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New insights into the classification of gastric neuroendocrine tumours expanding the spectrum of ECL-cell tumours related to hypergastrinemia

Stefano La Rosa[1], Enrico Solcia[2]

[1]Institute of Pathology, University Hospital and University of Lausanne, Lausanne, Switzerland
[2]Anatomic Pathology Unit, Department of Molecular Medicine, University of Pavia, and IRCCS San Matteo Hospital, Pavia, Italy

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Corresponding author:

Stefano La Rosa
Institut Universitaire de Pathologie, CHUV
25 rue du Bugnon
CH-1011 Lausanne
Switzerland
Tel: +41 (0)21 3147162
Fax: +41 (0)21 3147205
e-mail: stefano.larosa@chuv.ch

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Gastric neuroendocrine tumours (NETs) are a heterogeneous group of neoplastic proliferations including different categories characterized by peculiar and specific pathogenetic mechanisms, different metastatic potential and prognosis. Their incidence has increased over the last years and their diagnosis is not so rare into the diagnostic routine practice.[1] Gastric NETs need to be distinguished from gastric neuroendocrine carcinomas (NECs) and mixed neuroendocrine-nonnneuroendocrine neoplasms (MiNENs) that, although sharing a neuroendocrine phenotype, are different diseases in term of molecular background, pathogenesis, morphology, response to therapy, and outcome.[2,3]

Most gastric NETs are composed of histamine-producing ECL-cells and are traditionally separated into three categories (type 1, type 2, and type 3 NETs) (Table 1) on the basis of the patient's clinico-pathologic background, which includes morphology of the peri-tumoral mucosa, gastrin serum level, presence or absence of antral G-cell hyperplasia, and presence or absence of MEN1 syndrome.[4] Several studies have confirmed that this classification is *per se* strongly related to patient's outcome[5,6] and needs to be considered together with the Ki67 proliferative index for the prognostic classification of patients.[7]

Type 3 NETs represent a peculiar subtype not associated with hypergastrinemia, arising as solitary tumors in a normal oxyntic mucosa, with a high predisposition to metastatic dissemination to regional lymph nodes or liver, largely influenced by tumour stage and Ki67 proliferative index.[6] They have traditionally been considered as a subtype of ECL-cell NETs, but since histamine production or typical "ECL-type" secretory granules have not been demonstrated in all cases, the designation ECL-cell has been removed to identify this specific category of tumors.[8] Unlike type 3 NETs, the other traditionally known and well-characterized subtypes 1 and 2 are associated with severe hypergastrinemia, which plays a pivotal pathogenetic role. In type 1 ECL-cell NETs, hypergastrinemia is due to a compensatory antral G-cell hyperplasia secondary to oxyntic mucosa atrophy caused by autoimmune gastritis. In type 2 ECL-cell NETs, hypergastrinemia is due to the presence of a duodenal or, more rarely, pancreatic gastrinoma in the setting of MEN1 syndrome and in these patients the oxyntic mucosa is hyperplastic and/or hypertrophic. However, hypergastrinemia alone, which in these patients can reaches very high levels, does not seem sufficient alone for tumour development. Indeed, gastrin stimulus on ECL-cells acts in cooperation with other growth factors such as TGFα and bFGF in type 1 NETs, while in type 2 ECL-cell NETs the alterations of *MEN1* gene likely renders ECL-cells more sensitive to gastrin stimulation.[7]

In addition to type 1 and 2, rare ECL-cell NETs associated with hypergastrinemia, achlorhydria and parietal cell hyperplasia, but without gastrinoma and MEN1 syndrome, have been described[9,10] representing a peculiar entity for which the term type 4 ECL-cell NET has been proposed.[7] The pathogenesis of this subtype seems related to a compensatory hypergastrinemia secondary to inappropriate acid secretion from parietal cells, due to the defect/lack of proton pump function probably determined by an inactivating mutation of the

ATP4A gene encoding the α-subunit of gastric proton pump.[10,11] All these gastrin-related type 1, type 2 and type 4 ECL-cell tumours are indolent or less aggressive neoplasms than type 3 NETs. In this context, the paper by Trinh and co-workers expands the spectrum of hypergastrinemia-associated ECL-cell NETs by adding a new subtype, which arises in patients treated long term with proton pump inhibitors in the context of non-atrophic oxyntic mucosa with usually moderate hypergastrinemia.[12] Due to the wide use of these drugs, this entity may be not rare in current diagnostic practice and presents a clinical relevance. Since these tumours are associated with a normal or slightly hyperplastic peri-tumoral oxyntic mucosa, they mimic type 3 NETs, from which they need to be differentiated. Indeed, as the authors demonstrated in their study, this new category, which can be provisionally defined as type 5 ECL-cell NET, shows a better behaviour that type 3 NETs not requiring an aggressive surgical approach. In light of these observations, the spectrum of gastric NETs appears wider than that proposed by Rindi et al. in 1993, when long term proton pump inhibitors use was not yet widespread.[4] From a clinical and prognostic point of view, gastric NETs arising in the oxyntic mucosa can be separated into two categories: on one side tumors not associated with hypergastrinemia (type 3 NETs), which represent a specific and potentially aggressive neoplastic category[13] and, on the other side, a group of different ECL-cell NETs associated with hypergastrinemia that plays a pivotal pathogenetic role. The latter tumours, although showing peculiar clinico-pathologic features, are characterized by an indolent behaviour not requiring aggressive therapeutic approach (Fig. 1).

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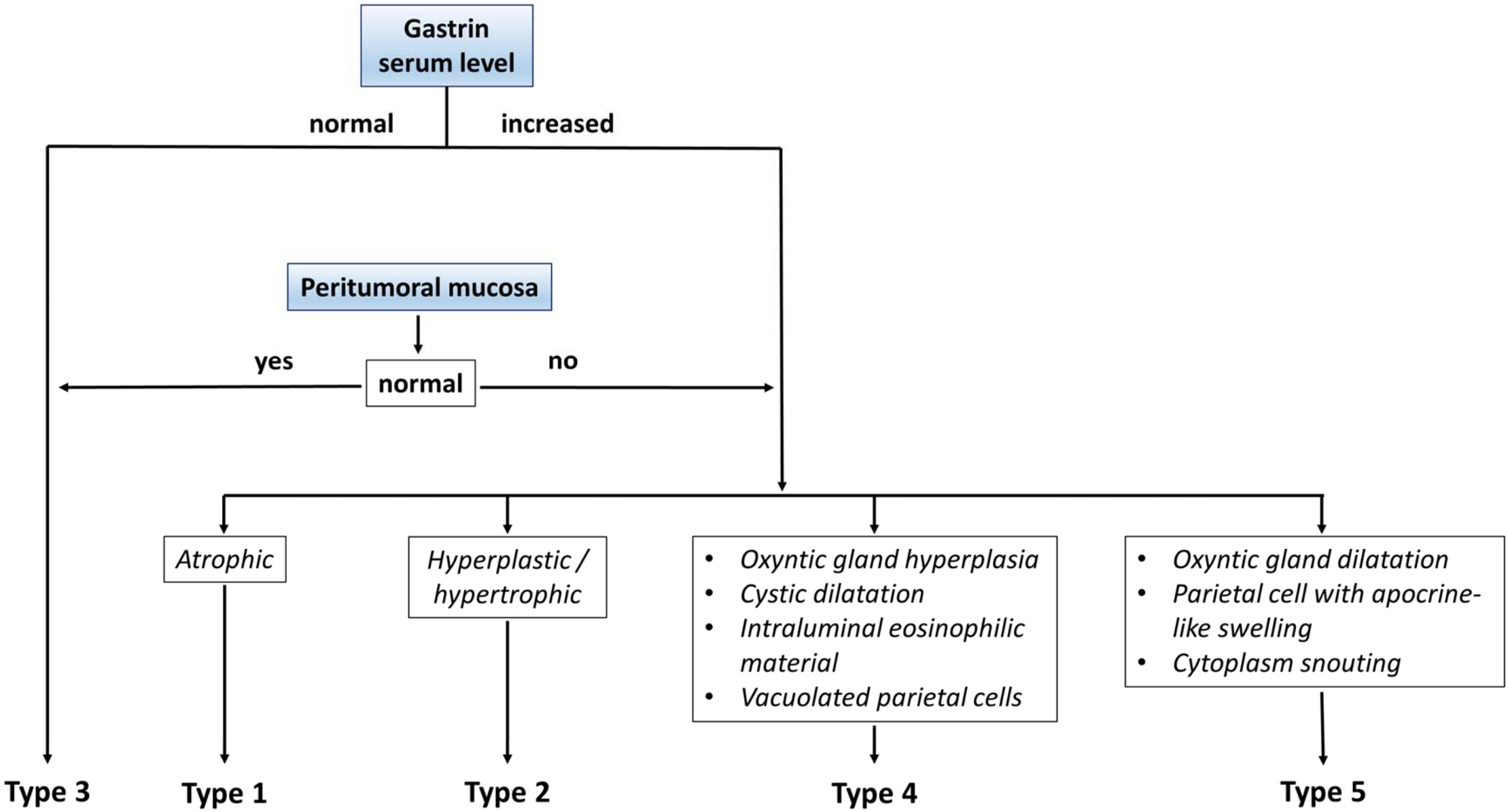
Figure 1 legend. Practical algorithm to diagnose gastric neuroendocrine tumors arising in the oxyntic mucosa.

Table 1. Clinico-pathological features of gastric ECL-cell NETs (see references 4-10, 12, 13).

	M:F ratio	%	Hyper-gastrinemia	Acid secretion	Peritumoral mucosa	ECL-cell proliferations	Grading	Metastasis	5-year survival
Type 1	1:2.5	80-90%	Yes	Low or absent	Atrophic gastritis	Yes	-G1 -G2, rare -G3, exceptional	1-3%	about 100%
Type 2	1:1	5-7%	Yes	High	Hypertrophic gastropathy	Yes	-G1 -G2, rare	10-30%	60-90%
Type 3	2.8:1	10-15%	No	Normal	No specific change	No	-G1, rare -G2 -G3, rare	50%	<50%
Type 4	Unknown	Rare	yes	Low or absent	Parietal cell hypertrophy	Yes	Unknown	Unknown	Unknown
Type 5	1.7:1	unknown	yes	Not evaluated	PPI effects	Yes	-G1 -G2 -G3, rare	15-17%	about 100%


Gastrin serum level
normal
increased
Peritumoral mucosa
yes
normal
no
Atrophic
Hyperplastic / hypertrophic
• Oxyntic gland hyperplasia
• Cystic dilatation
• Intraluminal eosinophilic material
• Vacuolated parietal cells
• Oxyntic gland dilatation
• Parietal cell with apocrine-like swelling
• Cytoplasm snouting
Type 3
Type 1
Type 2
Type 4
Type 5