Gastric Carcinoids (Neuroendocrine Neoplasms)

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KEYWORDS

• Carcinoid • Chronic atrophic gastritis • Gastrin • Menin
• Multiple endocrine neoplasia 1 • Neuroendocrine tumor • Proton pump inhibitor
• Zollinger-Ellison syndrome

KEY POINTS

- Gastric neuroendocrine neoplasms of the stomach can be divided into the usually well-differentiated, hypergastrinemia-dependent type I and II lesions and the more aggressively behaving gastrin-independent type III lesions.
- The observed incidence has increased more than 10-fold over the past 30 years.
- Small (<15–20 mm) localized type I and II lesions, which are slowly proliferating (<2%), can usually be managed conservatively through reduction of hypergastrinemia; the use of the specific gastrin receptor antagonist YF476 or gastrin antibodies may become useful for both type I and II lesions in future protocols.
- Infiltrating and metastasized tumors and type III lesions require a more aggressive approach with surgical resection and consideration of modalities such as cytotoxics and peptide receptor–targeted treatment.
- The mutational spectrum in gastric lesions is greater than MEN-1 (eg, NF-1 and MAPK alterations occur); studying menin and its complex interrelationship with gastrin may provide insight into tumor biology at the clinical level and in terms of basic cell biology (eg, the role of the epigenome in neuroendocrine cell proliferation), and lead to potential consideration of other targets that are known candidates for molecular-based therapies in other adenocarcinomas.

INTRODUCTION

Gastric carcinoids or, as they are currently called, "neuroendocrine neoplasms" (NENs),[1] have recently become the subject of substantial clinical and investigative interest. This fact reflects global concerns regarding the consequences of prolonged

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hypochlorhydria, long-standing hypergastrinemia (increased use of acid-suppressive pharmacotherapeutic agents), and the proposed putative relationship between gastric adenocarcinoma and gastric NENs.[2–6] These tumors were previously considered rare lesions,[7] overall representing fewer than 2% of all gastrointestinal NENs and fewer than 1% of all gastric neoplasms. The misconception of rarity is redundant because current cancer databases indicate that gastric NENs are increasing in incidence/prevalence and that the current figures are closer to 5%.[8,9] Whether this represents increased clinical awareness, more accurate pathologic identification, or more thorough endoscopic surveillance is debatable, but nevertheless provides a far larger group of patients whose disease requires management. Delineation of the regulation of enterochromaffin-like (ECL) cell proliferation, characterization of its degree of transformation, and determination of its malignant potential are necessary adjuncts for the development of a rational strategy for clinical management. As a result of these factors, an intense clinical and scientific scrutiny of gastric neuroendocrine ECL cell tumors has developed.[8]

Gastric NENs are usually derived from the histamine-secreting ECL cell but may occasionally have a phenotype indicating an origin from other cell type, such as serotonin-secreting enterochromaffin cells, somatostatin, or ghrelin cells.[10–12] ECL cell tumors are classified as either gastrin-dependent (type I/II) or gastrin-independent (type III), although the gastrin/CCK2 receptor is expressed on both types.[13] This article reviews each type of lesion, examines the pathobiologic insights generated from animal models, and determines the translational significance of these data.

Type I Gastric NENs

Type I gastric NENs occur in patients with chronic atrophic gastritis (CAG), with hypergastrinemia caused by an absence of gastric acid. Lesions are usually located in atrophic oxyntic mucosa in the fundus in individuals with CAG with or without pernicious anemia.

Most instances (70%–80%) are seen in patients with CAG and associated hypergastrinemia, whereas pernicious anemia is common (58%).[14,15] Among 367 individuals with atrophic gastritis, the prevalence was 2.4%, with an annual incidence of 0.4% during endoscopic follow-up.[16] In general, type I NENs occur more frequently in women, and 70% to 80% are diagnosed between the fifth and seventh decades.[17,18] Because of diminished acid secretion, serum gastrin levels are significantly elevated in patients with atrophic gastritis. On the same basis, a correlation between long-term proton pump inhibitor (PPI)–induced hypergastrinemia and the development of gastric NENs is possible and supported by recent epidemiologic data and case reports.[19,20] Serum gastrin and chromogranin A (CgA) levels can be elevated in approximately 100% and 95% of patients, respectively.[21]

Lesions, when identified, are usually small (<1 cm), polypoid, and multicentric (≈67% of cases). These tumors are mostly limited to the mucosa or submucosa, do not exhibit angioinvasion, and seem to be benign in behavior.[11] Larger tumors (1–2 cm) may exhibit low-grade malignant behavior, with or without angioinvasion. Tumors in this group may be either single or multiple, exhibit a low rate of lymph node invasion (3%–8%), and are rarely (≈2% of cases) associated with distant metastases.[22,23] In general, irrespective of their size, lesions are classified as stage I (87%).[21]

At a histologic level, ECL cell lesions have been classified as pseudohyperplasia (cell clustering unassociated with cell proliferation), hyperplasia (diffuse, linear, micronodular, adenomatoid), dysplasia (enlarged, adenomatous or fused micronodules, microinfiltration, nodular growth), and neoplasia (intramucosal or invasive carcinoids). The entire spectrum of ECL cell proliferation, from hyperplasia to dysplasia and

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