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Authors: La Rosa S, Solcia E

Journal: Histopathology

Year: 2020 Dec

Issue: 77

Volume: 6

Pages: 862-864

DOI: 10.1111/his.14226
New insights into the classification of gastric neuroendocrine tumours expanding the spectrum of ECL-cell tumours related to hypergastrinemia

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Running title: gastric ECL-cell NETs

Conflict of interest: the authors declare the absence of conflict of interest.

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Comment on: Trinh VQ, Shi C, Ma C. Gastric neuroendocrine tumors from long-term proton pump inhibitor users are indolent tumors with good prognosis [published online ahead of print, 2020 Jul 23]. Histopathology 2020;10.1111/his.14220. doi:10.1111/his.14220

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. Gastric NETs need to be distinguished from gastric neuroendocrine carcinomas (NECs) and mixed neuroendocrine-nonneuroendocrine neoplasms (MiNENs) that, although sharing a neuroendocrine phenotype, are different diseases in term of molecular background, pathogenesis, morphology, response to therapy, and outcome.

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. Several studies have confirmed that this classification is per se strongly related to patient’s outcome and needs to be considered together with the Ki67 proliferative index for the prognostic classification of patients.

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. 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. 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 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 representing a peculiar entity for which the term type 4 ECL-cell NET has been proposed. 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 \( \alpha \)-subunit of gastric proton pump.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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).

References


12. Trinh VQ, Shi C, Ma C. Gastric Neuroendocrine Tumors from Long-Term Proton Pump Inhibitor Users are Indolent Tumors with Good Prognosis [published online ahead of print, 2020 Jul 23]. Histopathology. 2020.


**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).

<table>
<thead>
<tr>
<th>Type</th>
<th>M:F ratio</th>
<th>%</th>
<th>Hypergastrinemia</th>
<th>Acid secretion</th>
<th>Peritumoral mucosa</th>
<th>ECL-cell proliferations</th>
<th>Grading</th>
<th>Metastasis</th>
<th>5-year survival</th>
</tr>
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<tbody>
<tr>
<td>Type 1</td>
<td>1:2.5</td>
<td>80-90%</td>
<td>Yes</td>
<td>Low or absent</td>
<td>Atrophic gastritis</td>
<td>Yes</td>
<td>-G1</td>
<td>-G2, rare</td>
<td>-G3, exceptional</td>
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<td>1-3%</td>
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<tr>
<td>Type 2</td>
<td>1:1</td>
<td>5-7%</td>
<td>Yes</td>
<td>High</td>
<td>Hypertrophic gastropathy</td>
<td>Yes</td>
<td>-G1</td>
<td>-G2, rare</td>
<td>-G3, exceptional</td>
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<td>10-30%</td>
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<tr>
<td>Type 3</td>
<td>2.8:1</td>
<td>10-15%</td>
<td>No</td>
<td>Normal</td>
<td>No specific change</td>
<td>No</td>
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<td>-G1, rare</td>
<td>-G2</td>
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<td>Type 4</td>
<td>Unknown</td>
<td>Rare</td>
<td>Yes</td>
<td>Low or absent</td>
<td>Parietal cell hypertrophy</td>
<td>Yes</td>
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<td>Type 5</td>
<td>1.7:1</td>
<td>unknown</td>
<td>Yes</td>
<td>Not evaluated</td>
<td>PPI effects</td>
<td>Yes</td>
<td>-G1</td>
<td>-G2</td>
<td>-G3, rare</td>
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<td>15-17%</td>
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