health Organization criteria as G1 tumors. Therefore, TI-GNETs tend to display nearly benign behavior with a low risk of progression or metastasis. Several treatment options are currently available for these tumors, including surgical resection, endoscopic resection, and endoscopic surveillance. However, debate persists about the best management technique for TI-GNETs.

Key words: Gastric neuroendocrine tumor; Narrow band imaging; Magnifying endoscopy; Endoscopic submucosal dissection; Endoscopic surveillance

Core tip: The incidence of type I gastric neuroendocrine tumors (TI-GNETs) has significantly increased, TI-GNETs are the most frequently diagnosed of all GNETs, accounting for about 70%-80%. Endoscopically, TI-GNETs are present as small (< 10 mm), polypoid lesions or, more frequently, as smooth, rounded submucosal lesions. Especially, narrow band imaging and high resolution magnification endoscopy may be helpful for the endoscopic diagnosis of TI-GNETs. TI-GNETs tend to display a nearly benign behavior and a low risk of progression or metastasis in spite of submucosal invasion. Therefore, endoscopic submucosal dissection is a feasible technique for the removal of TI-GNETs.

INTRODUCTION

Neuroendocrine tumors (NETs), originally termed

Table 1 Characteristics of gastric neuroendocrine tumors			
Characteristic	Type I GNETs	Type II GNETs	Type III GNETs
Proportion of all GNETs	70%-80%	5%-10%	10%-15%
Associated disease	Chronic atrophic gastritis	MEN type 1/ZES	None
Gender	Women > men	Women = men	Women < men
Tumor number	≥ 1	≥ 1	1
Tumor size	< 10 mm	< 10 mm	Often > 20 mm
Tumor location	Fundus or corpus	Fundus or corpus	Any region
Histology	Well differentiated	Well differentiated	From well to poorly differentiated
Invasion depth	Mucosa or submucosa	Mucosa or submucosa	Any depth
Serum gastrin level	High	High	Normal
Gastric pH	Low	High	Normal
Metastasis risk	2%-5%	10%-20%	> 50%
Tumor-related death	0	< 10%	25%-30%
Prognosis	Excellent	Good	Poor

GNET: Gastric neuroendocrine tumor; MEN: Multiple endocrine neoplasia; ZES: Zollinger-Ellison syndrome.

carcinoid tumors, arise from neuroendocrine cells of the diffuse neuroendocrine system[1]. NETs are rare neoplasms; however, the incidence of gastrointestinal NETs (GNET) is gradually increasing with all NETs[2,3], while the ratio of GNETs to all GI NETs has increased according to the latest reports[4-9]. This increase in the incidence of GNETs reflects the true increase (that the incidence of GNET is increasing); however, this also might be related to improvements in diagnostic technology including endoscopy and increased GNET awareness. Because of the increasing incidence and prevalence, GNETs represent a substantial clinical problem.

GNETs are classified into three distinct subgroups: types I to III[10]. Table 1 shows the clinical characteristics of these three types[11-19]. Type I GNETs (TI-GNETs) arise in patients with chronic atrophic gastritis (CAG), including autoimmune gastritis (AIG; i.e., type-A gastritis) and Helicobacter pylori (H. pylori)-associated atrophic gastritis. Most TI-GNETs are small (< 10 mm), multiple, located within the gastric fundus or corpus, and limited to the mucosa or submucosa. TI-GNETs comprise the great majority (70%-80%) of GNETs. TI-GNETs are generally considered benign, with low metastasis rates and a 100% long-term survival rate.

Type II GNETs, which account for 5%-6% of all GNETs, are associated with the gastrin-secreting neoplasms in multiple endocrine neoplasia-Zollinger-Ellison syndrome (MEN-ZES). Therefore, hyperacidity-induced peptic ulceration is often seen in patients with type II GNETs. Type II GNETs are also small, multiple, and considered benign. However, the survival rate of patients with type II GNETs is lower than that

of patients with type I because of the course of the gastrinoma[20].

On the contrary, type III GNETs are sporadic tumors whose development is unrelated to gastrin conditions. Type III NETs are often single and large, have a diameter around 20 mm, and comprise approximately 10%-15% of all GNETs. These GNETs behave more aggressively and are usually metastatic and spread to the regional lymph nodes or liver.

This review focuses on TI-GNET pathogenesis, endoscopic diagnosis, and management.

TI-GNET PATHOGENESIS

TI-GNETs are associated with CAG, which leads to hypergastrinemia and enterochromaffin-like (ECL) cell hyperplasia. The loss of fundic glands seen in CAG results in a lack of acid production (achlorhydria). In response to achlorhydria, antral G-cells undergo hyperplasia and secrete more gastrin, resulting in hypergastrinemia. Gastrin stimulates gastric epithelial cell proliferation and acts as a trophic factor for ECL cells and leads to ECL cell hyperplasia. Therefore, hypergastrinemia results in the progression to TI-GNET development.

In either AIG- or H. pylori-associated gastritis, under the CAG condition, a lack of gastric acid production results in hypergastrinemia and leads to TI-GNET progression. In the AIG, anti-parietal cell antibody acts on gastric parietal cells, leading to acid secretion disorder and resulting in more gastrin secretion by antral G-cells. The role of H. pylori in TI-GNET development is unclear. However, it is well known that H. pylori infection induces hypergastrinemia[21,22]. H. pylori induces gastric mucosal atrophy, resulting in low acid output[23]. The negative feedback loop created by this low acid output causes hypergastrinemia. One possible mechanism is that antibodies against H. pylori may act like those against parietal cells[24-26]. Furthermore, H. pylori lipopolysaccharide stimulates DNA synthesis in ECL cells, suggesting that it may contribute to ECL cell hyperplasia[27]. Some reports have suggested that H. pylori infection might be a risk factor for TI-GNET in humans due to hypergastrinemia[28,29]. However, a minority of patients with CAG had TI-GNETs; therefore, it has been proposed that other cofactors (i.e., Reg[30], mcl-1[31], MEN-1 gene mutation[32]) might play a role in TI-GNET development.

Proton pump inhibitors (PPI) create hypergastrinemia secondary to gastric hypoacidity. Therefore, PPI treatment causes ECL hyperplasia in rats[33,34]. In humans, there are some case reports of GNETs that developed after long-term PPI treatment[35-38], and one revealed disappearance of the tumors after PPI treatment discontinuation[38]. However, the number of reports about GNETs compared to those on PPI users remains very small, and it is generally accepted that continual PPI use is not associated with GNET development in
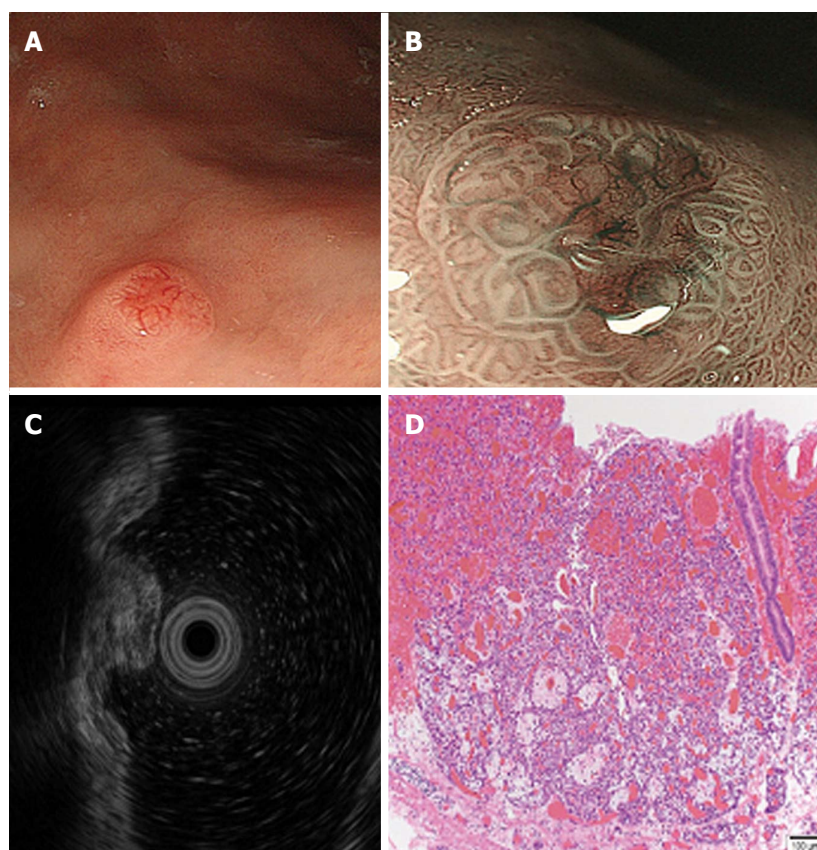
Figure 1 Type I gastric neuroendocrine tumor. A: Conventional endoscopic image taken under white light. A hemispherical reddish polyp with a central depression is visible; B: Magnifying endoscopic image taken with a narrow band imaging system. Gastric pit-like structures present on the tumor's surface, except for the central depression. In the central depression, the pit-like structure was not present, whereas dilated blackish-brown subepithelial vessels with cork-screw capillaries are visible; C: Endoscopic ultrasound showing a hypoechoic intramural structure in the second layer of the tumor; D: Histological appearance. Magnification (40 ×) of a hematoxylin-and-eosin–stained section of the tumor revealing a gastric neuroendocrine tumor limited to the mucosa.

humans.

TI-GNET DIAGNOSIS

Clinical features

Most patients with TI-GNETs have no specific symptoms related to "carcinoid syndrome"[39,40] such as flushing, tachycardia, and diarrhea. However, those with TI-GNET have nonspecific symptoms (nausea, abdominal pain, dyspepsia)[41] or pernicious anemia complicated by AIG. Therefore, TI-GNETs are detected incidentally during esophagogastroduodenoscopy.

TI-GNETs are more prevalent in women[14,16], a finding that is attributed to the fact that AIG occurs more commonly in females[42]. AIG is also substantially more common in patients with other autoimmune-related diseases (type 1 diabetes mellitus[43], autoimmune thyroiditis[44], and primary biliary cirrhosis[45]) than in the healthy population. Therefore, the existence of TI-GNETs should be also appropriately investigated in patients with those diseases. Moreover, under the condition of CAG, the stomach becomes unable to produce sufficient amounts of pepsinogen and pepsin due to gastric chief cell injury. Therefore, patients with CAG show the low pepsinogen I level and pepsinogen I

/II ratio on serological testing[46], while the measurement of pepsinogen I level and pepsinogen I/II ratio might be helpful for distinguishing TI-GNETs from the other two GNET types.

Serum chromogranin A (CgA) levels are increased in patients with TI-GNETs[39]. However, an elevated serum CgA level is not specific to GNETs. Therefore, measuring CgA is not recommended as a routine screening but rather as a surveillance marker for monitoring GNET progression.

Endoscopy

TI-GNETs are often small (< 10 mm), multiple, and found in the gastric corpus or fundus. Endoscopically, TI-GNETs present as polypoid lesions or, more frequently, as smooth and rounded submucosal lesions[47] 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[48]. The ME with NBI approach provides very clear images of the fine superficial structure and microvasculature of the gastric mucosa. Endoscopic TI-GNET images are shown in Figure 1. Endoscopy with white light revealed

Table 2 Histological grading of gastrointestinal neuroendocrine neoplasms

ENETS grading	Mitotic index (× 10 HPF)	Ki-67 proliferation index (%)	WHO classification 2010
G1	< 2	≤ 2	NET G1 (carcinoid)
G2	2-20	3-20	NET G2
G3	> 20	> 20	NEC G3; large-cell or small-cell type

ENETS: European neuroendocrine tumor society; HPF: High power field; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma.

a hemispherical reddish polyp with or without a central depression (Figure 1A). Most of the GNET surface is covered with normal mucosa; therefore, gastric pits can be visualized in ME using the NBI system. However, in the area of the central depression, gastric glands vanish, so the gastric pits cannot be visualized. The tumor grows expansively beneath the epithelium; therefore, abnormally dilated subepithelial vessels with blackish-brown or cyan corkscrew-shaped capillaries are visible (Figure 1B). This finding reflects the fact that the tumor grew beneath the epithelium without a gland structure. Differential diagnoses include gastric lymphoma and metastatic lesions (breast cancer, lung cancer, and melanoma), which also present as protruding tumors covered with non-tumorous mucosa.

Endoscopic ultrasonography (EUS) is useful for judging GNET invasion depth[49]. On EUS, GNETs are commonly seen in the second (deeper mucosa) or third (submucosa) echo layer and have a hypoechoic intramural structure (Figure 1C). The tumors generally have a hypoechoic structure with uniform echotexture. The tumor margins are typically well defined and smooth, and the overall shape is round and oval. A 20 MHz frequency ultrasound probe is generally useful for the evaluation of small GNETs; however, lesions > 20 mm may require the use of a lower frequency (12 MHz) probe[50].

Additionally, as documented above, the greater portions of these tumors are covered with normal mucosa; therefore, the collection of adequate endoscopic biopsy specimens in the deeper cut is required for diagnosis. Sampling biopsy should be taken of not only the TI-GNET lesion but also each antrum and corpus/fundus to assess for the presence of atrophic gastritis and hyperplastic/dysplastic proliferation of ECL cells as TI-GNET precursors[51].

Histology
TI-GNETs are composed of small uniform cells in nests and infiltrating strands with a ribbon-like, tubular, or acinar pattern (Figure 1D). According to the European Neuroendocrine Tumor Society (ENETS) consensus proposal in 2006, NETs are classified by counting mitosis and Ki67 index (Table 2)[52]. Based on this grading method, in 2010, the World Health Organization

(WHO) classification[53], histological classification of NETs is based on proliferation and differentiation: G1 NET, G2 NET, neuroendocrine carcinoma (NEC), mixed adenoneuroendocrine carcinoma, and hyperplastic and pre-neoplastic lesions. A G3 tumor classified by ENETS criteria would correspond to NEC on WHO criteria. Histologically, most TI-GNETs are G1 NETs.

Other imaging
Computed tomography or magnetic resonance imaging can provide useful information about local spread and distal metastasis to aid with tumor staging. The role of fludeoxyglucose positron emission tomography is unclear in the assessment of TI-GNETs[54]. Findings of somatostatin receptor scintigraphy, also known as an octreoscan, are often negative in TI-GNETs[55] because this method cannot usually identify small GI-NETs.

TI-GNET MANAGEMENT
The clinical management and treatment of TI-GNETs depends on tumor size and the presence of risk factors such as muscular wall infiltration, increased proliferation, and/or metastasis. Simple surveillance or endoscopic resection (ER) is generally recommended for TI-GNETs < 10 mm that have not invaded the muscularis propria or otherwise metastasized. The treatment of TI-GNETs 10-20 mm that are limited to the submucosa is controversial: ENETS guidelines recommend ER, whereas National Comprehensive Cancer Network (NCCN) guidelines[56] recommend both ER and endoscopic surveillance. Patients with TI-GNETs measuring > 20 mm, or those that have invaded beyond the submucosa, or have multiple lesions that are unsuitable for ER generally require surgical resection.

Endoscopic resection
Hitherto, endoscopic mucosal resection (EMR) has been recommended and is performed, as it is the most useful method of mucosal resection for local TI-GNETs. However, TI-GNETs frequently invade the submucosa; therefore, they are difficult to remove completely, even when small, using snare polypectomy or conventional EMR. In contrast, endoscopic submucosal dissection (ESD) is a feasible technique for the removal of tumors such as TI-GNETs within the submucosal layer. Recent reports have shown that the complete resection rate of GNETs using ESD was superior to that using EMR[57,58].

Surgical resection
Surgical resection is generally recommended for TI-GNETs > 20 mm in diameter or those that have invaded beyond the submucosa[52,56]. Moreover, surgery should also be performed in the presence of lymph nodal, distant disease spread, or poorly differentiated neoplasms[51]. For surgical therapy, local resection and/or antrectomy to reduce gastrin levels should

be chosen. Antrectomy removes G-cell–mediated hypergastrinemia; however, it might not effectively prevent recurrence and/or metastasis[59]. This suggests that TI-GNETs can grow autonomously independent of gastrin and beyond the gastrin responsive growing point. In the case of TI-GNET recurrence or persistence after local resection and antrectomy, total gastrectomy would be needed.

Medical management

Somatostatin analogs (SSAs) act on G-cells to inhibit gastrin secretion and play a role in reducing ECL cell hyperplasia. SSA treatment effectively reduces TI-GNET number and size[60-62]. However, its use cannot be recommended due to its short-term effects (*i.e.*, the tumor recurs after its cessation)[63] and its relatively high cost. Recently, natazepide (YF476), a peripheral gastrin (CCK-B) receptor antagonist, has been reported to suppress gastric acid output and ECL cell proliferation and reduce TI-GNET size and number[64]. However, there is no study on the long-term administration or large studies on CCK-B receptor antagonist treatment for TI-GNETs.

TI-GNET PROGNOSIS AND FOLLOW-UP STRATEGY

Patients with TI-GNETs generally have an excellent prognosis; in fact, disease-specific survival approaches 100%[39,40,59,60,65-74]. Tumor size and depth predict lymph node metastasis for GNETs[75], and presence of metastasis was the only factor that influenced long-term prognosis of patients with GNETs[40]. Moreover, histological tumor grading is well correlated with patient survival[68]. Therefore, the assessment of tumor metastasis, size, depth, and histological grade may predict patient prognosis. In fact, metastatic TI-GNETs are related to tumor size $\geq$ 1 cm, an elevated Ki-67 index, and high serum gastrin levels[76]. On the other hand, TI-GNET recurrence rates are relatively high; however, recurrent lesions are small, indolent, and unrelated to prognosis[39,72].

Post-treatment ENETS guidelines propose that endoscopic surveillance be provided every 12 mo for patients with recurrent TI-GNET and every 24 mo for patients without recurrence[51]. NCCN guidelines recommend that patients with small (< 20 mm) TI-GNETs who did not require ER or treatment be evaluated using patient history and a physical examination every 6-12 mo[56]. The guidelines also recommend that follow-up endoscopy be performed every 6-12 mo for the first 3 years and annually thereafter if no evidence of recurrence or progression is seen[56]. However, an optimal follow-up schedule as a clinical standard has yet to be established.

CONCLUSION

The incidence of NETs has increased significantly, and the vast majority of NETs are TI-GNETs. TI-GNETs present as small (< 10 mm) and multiple lesions that are generally limited to the mucosa or submucosa. TI-GNETs tend to display a nearly benign behavior and a low risk of progression or metastasis. Several treatment options are currently available for TI-GNETs; however, their optimal management has not yet been established. Further studies on TI-GNETs are needed to develop new promising management strategies for patients with TI-GNETs.

In routine clinical practice, the careful observation of the gastric mucosa in CAG and the knowledge of the endoscopic characteristic of TI-GNETs would be required for detection of TI-GNETs. When it exists, it would be important to choose appropriate treatment after the assessment of the size, invasion, metastasis and histological grading of the tumors.

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