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Well-Differentiated Gastric Tumors/ Carcinomas

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Introduction

Gastric endocrine tumors (GET) are increasingly recognized due to expanding indications of upper gastrointestinal endoscopy. Often silent and benign, GET may however be aggressive when sporadic and may sometimes mimic the course of gastric adenocarcinoma.

Epidemiology and Clinicopathological Features

Current incidence of GETs is estimated at around 8% of digestive endocrine tumors [1–3]. Yearly age-adjusted incidence is around 0.2 per population of 100,000. GETs may occur in two different situations: sporadic GETs (type 3 tumors) are very rare tumors without predisposing factors for their development. They are most often located in the fundus/gastric corpus, but antral localization is possible. Gastric ECLomas develop from gastric enterochromaffin-like cells (ECL cells) in response to chronically elevated gastrin. The latter may occur in two opposing conditions [4–18]: achlorhydria secondary to (auto-immune) atrophic fundic gastritis (type 1 tumors), or in response to hypergastrinemia resulting from tumoral secretion from gastrinomas (Zollinger-Ellison syndrome), mostly in patients presenting with multiple endocrine neoplasia type 1 (type 2 tumors). Table 1 summarizes the main characteristics of GETs.

Type 1 tumors (ECLomas in the course of atrophic gastritis) occur mostly in women and are rarely responsible for symptoms [19]. They are non-functioning tumors, typically found during upper GI endoscopy performed for dyspepsia or for macrocytic (but also iron deficiency) anemia [7, 12, 15, 17, 19]. ECLomas present frequently as multiple (2–10) polyps, usually <1 cm in diameter in the gastric fundus. Type 1 tumors are almost

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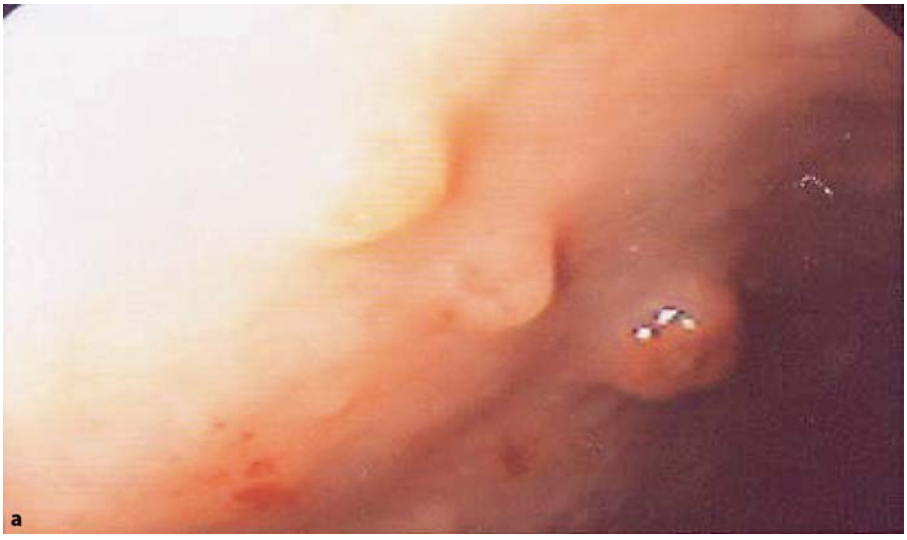

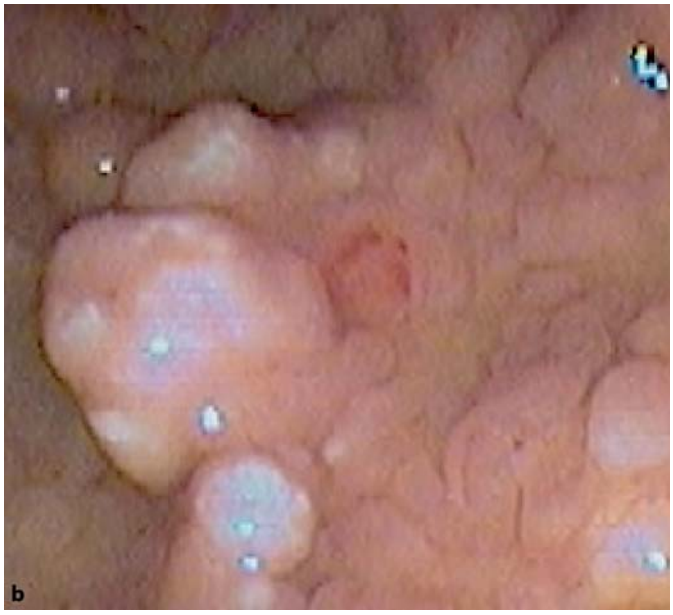

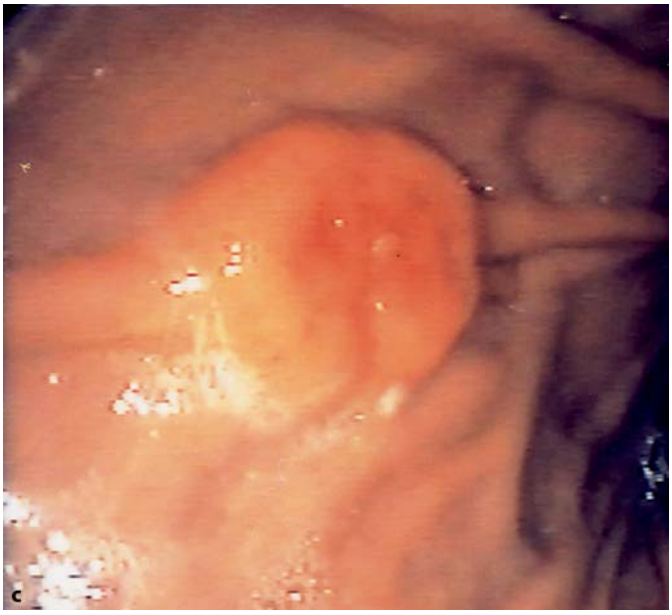

Fig. 1. Type 1 (**a**), type 2 (**b**) and type 3 (**c**) gastric ECLomas.

exclusively benign lesions with little risk of deep invasion of the gastric parietal wall [20]; the latter depends on tumor size [19, 21]. Type 2 tumors (ECLomas in the course of Zollinger-Ellison syndrome) are almost exclusively seen in MEN 1 patients [6, 22–24], occurring in 23–29% of such cases (as compared with 1–3% in sporadic gastrinomas) [24–26]. They appear as small (<1–2 cm) polyps and may involve the entire fundic mucosa. They are generally asymptomatic.

Type 3 tumors are usually solitary and mostly belong to WHO group 2: Ki 67 >2%, >2 cm in diameter with infiltrative growth; they occur mostly in men over 50 years of age [4–6, 19, 20, 27]. They may be discovered incidentally, but are often responsible for pain, weight loss, and iron-deficiency anemia. Atypical carcinoid syndrome due to histamine production is extremely rare (fig. 1).

Minimal Consensus Statements on Epidemiology and Clinicopathological Features

The yearly age-adjusted incidence of gastric type 1 and 2 endocrine tumors is approximately 0.2 per population of 100,000; however, these tumors are probably underdiagnosed. Type 1 tumors are the most common endocrine tumors of the stomach (70–85%) and they are usually benign (WHO group 1). Type 2 tumors,

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Table 1. General characteristics of gastric endocrine tumors (GETs) [adapted from 5, 13 and 14]

	Type 1	Type 2	Type 3
Proportion among GETs, %	70–80	5–6	14–25
Tumor characteristics	often small (<1–2 cm) and multiple, polypoid	often small (<1–2 cm) and multiple, polypoid	unique, often large (>2 cm) polypoid and ulcerated
Associated conditions	chronic atrophic gastritis	gastrinoma/NEM 1	none
Pathology	well-differentiated	well-differentiated	well or moderately differentiated
Serum gastrin levels	↑	↑	normal
Gastric pH	↑↑	↓↓	normal
Metastases, %	2–5	10–30	50–100
Tumor-related deaths, %	0	<10	25–30

Table 2. WHO classification of gastric endocrine tumors

Tumor type	WHO classification	Metastases	Invasion beyond submucosa	Histological differentiation	Tumor size, cm	Vascular invasion	Ki 67 %
Benign (low risk)	group 1	–	–	well-differentiated	≤1	–	<2
Benign or low-grade malignant (intermediate risk)	group 1	–	–	well-differentiated	>1	±	<2
Low-grade malignant	group 2	+	+	well-differentiated	>2	+	>2
High-grade malignant	group 3	+	+	poorly differentiated	any	+	>15

however, are much rarer; however up to 35% of cases are metastatic at presentation. Type 1 gastric carcinoids occur more frequently in women and 70–80% of tumors are classically diagnosed in the 5th and 7th decades, although with the more extensive use of endoscopy the age limit may be younger particularly in those patients with multiple autoimmune diseases.

Clinical subtyping of ECL cell tumors (that is, distinction between type 1 and 2 tumors) is important and effective in patient management. Type 1 have almost universally good prognosis with rare tumor-related death at follow-up. Among type 2 gastric carcinoids, death due to metastatic gastric carcinoid is exceptional.

Small gastric carcinoids are usually asymptomatic and very occasionally (<1%) patients may complain of flush and present the 'atypical carcinoid syndrome'.

Diagnostic Procedures: Imaging, Nuclear Medicine and Laboratory Tests

Imaging techniques such as CT scan and MRI are of very limited value for small type 1 and 2 tumors. These lesions are recognized by upper GI endoscopy. Endoscopic ultrasonography (EUS) may help to determine tumor invasion in the depth of the gastric wall (table 2). In case of small (<1 cm) ECLomas, upper GI endoscopy is usually the only recommended imaging procedure.

When there is a risk of metastases (table 1), and mainly in cases of sporadic tumors (type 3), an extensive search should be performed. EUS is useful in assessing regional lymph-node involvement and allows histological confirmation by fine-needle aspiration. Transabdominal ultrasonography, and mainly CT scan and MRI, have high sensitivity/specificity in looking for liver metastases. Somatostatin receptor scintigraphy (SRS) is recommended in these patients with well-differentiated tumors to search for liver, bone and lymph node metastases.

Laboratory tests are of major interest, especially in patients with type 1 or 2 ECLomas. In these patients, basal serum gastrin levels should be determined and are always elevated [11, 28, 29], as well as serum chromogranin A levels [30]. Further tests should be performed depending on the clinical context. In the majority of the cases (type

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1 tumors), no symptoms of ZES are present and upper GI endoscopy does not show any lesion related to peptic disease. The search for autoimmune disease should include anti-parietal cell and anti-intrinsic factor auto-antibodies, present in about 50% of the patients with GAC [5]. Determination of basal and pentagastrin-stimulated acid output by gastric aspiration is rarely necessary to establish the diagnosis and confirms achlorhydria in difficult cases. In patients with ZES, laboratory tests are limited to chromogranin A and serum gastrin levels measurement [22, 23, 31, 32]. In patients with type 3 sporadic tumors, which occur independent of hypergastrinemia, determination of serum chromogranin A level is useful in patients with well-differentiated tumors.

Minimal Consensus Statements on Diagnostic Procedures

Diagnosis is made at gastroscopy and biopsy samples should be taken from the antrum (2 biopsies) and fundus (4 biopsies) in addition to biopsies of the largest polyps. For type 1 and small type 2 tumors, endoscopy and biopsy usually suffice. For type 1 and type 2 tumors EUS should be performed in tumors above 1 cm in size. CT, MRI, SRS are not required with the exception of larger tumors and invasive tumors at EUS. The minimal biochemical tests in patients with type 1 and type 2 tumors includes serum gastrin and chromogranin A levels. These tests should be performed at diagnosis and chromogranin A may be useful at follow-up (although there are no strong data to support the latter).

Pathology and Genetics

Pathological diagnosis is mandatory in all cases and is easily obtained from tumor biopsies performed during gastroscopy (for type 3 GETs), or preferably upon examination of a whole tumor (polyp) removed using endoscopic mucosal resection (EMR) (ECLomas type 1 and 2). In case of multiple polyps, biopsies of fundic non-polypoid mucosa should also be performed in order to establish the diagnosis of associated atrophic gastritis. In this latter condition, polyps may be of various origin and correspond to hyperplastic or inflammatory polyps, adenomas or even early gastric adenocarcinomas, as well as ECLomas. Multiple biopsies of different lesions should thus be performed, especially if macroscopic appearance of one lesion differs from that of the others. Pathological diagnosis of GET is performed using conventional hematoxylin-eosin staining, immunohistochemical staining with chromogranin and synaptophysin [5, 8, 10, 18, 22]. Determination of mitotic index by counting 10 HPF and calculation of Ki-67 index by immunohistochemistry are mandatory [33]. The tumors should be classified according to the WHO knowing that the great majority of GETs fall within group 1 tumors (table 2).

Most ECLomas are preceded (or accompanied) by linear or micronodular hyperplasia or dysplasia of ECL cells [34]. This condition is associated with a 26-fold increase in the risk of developing ECLomas in patients with chronic atrophic gastritis [34]. Type 3 tumors may be well or moderately differentiated. Proliferative index using Ki-67 antibody is frequently elevated [20]. Genetic testing for hereditary tumor syndrome should only be performed in case of suspected or established diagnosis of Zollinger-Ellison syndrome. As outlined above, the presence of ECLomas in a patient with ZES makes the diagnosis of MEN 1 very likely.

Minimal Consensus Statements on Pathology and Genetics

Histology is always necessary to establish a diagnosis. Cytology may be helpful, but should be confirmed by histology. The minimal ancillary tests to support the histological diagnosis include immunohistochemistry for chromogranin A and synaptophysin. Both the mitotic count in 10 HPF (2 mm^2) and the Ki-67 index (the latter performed using immunohistochemistry, although the techniques and counting standards need to be established) are mandatory in all cases. Immunohistochemistry for p53 or SSR2A receptors in type 1 or type 2 tumors is not recommended.

Germline DNA testing is only recommended in the presence of a positive family history of MEN-1 or if multiple tumors are present in the absence of atrophic gastritis in the rare instances when MEN-1 diagnosis has not been done previously. Genetic analysis should also be performed in suspected cases of MEN-1. Genetic testing when performed should include mutational screening and sequencing, allowing for analysis of the entire coding gene and splice sites and genetic counseling should be sought prior to testing in all patients. Informed consent is mandatory prior to genetic testing. Somatic (tumor) DNA testing is not recommended.

Endoscopic/Surgical Therapy

In patients with type 1–2 ECLomas, it is generally accepted that annual surveillance is sufficient for patients with tumors <10 mm. When tumors are larger, endoscopic resection is recommended for up to 6 polyps not involving the muscularis propria (EUS is thus necessary) [19]. In the remaining patients, local surgical tumor resection should be performed. Antral resection to avoid

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repeated and chronic gastrin stimulation of ECL cells is effective in 80% of type 1 tumors [21, 35, 36]. In case of malignant development or recurrence despite local surgical resection, partial or total gastrectomy with lymph node dissection should be performed. In patients with type 3 tumors, surgical treatment should not differ from that of gastric adenocarcinomas (partial or total gastrectomy with lymph node dissection).

Minimal Consensus Statements on Endoscopic/ Surgical Treatment

Tumors <10 mm should undergo surveillance. For larger tumors local endoscopic ablation (following EUS) should be performed. Endoscopic mucosal resection (EMR) is recommended for lesions close to and above 1 cm but without invasion of the muscularis propria. In the presence of deep gastric parietal wall invasion and positive margins following EMR, antrectomy and local resection is performed in type 1 ECLomas. Antrectomy is effective in most patients (type I, >80%) and more radical surgery is required if lymph nodes are positive. In type 2, only local excision is recommended. Presence of multiple tumors does not per se influence surgical management.

Medical Therapy

The antiproliferative effect of somatostatin analogues on ECL cells has been shown in both animals and humans [37–41]. Although tumor regression of ECLomas has been reported, the use of somatostatin analogues is not justified in current practice. Intravenous cytotoxic chemotherapy may be used in patients with metastatic tumors (mainly type 3). Cytotoxic protocols depend on tumor differentiation.

Minimal Consensus Statements on Medical Therapy

Biotherapy is not currently recommended in patients with type 1 and 2 tumors except in patients with functioning tumors and in type 2 patients if indicated for the underlying tumor disease (i.e. other endocrine tumors). Exceptions may be made in case of metastatic disease in reference centers. There is usually no place for chemotherapy in patients with type 1 or type 2 tumors (with the exception of metastatic disease which is rare). Peptide receptor radionuclide therapy (PRRT) may be considered as a treatment option (no data currently available to support its use in this setting) on a compassionate basis or as part of academic research studies in patients with distant metastases, provided no other treatment options are available. A positive somatostatin receptor scintigraphy is required prior to use of PRRT (preferably using ^{90}Y- or ^{177}Lu-labeled analogues).

Follow-Up

No clinical study clearly indicates how often patients with type 1–2 ECLomas should undergo endoscopic surveillance, depending on the number and size of polyps and previous EMR. Recommendation is that surveillance should be performed every 2 years (type 1) or yearly (type 2) with EMR of polyps when >10 mm. In patients with chronic atrophic gastritis, the risk of gastric adenocarcinoma developing from intestinal metaplasia would also justify biopsies on flat mucosa. In patients with type 3 tumors, follow-up should depend on tumor subtype. In well-differentiated tumors and after curative resection, imaging (according to the initially positive study and to local experience) and chromogranin A should be performed at 6-month intervals for the first 2 years, and then yearly for 3 more years. In well-differentiated metastatic tumors, follow-up investigations (CT/MRI) should be done every 3 months.

Minimal Consensus Statements on Follow-Up

Gastroscopy should be performed every 2 years in patients with type 1 tumors and yearly in the case of type 2 tumors.

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