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REVIEW

Classification, clinicopathologic features and treatment of gastric neuroendocrine tumors

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Abstract

Gastric neuroendocrine tumors (GNETs) are rare lesions characterized by hypergastrinemia that arise from enterochromaffin-like cells of the stomach. GNETs consist of a heterogeneous group of neoplasms comprising tumor types of varying pathogenesis, histomorphologic characteristics, and biological behavior. A classification system has been proposed that distinguishes four types of GNETs; the clinicopathological features of the tumor, its prognosis, and the patient's survival strictly depend on this classification. Thus, correct management of patients with GNETs can only be proposed when the tumor has been classified by an accurate pathological and clinical evaluation of the patient. Recently developed cancer therapies such as inhibition of angiogenesis or molecular targeting of growth factor receptors have been used to treat GNETs, but the only definitive therapy is the complete resection of the tumor. Here we review the literature on GNETs, and summarize the classification, clinicopathological features (especially prognosis), clinical presentations and current practice of management of GNETs. We also present the latest findings on new gene markers for GNETs, and discuss the effective drugs developed for the diagnosis, prognosis and treatment of GNETs.

Key words: Gastric neuroendocrine tumor; Classification; Clinicopathological significance; Diagnosis; Prognosis; Treatment

Core tip: Gastric neuroendocrine tumors (GNETs) comprise distinct tumor entities that have been classified on the basis of pathogenesis and histomorphologic characteristics into 4 types that differ in biological behavior and prognosis. To plan the correct management and optimal therapeutic approach in patients with GNETs, it is essential to obtain an adequate clinical evaluation and assessment of the pathological features of the tumor. Development of new gene markers as well as effective drugs is expected for the better diagnosis, prognosis and treatment of GNETs.

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INTRODUCTION

Gastric neuroendocrine tumors (GNETs) are rare tumors, occurring in 1 to 2 cases/1000000 persons per year, and accounting for 8.7% of all gastrointestinal neuroendocrine tumors[1]. However, over the last 50 years, the incidence of GNETs has increased in most countries, in part because of better awareness and more widespread

Table 1 Features of gastric neuroendocrine tumors

	Type Ⅰ GNET	Type Ⅱ GNET	Type Ⅲ GNET	Type Ⅳ GNET
Proportion of GNETs	70%-80%	5%-6%	14%-25%	Rare
Tumor features	Usually multiple, small (1-2 cm), polypoid or intramucosal	Usually multiple, small (1-2 cm), polypoid	Single, large (> 2 cm, mean 5.1 cm)	Single, large (largest 16 cm)
Risk of metastases	2%-5%	10%-30%	50%-100%	100%
Tumor-related death	< 0.5%	< 5%	Well-differentiated: 25%-30%, poorly differentiated: 75%-87%	100% (Mean survival of 6.5-14.9 mo)
Proliferation (Ki67)	< 2%	< 2%	> 2%	> 30%
Immunohistochemistry	CgA, NSE, VMAT 2 positive	CgA positive	CgA negative	Synaptophysin, NSE, PGP9.5 positive; CgA negative
Histology	Mitoses (absent or occasionally)	mitoses < 1 per 2 HPFs	Mitoses > 1 per HPF	Severe grade 3 histology

GNET: Gastric neuroendocrine tumor; CgA: Chromogranin A; NSE: Neuron specific enolase; VMAT: Vesicular monoamine transporter; HPF: High power field.

use of upper gastrointestinal endoscopy[2]. Gastric neuroendocrine carcinoma has also been recently reported in a patient with long-term use of a proton pump inhibitor[3]. GNETs are classified into four types, based on pathogenesis and histomorphologic characteristics; these types differ in biological behavior and prognosis[4-6], ranging from benign to highly malignant biological behavior and extremely poor prognosis[7]. Novel strategies for treating GNETs have been developed recently.

CLASSIFICATION

The four GNET subgroups are listed in Table 1. Classification is based primarily on their clinicopathological features[4-6]. Type Ⅰ GNET is mostly related to chronic atrophic gastritis, reflected by the presence of multiple small neoplasms; it has an excellent prognosis after resection[8,9]. Because of its low metastatic potential, type Ⅰ GNET is the most benign type, with death from metastatic disease reported in only three patients out of 724 cases reviewed; however, despite their generally benign course, the malignant potential of type Ⅰ GNET should not be ignored when planning the medical workup of these patients[10]. Type Ⅱ GNET is histologically similar to type Ⅰ, and is usually associated with *MEN1* syndrome or Zollinger-Ellison syndrome[11-13]. It is also usually considered to be benign, with a low risk of malignancy[14]. Type Ⅲ GNET is a solitary sporadic tumor that quite often infiltrates the muscularis propria and serosa; it is usually not associated with other gastric conditions or hypergastrinemia and frequently presents as a large lesion, greater than 10 mm in size, which is well-differentiated, and is accompanied by angioinvasion and lymph node and liver metastases, resulting in a poor prognosis[15]. Type Ⅳ GNET is an uncommon tumor, and usually is single, large, poorly differentiated, and highly malignant; it is typically accompanied by vascular invasion and metastases, and has an extremely poor prognosis[16].

Types Ⅰ to Ⅲ GNETs are comprised of enterochromaffin-like (ECL) cells, while type Ⅳ consists of other types of endocrine cell tumors (that secrete serotonin, gastrin, or adrenocorticotrophic hormone), poorly differentiated endocrine carcinomas, and mixed endocrine-exocrine tumors[17]. Well-differentiated tumors generally originate from ECL cells that are located in the corpus/fundus mucosa of the stomach, and represent the major proliferative target of gastrin, which is considered to be the main stimulus for the growth both of type Ⅰ and type Ⅱ GNETs. On the contrary, type Ⅲ and type Ⅳ GNETs are "gastrin-independent".

CLINICOPATHOLOGICAL FEATURES

Type Ⅰ GNET

Seventy to eighty percent of gastric GNETs are type Ⅰ tumor and they are usually less than 10 mm in diameter, multiple, mostly related to chronic atrophic gastritis, and localized in the gastric fundus or body[18]. The histological features show a typical GNET, a trabecular or solid arrangement. Tumor cells are monomorphic and medium sized, of regular shape with round nuclei. Mitoses are either absent or are seen occasionally. Tumor extension is limited to the mucosa or submucosa. The gastrin-dependent GNETs are consistently associated with generalized proliferation of endocrine cells in the extratumoral fundic mucosa. A histopathological classification has been formulated for the spectrum of proliferative lesions presented by fundic endocrine cells of hypergastrinemic patients; it arranges type Ⅰ tumors in a sequence presumed to reflect the temporal evolution of the process and the increasing oncologic risk for patients[19]. Diagnosis of GNETs requires efficient histopathological, biochemical and diagnostic imaging analyses[20-22].

Most type Ⅰ tumor cells are strongly positive for endocrine markers such as chromogranin A (CgA), neuron-specific enolase (NSE), and vesicular monoamine transporter 2, which characterize the cells as histamine-producing cells. Once the diagnosis of a type Ⅰ GNET is suspected, determination of CgA expression can be helpful. However, the concentration of CgA correlates with the number of ECL cells; thus, a pathologically high CgA concentration is neither pathognomonic nor essential for the diagnosis of type Ⅰ GNET. The proliferation marker MKI67 is typically expressed in less than 2% of the tumor cells. Patients are usually asymptomatic, with diagnosis usually occurring during gastroscopy. Destruc-

tion of parietal cells from longstanding chronic atrophic gastritis may lead to reduced intrinsic factor secretion and consequently to an impaired resorption of vitamin B12; thus, vitamin B12 deficiency and hyperchromic macrocytic anemia are often associated with autoimmune atrophic gastritis and hypergastrinemia[23].

Type I GNET is very rarely metastatic (5% to local lymph nodes; less than 2% showing distant metastases), with no related deaths and a reported long-term survival rate of 100%[23-25]. Thus, initial staging is recommended. Endoscopic ultrasound can be helpful to demonstrate localized disease, *i.e.*, lack of submucosal infiltration, while an upper abdominal computed tomography (CT) scan could aid in detecting metastatic hepatic disease[26]. Depending on the size and number of the lesions, endoscopic tumor resection is the treatment of choice[27].

Netazepide (YF476) is a potent and highly selective cholecystokin 2 receptor antagonist of the benzodiazepine class[28]. It is an orally active, highly selective and competitive antagonist of gastrin receptors[29]. Netazepide is a tool used to study the physiology and pharmacology of gastrin, and merits application in patients, to assess its potential to treat gastric acid-related conditions and the trophic effects of hypergastrinemia[30]. Although repeated doses of netazepide lead to tolerance with regard to the drug's effect on pH, the accompanying increase in plasma gastrin is consistent with continued inhibition of acid secretion by antagonism of the gastrin receptor and by gene up-regulation[31]. It was reported that treatment of GNET type I with YF476 results in regression of the tumor and normalization of serum chromogranin A[32].

Ravizza *et al*[25] recommend use of endoscopic/histological examination to follow patients with type I GNET, along with an annual abdominal ultrasound scan; and that endoscopic ultrasonography, CT and somatostatin receptor scintigraphy be reserved for lesions with a diameter greater than 10 mm, or when clinically indicated to plan an adequate endoscopic/surgical resection of the lesions. However, despite their generally benign course, type I GNET may have malignant potential, a finding that should be considered when planning the medical workup of these patients[10].

Type Ⅱ GNET

Five to six percent of GNETs reportedly are type Ⅱ tumors, which occur as a result of a gastrin-secreting neoplastic tissue in Zollinger-Ellison syndrome. Clinically, type Ⅱ GNET behaves similarly to the type I tumors described above, with small (1-2 cm), multiple, and well differentiated lesions. The proliferation marker MKI67 is expressed in < 2% of the tumor cells. Endocrine markers such as CgA are increased in type Ⅱ GNET, but this may be due to other manifestations of a GINET[19]. Type Ⅱ GNET is usually limited to the mucosa and/or submucosa, with metastases seen in ten to thirty percent, and tumor-related death in less than 5% of cases, according to the literature[33]. Tumors show moderately enlarged lobules and trabeculae, and moderate cellular atypia, which include nuclear polymorphism, hyperchromasia, prominent nuceoli, and a slight increase in mitotic count, < 1 per 2 high power fields (HPFs). Small regions of necrosis may also be visible[34]. The diagnosis is usually made by gastroscopy. In addition to endoscopic resection, the somatostatin analogue octreotide induces tumor regression and a marked decrease in plasma gastrin levels; the medical approach plays a key role in the management of patients with type Ⅱ GNET, because of the presence of multiple tumors that are not amenable to endoscopic excision[35].

Type Ⅲ GNET

Fourteen to twenty-five percent of GNETs are classified as type Ⅲ, and are non-gastrin dependent, large (> 2 cm, mean 5.1 cm), usually occur singly, and grow from the gastric body/fundus in the context of a normal (non-atrophic) surrounding mucosa[36]. Type Ⅲ GNET is considered to be an aggressive cancer, associated with deep invasion and metastases, and has a poor prognosis. Typically, more than 2% of tumor cells express the proliferation marker MKI67 but are negative for CgA. Histologically, this type of tumor is characterized by large, poorly defined, solid aggregates or diffuse sheets of round or spindle-shaped cells. Abundant mitoses are detected (> 1 per HPF)[37], and focal necrosis is common. Ultrastructural studies document the presence of endocrine granules. Whenever possible, surgical resection and lymph node dissection are the treatment of choice[38]. Depending on local growth characteristics of malignant type Ⅲ tumors, this could include extended radical surgery including gastric resection and regional lymphadenectomy[39].

Type Ⅳ GNET

Type Ⅳ GNET is uncommon, large, poorly differentiated tumors that occur singly and are highly malignant[36]. The largest known type Ⅳ GNET was reported by Bordi *et al*[39] to be 16 cm. In most cases, type Ⅳ GNET shows lymphoinvasion, angioinvasion, and deep wall invasion at the time of diagnosis. Poorly differentiated type Ⅳ GNETs display a severe histology, with a prevalent solid structure, abundant central necrosis, and severe cytological atypia with frequent atypical mitoses and high levels of MKI67 (> 30). CgA is normally absent or expressed only focally, consistent with the rare electron-dense granules observed ultrastructurally, while synaptophysin and the cytosol markers NSE and PGP9.5 are diffusely and strongly expressed[37]. Although rare, the poorly differentiated type Ⅳ GNETs deserve particular attention owing to their aggressive nature and extremely poor prognoses - mean survivals of 6.5 to 14.9 mo have been reported[36].

Surgical resection is the most appropriate form of treatment for this type of tumor. Multi-drug chemotherapy is promising, but remains to be evaluated in larger clinical studies[40]. Type Ⅳ GNET demands an aggressive surgical approach followed by chemotherapy and multimodality adjuvant therapy[41].

Table 2 New tissue and serum tumor markers for specific diagnostics and prognostics of gastric neuroendocrine tumors

Ref.	Case	Hormones, amines and peptides for specific diagnostic and prognostics of GNETs	Expression
Giandomenico *et al*[42]	15	CD133	20% positive
Mia-Jan *et al*[43]	2	ISL1	Complete loss
Agaimy *et al*[44]	1	c-kit	Overexpression
Mori *et al*[45]	51	Cyclin E	Independent prognostic factor
		Cyclin E and P53	Prognostic relevance
Namikawa *et al*[41]	5	Chromogranin A	40% positive
		Synaptophysin	60% positive
		CD56	60% positive
		Neuron-specific enolase	40% positive
		p53 protein	100% positive

GNET: Gastric neuroendocrine tumor; ISL1: Islet-1.

NEW TISSUE AND SERUM TUMOR MARKERS FOR SPECIFIC DIAGNOSTICS AND PROGNOSTICS OF GNETS

Tumor biomarkers or molecular markers that predict patient outcome are being discovered for increasing numbers of tumors. Tumor markers that are specific for GNETs include Histamine, Gastrin, gastrin-releasing peptide, Ghrelin, and Obestatin[42]. Mia-Jan *et al*[43]. evaluated the expression of CD133 in GNETs (n = 15) and found that it was strongly expressed in about 20% of GNETs. It is expressed in poorly differentiated as well as in well-differentiated GNETs. The human insulin gene enhancer-binding protein islet-1 (ISL1) is a transcription factor involved in the differentiation of the neuroendocrine pancreatic cells and recent studies have identified it as a marker for well-differentiated pancreatic neuroendocrine neoplasms. Agaimy *et al*[44] showed that ISL1 is expressed in endocrine cells of the normal stomach and colorectal tissue, in contrast to with the complete loss of this protein in some gastrointestinal neuroendocrine carcinomas (n = 2), similar to the distribution of this protein in normal and neolpastic pancreatic tissues. In addition, Mori *et al*[45] report the presence of focal neurondocrine differentiation and diffuse c-kit overexpression in a case of gastric undifferentiated carcinoma: immunohistochemistry shows that the tumor cells are diffusely positive for cytokeratin, vimentin, and c-kit, and focally positive for CgA and synaptophysin. These authors hypothesized that c-kit overexpression in these tumor cells can be attributed to neuroendocrine differentiation. To characterize the expression of the proteins cyclin D1, cyclin E and P53 in gastroenteropancreatic neuroendocrine tumors and assess their prognostic impact, tumor specimens from 68 patients (including 51 cases of gastric tumor origin, with a complete follow-up) were studied immunohistochemically for cyclin D1, cyclin E and P53 expression, but no significant correlation was found between the expression of cyclin D1 and any clinicopathological variables. Results from Agaimy and colleagues indicate a prognostic relevance for cyclin E and P53 immunoreactivity: cyclin E may be an independent prognostic factor from the 2010 WHO Classification, and it should be evaluated in further studies[46]. In a study cohort of GNETs, it was reported that positive rates of neuroendocrine markers were 40% for chromogranin A, 60% for synaptophysin, 60% for CD56, 40% for neuron-specific enolase, and 100% for p53 protein[41]. Table 2 summarizes new tissue and serum tumor markers for specific diagnostics and prognostics of GNETs.

TREATMENTS DEVELOPMENT

The only curative therapy for GNETs is the complete resection of the tumor. Regardless of type, endoscopic resection is recommended as an initial treatment of NETs that are not yet at the advanced stages; if this is not possible, minimally invasive surgery that involves wedge resection should be considered as an alternative. However, while endoscopic submucosal dissection (ESD) or local resection can be performed in early stage tumors, radical surgery with lymph node dissection is recommended for all advanced GNETs[47,48]. The present study indicates that because of complete resection, ESD may reasonably serve as a radical treatment for GNETs when lesions are within the existing criteria. In addition, endoscopic treatment can be also considered in patients with a high risk of perioperative complications due to age or advanced comorbidity: for example, if other contraindications to major surgery exist, ESD would be the treatment of choice, even when lesions are little beyond the existing criteria[2].

Complete surgical resection is associated with better long-term survival[49]. Many case series have recently been published that advocate antrectomy as a means of gastrin suppression in type I GNET[50,51]. While there is universal consensus on the use of surgical treatment of type Ⅲ GNET, current options for type I and Ⅱ GNETs include simple surveillance, endoscopic polypectomy, surgical excision with or without surgical antrectomy, or total gastrectomy[52].

Chemotherapy is a palliative option for patients with type Ⅳ GNET, and is reserved for those with significant symptoms related to advanced disease, or with a poor prognosis (related to poor tumor differentiation, rapid disease progression, or progression on somatostatin analogues)[53]. Response rates to single-agent chemotherapy are low, so combination chemotherapy regimens are most commonly administered. Interferon-α (IFN-α) is also effective in decreasing symptoms associated with secretion of peptides by the tumor in 30%-70% of patients with GNETs. However, the onset of effect of IFN-α is delayed, and adverse effects (including fever, fatigue, weight loss, and anorexia) may be significant and are dose dependent. Combination chemotherapy, such as

Table 3 Summary of medical treatments for patients with gastric neuroendocrine tumors

	Type Ⅰ GNET	Type Ⅱ GNET	Type Ⅲ GNET	Type Ⅳ GNET
Resection	Simple surveillance, endoscopic polypectomy, surgical excision associated with or without surgical antrectomy, total gastrectomy	Simple surveillance, endoscopic polypectomy, surgical excision associated with or without surgical antrectomy, total gastrectomy	Radical surgery	Radical surgery
Chemotherapy				Combination chemotherapy: Etoposide + cisplatin (CDDP)/ carboplatin octreotide and pasireotide (SOM230); Somatosatin analogues; CDDP + CPT-11
Targeted radio therapy				117Lu- and 90Y-labelled somatostatin analogues; Selective internal radiation therapy
Biological therapy	Interferon-α			
Molecular targeted therapy	Inhibition of angiogenesis or molecular targeting of growth factor receptors, including sunitinib and imatinib			

GNET: Gastric neuroendocrine tumor.

etoposide+cisplatin (CDDP)/carboplatin, is a useful medical treatment for unresected NET, and the somatostatin analogues octreotide and pasireotide (SOM230) reportedly provide the benefit of hormonal symptom control as well as suppression of tumor growth[49]. Somatostatin, a naturally occurring regulatory hormone that binds to somatostatin receptors and inhibits tumor secretion of regulatory peptides, is another palliative treatment[54-56]. Although there are no standard chemotherapy regimens for GNETs that use these receptors, treatment with CDDP plus irinotecan (CPT-11) is effective against this disease, with an overall response rate of 75% and a progression-free survival of 212 d[34,41,57].

Patients with type Ⅳ GNET have reportedly benefitted from targeted radiotherapy. Recently, the effect of 177Lu-octreotate (177Lu), administered in repeated doses of 100-200 mCi, with intervals of 6-9 wk up to a final cumulative dose of 600-800 mCi, was investigated in 131 patients with GNETs. The shorter range for 177Lu in tissues may indicate that this isotope is better for treatment of smaller tumors, while 90Y might be more suitable for larger ones[58-64]. Since metastases often are of varying size, the best option may be to combine 117Lu- and 90Y-labelled somatostatin analogues. Targeted irradiation therapy involving the use of selective internal radiation therapy, which has been used in patients with primary hepatocellular cancer and metastatic colorectal cancer, was recently tried in patients with GNETs: preliminary results are encouraging, but further studies are warranted[58,65,66]. Grin reports that anti-*Helicobacter pylori* drugs may be helpful in treating patients with duodenal gastrinoma with multiple GNETs secondary to chronic *Helicobacter pylori*-induced gastritis[67].

Novel principles for treating cancer patients, such as inhibition of angiogenesis, or molecular targeting of growth factor receptors[68], have been developed recently. For example sunitinib, an oral tyrosine kinase inhibitor that inhibits VEGFR, is generally well tolerated[69]. Imatinib, another tyrosine kinase inhibitor that selectively inhibits PDGFR, was also tried in patients with various NETs without any objective responses, and causing significant toxicity[70].New diagnostic techniques have led to increasingly early recognition of early gastrointestinal NETs. Most patients with early, well differentiated NET can be treated conservatively, and followed by endoscopic surveillance. Note that patients with (previous) NET/carcinoid disease have a 15%-25% risk for second malignancies in the breast, prostate, colorectum[71]. Such carcinomas demand an aggressive surgical approach followed by chemotherapy and multimodal adjuvant therapy, and randomized, prospective clinical trials that include a search focused on MKI67 labeling index are required to demonstrate an unequivocal survival advantage for patients who receive chemotherapy or radiation therapy after resection of NETs[41]. Table 3 summarizes medical treatment for patients with GNETs.

CONCLUSION

GNETs comprise distinct tumor entities that have been classified on the basis of pathogenesis and histomorphologic characteristics into 4 types that differ in biological behavior and prognosis. To plan the correct management and optimal therapeutic approach in patients with GNETs, it is essential to obtain an adequate clinical evaluation and assessment of the pathological features of the tumor. Patients who are diagnosed with NETs early and accurately have a greater chance for complete cure. Over the past two decades, there has been a major turnover in diagnostic methods. In a word, development of new gene marker as well as effective drugs is expected for the better diagnosis, prognosis and treatment of GNETs.

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