Invited Review

Gastric neuroendocrine tumors: Biology and management

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SUMMARY

Neoplasms may originate from any of the endocrine cells of the gastric wall, most commonly the enterochromaffin-like (ECL) cells of the oxyntic mucosa. In recent years, the increasing number of screening gastroscopies and biopsies, and the widespread application of sophisticated immuno-histochemical stains for neuroendocrine markers, have resulted in the frequent detection of ECL tumors. The latter are regarded as a separate clinicopathological entity seen in the setting of hypergastrinemic states, and their pathogenesis follows the sequence "hyperplasia – dysplasia – neoplasia". According to the most recent WHO classification, gastric neuroendocrine tumors (NETs) are generally divided into "well-differentiated NETs" (class 1a), "well-differentiated neuroendocrine carcinomas (NECs)" (class 1b) and "poorly differentiated NECs" (class 2). Well-differentiated tumors (NETs and NECs), for which the historic term "carcinoid" is still in use, include three subgroups: Type I (70-80%), associated with chronic atrophic gastritis, which are benign (class 1a) ECL cell tumors in the vast majority of cases; Type II (<10%), associated with gastrinoma in patients with multiple endocrine neoplasia type1 (MEN1), which are usually benign; and Type III or sporadic (25-25%), which tend to behave aggressively (usually class 1b). Resent advances in the diagnosis and management of these tumors include the measurement of serum chromogranin-A levels, which reflect tumor mass, the use of synthetic somatostatin analogues for imaging and therapeutic purposes, and the introduction of aggressive multimodality protocols for the management of metastatic disease. Little progress has been made in the treatment of the rare, highly malignant, poorly differentiated neuroendocrine carcinomas, which are rapidly fatal, showing only short-lived responses to chemotherapy. Research is currently focusing on the study of the molecular pathways of gastric endocrine cell tumorigenesis, including the role of various growth factors and gene regulation mechanisms.

Key words: neuroendocrine tumor, carcinoid, gastric tumor, gastric polyp, atrophic gastritis, enterochromaffin-like cells, gastrin, gastrinoma.

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INTRODUCTION

The term "neuroendocrine tumor" (NET) is used for the description of a heterogeneous group of neoplasms consisting of cells with phenotypic features of both endocrine and neural cells. The "neuroendocrine phenotype" is characterized by positive immunocytochemical staining for certain proteins such as chromogranin-A, synaptophysin and neuron-specific enolase, combined with the presence of secretory granules on electron microscopy. This phenotype is shared by a variety of hormone and amine producing cells, which constitute the so-called "diffuse endocrine system" (DES), a concept introduced by Feyrter (1938)[1] and developed further by Pearse (1969),[2] who described a diffuse system of "APUD" (Amine Precursor Uptake and Decarboxylation) cells including the endocrine cells of the gut.[3] In recent years, it has become evident that neuroendocrine features can be encountered in different cell types, like immunocytes and myocardial cells, whose embryological origin is entirely different from that of neural or endocrine cells. It has therefore been proposed that the "neuroendocrine concept" should be revised, to include the potential expression of a partial or even complete neuroendocrine phenotype by a variety of cells, through activation of specific genetic "switches".[4]

The first reports of tumors with the characters of gastrointestinal (GI) NETs can be traced in the medical literature of the late 19th century. Lubarsch (1888)[5] is credited with the first detailed description of such tumors in autopsy material, while Ranson (1890)[6] described a patient with a tumor of the terminal ileum, hepatic metastases, diarrhoea and postprandial exacerbation of dyspnoea. In 1907, Oberndorfer coined the term "carcinoid" (Karzinoid) to contradistinguish the more benign course of these rare tumors from that of the much commoner adenocarcinomas.[7] The first two cases of gastric NET were described by Askanazy in 1923[8] and in 1961, Christodoulopoulos and Klotz listed 79 cases published in the international literature,[9] noting that their diagnosis was usually delayed and was often made at autopsy. Until recently, such tumors were regarded as rather rare, representing a small fraction of GI NETs.[10,11]

The widespread application of upper GI endoscopy, in association with the development of more sophisticated techniques for histopathologic evaluation of gastric biopsies was followed by a spectacular and continuing rise in the relative frequency of gastric NETs, which varies greatly among published series, fluctuating between 3% and 41% of all GI NETs (epidemiological data extensively reviewed by Modlin[12,13]). The increased frequency of the histological diagnosis of gastric NET following screening gastroscopy and biopsy, especially in the clinical setting of atrophic gastritis, even in the absence of macroscopic lesions,[14] highlights the need for clear guidelines regarding the optimal management of these patients. Moreover, the recognition of the fact that most gastric NETs are associated with hypergastrinemic states, raises obvious questions concerning the long term consequences of treatment with powerful acid-suppressive medications.

As gastric NETs represent a heterogeneous group, any discussion of their biology and management must be based on a prognostically meaningful classification. In the present review, a brief description of the cells forming the endocrine milieu of the stomach is followed by a critical account of the current classification systems and basic principles for the diagnosis and management of gastric NETs.

GASTRIC ENDOCRINE CELLS AND THE PATHOGENESIS OF GASTRIC NETS

The gastric DES is composed of a variety of endocrine cells, constituting less than 2% of the total cell mass of the gastric mucosa. Some of these cells are not fully characterized (Table 1). In common with DES cells in the rest of the GI tract, gastric endocrine cells possess two regulated pathways of secretion, corresponding to the assembly, storage and release of two different secretory vesicles: the *large dense core vesicles* (LDCV), which are the electron-dense granules of the endocrine cells, and the smaller synaptic-like microvesicles (SLMV), similar to the vesicles of nerve synapses.[15] The secretory products (hormones and biogenic amines) may act at distant targets (endocrine effect) or locally (paracrine or autocrine effects). Gastric DES cells participate in complex regulatory mechanisms extending from the ingestion of a single meal[16] to body weight homeostasis.[17-19] The three major gastric endocrine cell types are the enterochromaffin-like (ECL) cell, the G cell and the D cell. The ECL cell is the dominant endocrine cell in the oxyntic mucosa, constituting normally about 35% of the endocrine cell population of the gastric body and fundus. Its main secretory product is histamine. In the antrum, the

Table 1. Endocrine cells of the human gastric mucosa[156-160]

Cell type	Hormone or amine product	Location
ECL	Histamine	body, fundus
G	Gastrin	antrum
D	Somatostatin	body, fundus, antrum
P/D$_1$	Ghrelin	body, fundus, antrum (few)
EC	5HT	body, fundus, antrum, cardia
A*	Glucagon	body, fundus
X(A-like)	?Endothelin	body, fundus
E	β-microseminoprotein, gastrin	antrum
P-like	Leptin[17]	body, fundus

ECL: enterochromaffin-like, EC: enterochromaffin
* Only in embryo and newborn.

gastrin-producing G cells predominate (60%), while somatostatin-producing D cells are present in the entire mucosa (´25%). The functional integration of these three cell types determines the degree of parietal cell stimulation for acid production:[20] In response to falling gastric acidity, gastrin secreted by antral G cells stimulates ECL cells to secrete histamine, a potent stimulus for acid release by parietal cells. Somatostatin exerts a regulatory inhibitory effect on both G and ECL cells. Less frequently encountered endocrine cells like the Ghrelin-producing P/D_1 cells and the serotonin (5HT)-producing enterochromaffin (EC) cells play less well defined physiological roles. There is evidence from animal experiments that the total mass as well as the cellular composition of the gastric DES can change in systemic pathological states like uremia and cancer.[21,22]

Normal endocrine cells of the human GI tract appear to be terminally differentiated and non-proliferating.[23] Increases in their numbers are likely to be the result of the entry of new endocrine-committed cells along the differentiation path of multipotent primitive cells residing in the isthmus and neck of gastric glands[24] following molecular genetic signals, the nature of which is currently being investigated.[25] The best studied example of an increase in the number of gastric endocrine cells is the hyperplasia of ECL cells seen in hypergastrinemic states.[26-28] A pivotal role in regulating ECL cell proliferation and differentiation in response to gastrin appears to be played by the CCK-B/gastrin receptor (CCK2R), as shown in experiments of targeted CCK2R gene disruption in mice.[29] The binding of gastrin to CCK2R has been shown to activate the genes encoding *HDC* (*histidine decarboxylase*, the rate-limiting enzyme for histamine biosythesis), *VMAT2* (*vesicular monoamine transporter molecule 2*, responsible for the storage of histamine in secretory vesicles) and *CgA* (*Chromogranin-A*, a matrix protein packaged and secreted with other secretory products into the vesicles of ECL cells),[30] but the sequence of molecular events connecting hypergastrinemia with ECL cell hyperplasia is not known. Hyperplasia is defined as the presence of more than twice the normal number of ECL cells and is considered a preneoplastic condition because it can, in certain circumstances, evolve into dysplasia and neoplasia according to the model described by Solcia et al:[31,32] Simple, diffuse hyperplasia may progress to linear, chain-like and nodular formations, while dysplasia is characterized by micronodules >150 μm in diameter, fusion of micronodules, infiltration of the lamina propria, and presence of new stroma formation within the micronodules. Any such growth that extends beyond the muscularis mucosa or invades vessels is considered neoplastic.

It has been observed that omeprazole- and ranitidine-induced hypergastrinemia can lead to development of gastric ECL cell tumors in laboratory animals.[33,34] It should nevertheless be noted that no such lesions have been observed in man, despite prolonged use of potent acid-suppressive medications.[35,36] It therefore appears that, although gastrin is an adequate trophic stimulus for the development of ECL hyperplasia in humans, hypergastrinemia alone cannot explain the neoplastic transformation of ECL cells (or their progenitors). A number of growth factors that have been detected in ECL cells and their tumors, including bFGF (basic fibroblast growth factor) and TGF-α (transforming growth factor alpha), may promote cell proliferation and differentiation in the tumor itself or in other host tissues.[37] The importance of genetic factors in gastric NET tumorigenesis is demonstrated by the frequent development of ECL cell tumors in patients with Zollinger-Ellison syndrome (ZES) associated with Multiple Endocrine Neoplasia type 1 (MEN1), which is usually caused by mutations in the tumor suppressor gene *MEN1*.[38] In contrast, such tumors seldom develop in sporadic ZES, despite the presence of marked hypergastrinemia.[39] Moreover, loss of heterozygocity at the *MEN1* locus (11q13) is found in a significant fraction of ECL tumors of different degrees of malignancy, unrelated to MEN1.[40,41] Inactivation of the INK4a/ARF tumor suppressor gene complex on chromosome 9q21 has also been implicated in the pathogenesis of gastric NETs.[42] Finally, it has been reported that malignant evolution of gastric NETs is associated with large deletions of the X-chromosome.[43] Based on the above, one might speculate that inherited or acquired defects of tumor suppressor genes combined with gastrin-induced increased transcriptional activity form the basis of ECL cell oncogenesis.

CLASSIFICATION AND HISTOPATHOLOGY OF GASTRIC NETS

The considerable confusion in the literature regarding the classification of gastric NETs[44,45] reflects the lack of an established classification system for NETs in general. So, the historic term "carcinoid" has been used loosely to describe a wide variety of tumors with neuroendocrine characters, irrespectively of anatomical site, histological grade of malignancy and clinical behavior.[46,47] The division, according to embryological origin, into *foregut, midgut* and *hindgut* "carcinoids"[46] is of limited clinical use because it does not correlate well with clinical behavior and prognosis. In an effort to formulate a

prognostically meaningful classification, Capella et al[48] proposed the division of NETs into "well-differentiated NETs" and "neuroendocrine carcinomas (NECs)". The latter were further divided into "well differentiated" and "poorly differentiated" NECs. In this classification, which was subsequently endorsed by WHO,[49] the term "carcinoid" is not entirely abandoned, but is reserved for well-differentiated NETs of the stomach, bowel, bronchial tree and thymus, while the terms "malignant carcinoid" and "atypical carcinoid" are used for the description of well-differentiated NECs at these anatomical sites. In the present review we follow the WHO classification (Table 2) although we believe that it needs further refinement. In particular, the meanings of the terms "tumor" and "carcinoma" are overlapping and, ideally, they should not be used to describe two discrete pathological entities in the classification, as is the case with "well differentiated NE tumor" and "well differentiated NE carcinoma". It is also our view that terms like "malignant carcinoid" or "atypical carcinoid" could be confusing and their use should be discouraged. Finally, it appears that the most recent WHO classification favors the term "endocrine tumor" which at present is used interchangeably with "neuroendocrine tumor".[49]

Microscopically, well differentiated NETs consist of a monomorphic population of small or medium sized, round or polygonal cells with variably eosinophilic cytoplasm and uniform, central, round nuclei with fine chromatin pattern, small nucleoli and absent or scanty mitoses. The tumor shows various patterns of growth, including trabecular or ribbon-like with anastomosing features, solid, nodular or insular cords, nest, rosette-like or pseudoglandular formations or any combination of the above. Very occasionally, entirely different cell types,

e.g. plasmacytoid, spindle-shaped and poorly differentiated cells may be present, making difficult the differential diagnosis from other tumors including lymphoma, leiomyoma, hamartoma or carcinoma.[50] As can be seen in Table 2, well-differentiated gastric NETs are further subdivided into two subgroups: *benign* and those with *uncertain behavior*. The latter highlight the fact that it is practically impossible to accurately predict the clinical behavior of a well-differentiated NET based on cell morphology alone. A number of criteria are useful predictors of malignant behavior:[51] tumor size, angioinvasion and invasion of perineural spaces, small areas of necrosis, cell atypia (e.g. nuclear polymorphism, prominent nucleoli), >2 mitoses per 10 microscopic high power fields (HPF), Ki67 index >100/10 HPF (or >2%), loss of CgA (or other secretory marker) immunoreactivity, nuclear p53 accumulation, and aneuploidy of tumor cells. In addition, well-differentiated gastric NETs are characterized as *functioning* or *non-functioning*, depending on the presence of an overt clinical syndrome due to hormonal secretion by the tumor.

Histochemically, most gastric NETs are argyrophilic. Nowadays, staining with silver salts is only of historical interest as it has been superceded by immunostaining with antibodies to a variety of molecules contained in the neuroendocrine granules.[50,52,53] Among them, staining for CgA is the most useful, being positive in practically all cases of well-differentiated NETs, followed by synaptophysin and neuron-specific enolase.

Types of well-differentiated tumors (benign and malignant gastric carcinoids)

From a pathophysiological viewpoint, well differentiated gastric NETs are divided into two broad categories: *gastrin-dependent*, which are always associated with hypergastrinemia, and *non-gastrin dependent* or *sporadic*, which are independent of the trophic effect of gastrin. Gastrin-dependent NETs are further subdivided into two groups: Type I, associated with chronic atrophic gastritis (CAG) and Type II, seen in the setting of ZES in patients with MEN1, a familial polyendocrinopathy with autosomal dominant pattern of inheritance, characterized by tumors of the parathyroids, pituitary and endocrine pancreas.[52,54] Type III includes the heterogeneous group of well-differentiated gastric NETs not associated with either CAG or MEN1/ZES, but it should be noted that some well-differentiated tumors will remain difficult to classify.[55,56] There is a tendency by some workers to label poorly differentiated gastric neuroendocrine carcinomas (i.e. Class 2 tumors of the general WHO classification shown in Table 2) as "Type IV" gastric NETs.[45]

Table 2. Classification of gastric NETs (WHO 2000[49])

1a. Well differentiated NET (synonym: carcinoid)

  - *Benign*: =1 cm in size, confined to mucosa-submucosa, no angioinvasion.

  - *Uncertain malignant potential (benign or low grade malignant)*: =2 cm in size, confined to mucosa-submucosa, with or without angioinvasion.

1b. Well differentiated NEC (synonym: malignant carcinoid)

  - *Low grade malignant*: >2 cm in size, invading muscularis propria and beyond, or metastases.

2. Poorly differentiated NEC

  - *High grade malignant*

NET: Neuroendocrine tumor, NEC: Neuroendocrine carcinoma

Type I gastric NETs, also known as *Type I gastric carcinoids*, are the commonest (70-80 %).[54] Hypergastrinemia is thought to be the main pathogenetic factor in this type of tumor, leading sequentially to hyperplasia, dysplasia and finally neoplastic transformation of the histamine-secreting ECL cells, as described in the previous section. Type I NETs are usually diagnosed during the fifth and sixth decades of life, although they have been described in patients from 15 to 88 years of age,[57] and they are commoner in women (sex ratio 2-3:1).[58] They were originally thought to be exclusively seen in the clinical setting of autoimmune chronic atrophic gastritis type A (CAG-A), often in association with pernicious anemia. The prevalence of gastric NETs in the latter is reported to be 5-9%[59,60] but it is now clear that these tumors can occur in any type of atrophic gastritis, including that associated with *H.Pylori* infection.[61,62] They are usually multiple and small (<1 cm), and appear as polypoid lesions in the body and fundus of the stomach, occasionally with central ulceration.[54,63] Most of these tumors are classified as 1a and only a small minority as 1b NETs (Table 2), and their prognosis is therefore excellent.[54,64] In most cases they are non-functional and asymptomatic and only rarely metastasize (14-20% of class 1b tumors, mainly to lymph nodes), while fatalities are exceedingly rare.[50,52,54,64] The possibility of benign lesions transforming into aggressive ones cannot be excluded.[65] Given the association of pernicious anemia with other autoimmune disorders (e.g. thyroiditis, vitiligo, diabetes mellitus, adrenal insufficiency, blood cytopenias, rheumatoid arthritis and other collagenoses) it is not surprising that many of these conditions appear to have higher prevalence in patients with Type I gastric NETs.[12,66-68] Due to the small size of most of these tumors, endoscopic resection is easy and usually curative and an operation is seldom necessary.[64] The latter may be considered for relatively large, numerous (>5) or relapsing tumors. In selected cases, antrectomy may lead to tumor regression.[69] (Figure 1).
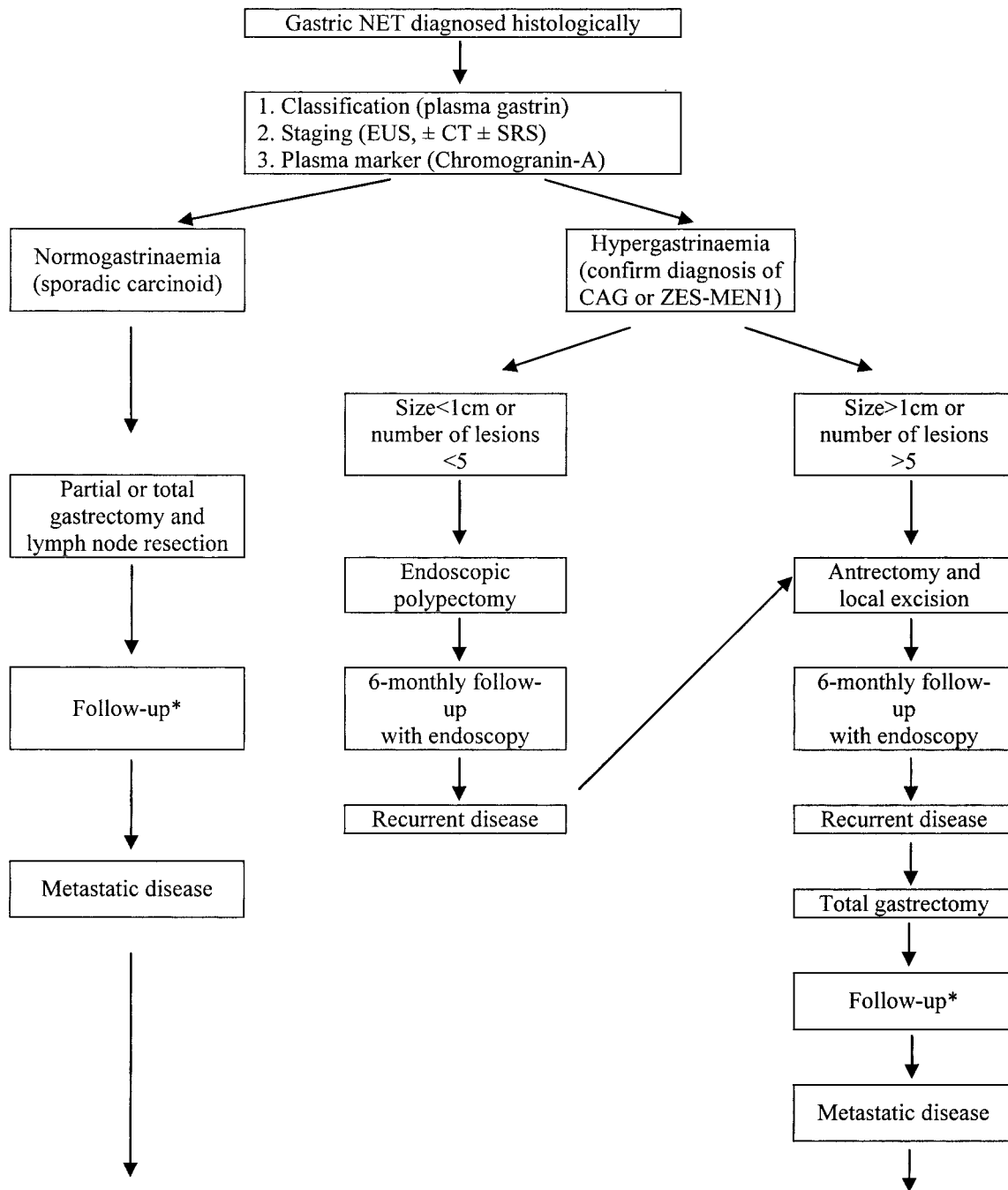
Type II gastric NETs (carcinoids) are NETs associated with ZES in patients with MEN1 syndrome. They were recognized as a separate entity by Solcia et al[28] and represent 5-10% of class 1a gastric NETs.[38,54] These tumors are present in 15-50% of patients with MEN1/ZES, the prevalence depending on the observation period.[70] In this setting, hypergastrinemia plays the same pathogenetic role as in Type I NETs, with the additional involvement of a genetic factor (usually a mutation in the tumor suppressor gene *MEN1*), as described in the previous section. Exceptionally, multiple gastric NETs have been described in the absence of hypergastrinemia in patients with MEN1,[71,72] and there is evidence that independence of the trophic effect of gastrin is associated with aggressive clinical behavior. Furthermore, it should be noted that co-existence of hypergastrinemia and multiple gastric NETs with a single lesion belonging to the MEN1 spectrum (hyperparathyroidism, pituitary adenoma, pancreatic NET) is not always due to incomplete expression of the MEN1 syndrome.[73-76] Compared with Type I tumors, typical Type II carcinoids tend to be larger (often >1 cm), occur with the same frequency in both sexes, are diagnosed at a younger age, and may follow a slightly more aggressive clinical course, with local metastases in up to 30% of cases.[52,54,63] A recent report has drawn attention to the aggressive behavior of gastric NETs in the setting of long-standing MEN1/ZES.[70] Their management is similar to that of Type I tumors (Figure 1).

Type III or sporadic gastric NETs (carcinoids) are also relatively uncommon (15-25 % of well-differentiated NETs).[54] They usually develop in middle-aged persons (75% men) and are large (often >2 cm at diagnosis) and solitary, surrounded by normal mucosa.[52,54] These tumors constitute a heterogeneous group and can be found in any part of the stomach. They usually consist of ECL cells but may contain a variety of other endocrine cells (mainly EC and G), and on rare occasions overproduce serotonin or gastrin.[63] Peptides not normally recognized as secretory products of gastric endocrine cells have also been sporadically detected.[77] The majority of Type III tumors are classified as 1b NETs (well-differentiated neuroendocrine carcinomas) and follow an aggressive clinical course with invasiveness and early metastases (>60% at time of diagnosis).[52,78] As a rule, Type III gastric NETs are not associated with hypergastrinemic states, but the exceptional case where the tumor itself is the source of gastrin should be kept in mind. It is thought that a complex genetic background is involved in their pathogenesis, which does not involve hypergastrinemia. Abnormalities of p53 and other genes have been implicated.[79,80] In view of its aggressive nature and significant mortality, this type of gastric NET should be treated with partial or total gastrectomy[64] (Figure 1).

Poorly differentiated NECs

These rare gastric tumors represent high-grade invasive malignancies, usually composed of small to medium-sized round or spindle-shaped cells, although large cell variants have also been described.[81] Their histology is characterized by marked cellular atypia, frequent central necrosis of solid tumors, high mitotic index (>1 per HPF), and high proliferative status (>30%) by Ki-67.[37,45,53] On immunocytochemistry, at variance with the general

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                        │  Gastric NET diagnosed histologically │
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                        │ 1. Classification (plasma gastrin)    │
                        │ 2. Staging (EUS, ± CT ± SRS)          │
                        │ 3. Plasma marker (Chromogranin-A)     │
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- Normogastrinaemia (sporadic carcinoid)
  - Partial or total gastrectomy and lymph node resection
  - Follow-up*
  - Metastatic disease

- Hypergastrinaemia (confirm diagnosis of CAG or ZES-MEN1)
  - Size<1cm or number of lesions <5
    - Endoscopic polypectomy
    - 6-monthly follow-up with endoscopy
    - Recurrent disease
  - Size>1cm or number of lesions >5
    - Antrectomy and local excision
    - 6-monthly follow-up with endoscopy
    - Recurrent disease
    - Total gastrectomy
    - Follow-up*
    - Metastatic disease

Consider (in this order): long-acting somatostatin analogues, addition of α-IFN in case of tumor progression, receptor-targeted treatment preferably with 177Lu-labelled somatostatin analogues, hepatic resection or chemoembolization, liver transplant, systemic combination chemotherapy. Irradiation of bone or CNS disease.

* There are no published data regarding optimal follow-up after total gastrectomy. The authors recommend 6-monthly measurements of plasma chromogranin-A (or other marker peptide or amine) combined with an imaging method: Somatostatin receptor scintigraphy (or alternative scintigraphic method), CT (with I.V. contrast enhancement), MRI or PET in selected cases.

IFN: interferon, CNS: central neural system.

Figure 1. Algorithm for the management of patients with well-differentiated gastric NETs. (Modified from Gilligan et al[64]).

tendency of poorly differentiated GI NECs (PDNECs) to show weak, if any, and focal positivity for CgA, while retaining the expression of synaptophysin and NSE,[37,45] all of 10 gastric PDNECs studied by Yu et al were clearly positive for CgA.[53] They are usually diagnosed in the elderly (mean age 63-70 years) with a male sex preponderance.[54,81] Hypergastrinemia is present in one third of cases and CAG frequently co-exists (82%).[54] At the time of diagnosis their size usually exceeds 4 cm and distant metastases to liver and lymph nodes are already present.[54,81,82] Reported survival times from the time of diagnosis are 7-15 months.[53,54,81] The treatment of PD-NECs is the same as for gastric adenocarcinomas.

Gastric NETs and gastric adenocarcinomas

There is a significant volume of literature concerning the co-existence of gastric NETs and adenocarcinomas either independently,[83-85] or, more frequently, as part of the same tumor.[86-89] Neuroendocrine carcinomas with sarcoma components have also been described.[90,91] Evolutionary transition between different neoplastic phenotypes in response to genetic "switches" or, alternatively, parallel multiple clonal expansions of multipotent stem cells can be reasonably speculated. In a study of gastric neuroendocrine carcinomas with an adenocarcinoma component, overexpression of p53 protein was observed in the majority of tumors and, interestingly, common p53 mutational status between the two components was revealed.[92] The reported frequency of neuroendocrine differentiation of gastric carcinomas (GCs) fluctuates from 10% to 30%,[93,94] and it has been suggested that positivity for endocrine markers might be associated with adverse prognosis, possibly due to faster metastatic spread to lymph nodes.[95,96] There is convincing evidence that many GCs originate from ECL cells, which have lost part of their endocrine phenotype during tumoral evolution.[97,98] In a recent report, strong expression of the PDX-1 transcription factor was found in hyperplastic endocrine cells and in the surrounding gastric glands in chronic atrophic gastritis but not in normal gastric mucosa or non-atrophic gastritis.[99] These data, albeit insufficient to directly link hypergastrinemia with gastric cancer, provide a basis for further study of this controversial issue.

CLINICAL MANIFESTATIONS

In the majority of cases there are no specific symptoms associated with gastric NETs. These tumors usually represent incidental findings in the course of endoscopic investigation undertaken for a variety of complaints, or as part of screening of asymptomatic patients at high risk for gastric neoplasia (e.g. those with CAG or MEN1 syndrome). Epigastric pain, vomiting, upper gastrointestinal haemorrhage and iron deficiency anaemia are common clinical manifestations of symptomatic gastric NETs.[50,100] The clinical picture depends on the size and location of the tumor, its secretory products, the presence of hepatic metastases and the coexistence of associated conditions (e.g. pernicious anaemia and other autoimmune disorders in Type I, ZES and MEN1 manifestations in Type II NETs). Bleeding may occasionally be severe,[101,102] especially in the rare cases with associated vascular malformations,[103] and could be aggravated by local vasodilation in cases of tumors producing neuroendocrine mediators, in particular serotonin.[104] Histologically aggressive tumors can present as giant masses,[105,106] or with symptoms of gastric outlet obstruction.[107] In contrast to small bowel NETs, development of the typical carcinoid syndrome is extremely unusual. Atypical carcinoid syndrome manifesting as episodic flushing due to histamine release can occur in Type III (sporadic) NETs.[52] Isolated cases of ectopic ACTH production by gastric NETs manifesting as Cushing's syndrome have been described.[108-110] Paraneoplastic syndromes in the form of cerebellar degeneration[111,112] or hypercalcemia due to production of parathormone-related peptide have also been reported in association with gastric NECs.[113]

DIAGNOSIS AND STAGING

The diagnosis is usually made by *endoscopic biopsy*. The tumors appear as submucosal masses or small, yellowish (a result of cholesterol and lipid accumulation within the tumour) polypoid protuberances, occasionally with a central erosion or ulceration. Because of their submucosal location, a standard biopsy may be insufficient to obtain adequate diagnostic material, and a partial polypectomy with endoscopic snare excision or a ultrasonographically guided needle biopsy are preferable.[114] It is also rewarding to take biopsies from the surrounding gastric mucosa in order to confirm or exclude the presence of atrophic gastritis. Thorough endoscopic sampling is mandatory in the setting of multiple polypoid lesions of the stomach, where NETs may coexist with hyperplastic/regenerative polyps.[115] Even in the presence of an endoscopically unremarkable mucosa, extensive sampling of both the lesser and greater curvatures is recommended in hypergastrinemic patients, as it has been shown that the rate of diagnosis of dysplastic and neoplastic lesions correlates with the number of specimens

examined.[116]

Measurement of *plasma gastrin* levels allows the differentiation of gastrin-dependent (Types I and II) from sporadic (Type III) gastric NETs. Hypergastrinemia in the absence of CAG requires further investigation in the direction of MEN1-associated ZES.

The importance of adequate staging cannot be overemphasized, especially when dealing with histologically aggressive gastric NETs. One should have in mind the tendency of these tumors to give early hepatic metastases[117] and the fact that minute primary tumors may have regional lymph node metastases at presentation.[118,119] Staging begins with the assessment of the depth of gastric wall infiltration. This can be achieved in 90% of cases with *endoscopic ultrasound* (EUS), while the same technique allows detection of infiltrated perigastric lymph nodes in 75% of cases.[120,121] Information about gastric wall infiltration and extragastric extent of disease can also be obtained by intravenously *contrast enhanced computed tomography* (CT) and magnetic resonance imaging (MRI). Modern CT-based imaging techniques like dedicated multi-detector CT of the stomach allow high-quality multiplanar reformation and three-dimensional reconstruction of gastric images and are potential high sensitivity tools to be used as an adjunct to endoscopy for preoperative staging.[122] Positron emission tomography (PET-scanning) employing 11C-labeled amine precursors has been used for diagnosis and follow-up of GI NETs, and, although experience with this method remains limited, preliminary results appear very promising.[123]

Gastric NETs are often rich in somatostatin receptors of subtype 2 (SSTR2). In a prospective study of a population at high risk for development of gastric ECL cell tumors, *Somatostatin Receptor Scintigraphy* (SRS) was shown to have a 75% sensitivity and 95% specificity in detecting such tumors.[124] SRS enables not only the mapping of regional and distant metastases but also the intraoperative detection of NETs using hand-held gamma cameras.[125] SRS employing octreotide labeled with indium-111 diethylenetriamine pentaacetic acid (OctreoScan®) has now displaced the previously popular but of low specificity iodine-131 metaiodobenzylguanidine (MIBG) scanning. Another alternative to SRS is immunoscintigraphy, which employs monoclonal antibodies to chromogranin-A and can be used for diagnostic, staging and follow-up purposes, especially in cases of tumors poor in somatostatin receptors.[126]

Chromogranin-A (CgA) is the most useful plasma marker in the routine diagnostic work-up and the follow-up after treatment of gastric NETs, as its levels reflect with high sensitivity the total mass of gastric endocrine cells (mainly ECL cells).[78,127,128] Its sensitivity for detecting ECL hyperplasia or tumor approaches 100%. This is at a cost of low specificity (23%) for NET diagnosis, as it cannot differentiate between hyperplastic and neoplastic lesions.[128] Plasma histamine and serotonin levels and urinary 5-HIAA measurements are seldom diagnostically helpful.[127]

TREATMENT AND FOLLOW-UP

Due to the rarity of these tumours, evidence from large, randomized studies is lacking and the recommendations are based on small, uncontrolled series. Moreover, in many published trials, gastric NETs are lumped together with other GI NETs and the results are difficult to analyze. Therefore, the treatment of gastric NETs is essentially empirical. Surgical removal of tumors is the only potentially curative approach. Even in the presence of metastases, gastric surgery including antrectomy may be beneficial through amelioration of the hypergastrinemia, which represents the main trophic stimulus for many of these tumors.[129-132] Management dilemmas may be posed by the usually benign NETs, which are often discovered in the setting of chronic atrophic gastritis with associated hypergastrinemia. Extensive gastric surgery is often performed[133] but appears to be unnecessary in the majority of these patients, where endoscopic surveillance with resection of larger lesions is probably sufficient.[64,134] On the other hand, endoscopic resection, even when the depth of invasion and vascularity of submucosal tumors have been determined by means of EUS, may lead to uncertainty regarding the completeness of excision, as evidenced by the frequent finding of tumor at the excision margin.[135] Minimally invasive laparoscopic surgery has been employed with good results, but experience remains limited.[136,137] An algorithmic description of the recommended management of patients with a newly diagnosed well-differentiated gastric NET is presented in Figure 1.

All patients with gastric NETs will need regular, lifelong follow-up, the kind of which may vary depending on the initial treatment. It may include endoscopy, EUS, measurements of plasma levels of markers of disease activity and a range of imaging methods, most notably the highly sensitive SRS. It is important to avoid depending on one modality alone to assess disease status. For example, falsely negative SRS can occasionally be a re-

sult of either down-regulation of SSTR on tumor cells following administration of steroids, chemotherapy or prolonged courses of somatostatin analogues, or the emergence of clones of tumor cells lacking somatostatin receptors.[138,139] It should also be noted that, besides monitoring the original tumor, follow-up should include screening for common cancers (colon, breast, lung, prostate), as it is known that synchronous or metachronous second malignancies occur in 5-25% of patients with gastric NETs.[13]

The detection of metastatic gastric NET should not be seen as a catastrophic event, in view of the fact that some of these tumors are slow-growing and patients can remain asymptomatic for years. A period of observation may therefore allow for a better decision to be made concerning optimal supportive care or more specific antitumor treatments. On the other hand, it is becoming increasingly apparent that an appreciable percentage of the tumors are more aggressive, necessitating the development of effective treatment protocols.

The advent of somatostatin and its analogues has generated new prospects for medical treatment of SRS-positive metastatic NETs. Somatostatin is a 14-aminoacid peptide that inhibits the secretion of growth hormone and most gastrointestinal hormones by binding to G-protein-coupled transmembrane receptors (of which there are 5 subtypes, SSTR1-5). Octreotide, a 8-aminoacid long-acting somatostatin analogue has a plasma half-life of 1,5-2 hr and acts by binding mainly to SSTR2. Other long-acting analogues are lanreotide and the more recently introduced octreotide acetate. Ferraro et al[140] showed that administration of octreotide controlled the growth of ECL cells in the setting of atrophic gastritis-related hypergastrinemia. Other investigators have shown that somatostatin analogues could induce regression of both hypergastrinemia-related[141] and sporadic[142] gastric NETs. It therefore appears that somatostatin analogues are well suited for the management of metastatic gastric carcinoid, as they exert inhibitory action on both the trophic stimulus (gastrin) and the tumor itself. These agents have an excellent safety profile in adults, their main adverse effects being steatorrhoea, which may require pancreatic enzyme replacement, and development of gallstones. Local irritation at the site of injection is a common complaint. Some therapeutic regimens have successfully combined somatostatin analogues with interferon, occasionally with spectacular results.[78,132,143] Interferon administered as monotherapy has been shown to benefit some patients with advanced GI NETs, although the overall response rate in most trials does not exceed 20%.[144]

Receptor-targeted therapy with a radioactive isotope attached to a somatostatin analogue or other peptide is currently being used on an experimental basis in patients with unresectable NETs expressing receptors for the respective peptides. The most encouraging preliminary results have been reported with [^{177}Lu-DOTA(0),Tyr(3)]-octreotate (^{177}Lu-OctreoTate):[145] In a series of 76 patients with inoperable GI NETs, 30% complete or partial remissions were observed, while 12% of the patients showed minor responses. Side effects were few and mild and the duration of the therapy response was more than 2 years.

Various chemotherapeutic agents alone or in combination have been employed for treating metastatic NETs. Most protocols have included classic cytotoxic drugs like 5-fluorouracil (5-FU), streptozotocin, anthracyclines, alkylating agents, cisplatin and etoposide, but the results in general have been poor. This is particularly the case with well-differentiated gastric NETs, where conventional chemotherapy has very little place, if any. Poorly differentiated NECs are more chemosensitive, although responses are usually short lived. The combination of cisplatin with etoposide has given the best results in this setting.[146] Selecting the most effective chemotherapy for the individual patient by means of drug resistance testing on cells cultured from tumor biopsies, is a promising technique currently under investigation.[147]

Many aggressive approaches have been applied to the treatment of hepatic metastases of GI NETs, ranging from simple resection of isolated lesions,[148] to liver transplantation.[142,149] The latter appears to offer good symptomatic relief and long survival (up to 80% at 5 years) in selected cases of well-differentiated NETs with low proliferative index, metastatic only to the liver.[149] Temporary successes have been reported with a range of ablation techniques (radiofrequency,[150,151] cryotherapy[152]) and hepatic artery chemoembolization,[153] while multimodality treatment approaches are often required in cases of extensive disease.[142,154] Finally, irradiation should be considered in cases with metastatic bone or CNS disease.[155]

ACKNOWLEDGMENT

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