Clinicopathologic features of non–type 1/2 gastric neuroendocrine tumors and their associated mucosal changes

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ABSTRACT

Objectives: The pathogenesis for non–type 1/2 gastric neuroendocrine tumors (G-NETs) remains unclear. The aim of this study was to examine the clinicopathologic features of G-NETs and associated mucosal changes.

Methods: The electronic health records of patients with non–type 1/2 G-NETs were reviewed. H&E slides were reviewed for pathologic features and mucosal changes. The *t* test and Fisher exact test were used for statistical analysis.

Results: In total, 33 patients were assigned to either group 1 (n = 23) or group 2 (n = 10). Group 1 included patients with a history of proton pump inhibitor (PPI) use, increased gastrin levels, or significant PPI effect (PPI/gastrin-associated). All other patients were assigned to group 2. There was no significant difference in age and sex between the 2 groups. Group 2 tumors were more likely to be larger, invade deeper, and develop metastases (P < .05). Tumors in patients with cirrhosis tended to be larger. Peritumoral mucosal changes included loss of oxyntic glands, foveolar hyperplasia, and intestinal metaplasia. Background mucosa in group 1 patients showed PPI effect and neuroendocrine hyperplasia or dysplasia.

Conclusions: Although PPI/gastrin-associated non–type 1/2 G-NETs were smaller and more indolent than typical type 3 G-NETs, tumors in patients with cirrhosis tended to be larger. Additionally, peritumoral mucosal changes could mimic chronic atrophic gastritis.

INTRODUCTION

Over the past few decades, neuroendocrine tumors (NETs) have significantly increased in incidence and prevalence. Approximately two-thirds of NETs occur in the gastrointestinal (GI) tract, with the following incidence in descending order: small intestine, rectum, stomach, appendix, and colon. Of all neuroendocrine tumors, gastric NETs (G-NETs) saw the greatest increase in incidence (15-fold).[1] Like other digestive NETs, G-NETs are assigned a grade (G1, G2, and G3) based on mitoses and Ki-67 index.[2] In addition, G-NETs are further subclassified into 3 types based on background mucosal change, serum gastrin levels, and the presence or absence of multiple endocrine neoplasia type 1 (MEN-1) syndrome. Each subtype has its distinct clinical, pathologic, and prognostic features.

Type 1 G-NETs constitute 70% to 80% of G-NETs and occur in a background of chronic atrophic gastritis.[3,4] Atrophic gastritis leads to hypochlorhydria, compensatory G-cell hyperplasia, and subsequent hypergastrinemia, which causes enterochromaffin-like (ECL) cell hyperplasia and contributes to type 1 tumor development.[4-6] These tumors are commonly

multifocal, small, and confined to the mucosa or submucosa.[3,4,6] Associated mucosal changes include ECL cell hyperplasia, atrophy of oxyntic mucosa with loss of parietal cells, and intestinal metaplasia.[4,7] Type 1 G-NETs have a good prognosis, with a 5-year survival rate of approximately 100%. Type 2 G-NETs correspond to 5% to 10% of G-NETs and are observed in patients with duodenal or pancreatic gastrinomas, often in the setting of MEN-1 syndrome. Associated mucosal changes include hypertrophic gastropathy.[7] These tumors are largely indolent, but the prognosis is slightly worse than for type 1 lesions, with a higher rate of metastasis[4,8] and a 5-year survival rate of 60% to 90%.[7]

Unlike type 1 and 2 G-NETs, type 3 lesions are not associated with any known clinical condition and are considered "sporadic."[4] They constitute 10% to 15% of all G-NETs and usually present as single lesions greater than 1 cm in size, typically arising in normal background mucosa.[4,7] These tumors are considered more aggressive, with a 5-year survival rate under 50%. Type 3 G-NETs, however, are not a single entity; rather, they are a heterogeneous group of tumors.[7] Recently, 2 provisional groups—type 4 and type 5—have been proposed as distinct entities, parting from typical type 3 G-NETs. Both types are associated with hypergastrinemia. Provisional type 4 G-NETs are caused by defective parietal cell H+/K+ adenosine triphosphatase (ATPase) pump, which leads to inadequate acid secretion and compensatory antral G-cell hyperplasia and hypergastrinemia.[9] Provisional type 5 G-NETs have recently been described in patients who have been on long-term therapy with proton pump inhibitors (PPIs) but do not have chronic autoimmune atrophic gastritis, gastrinoma, or MEN-1 syndrome.[7] This subtype is considered less aggressive than typical type 3 tumors, with a more indolent disease course.[10] Unfortunately, the literature on non–type 1/2 G-NETs is limited. Therefore, the aim of this study was to further examine the clinicopathologic features of these tumors and their associated mucosal changes.

METHODS

The study protocol was approved by our institutional review board (No. Pro00107127). The surgical pathology archives were searched for neuroendocrine tumors of the stomach between 2003 and 2022. The following cases were excluded from the study: (1) insufficient background gastric mucosa for evaluation, (2) clinical or pathologic indications of MEN-1 syndrome or chronic autoimmune atrophic gastritis, and (3) poorly differentiated neuroendocrine carcinoma or mixed neuroendocrine nonneuroendocrine neoplasm **FIGURE 1**. The electronic health records of all included cases were retrospectively reviewed. Clinicopathologic data were collected from clinical notes; serum gastrin levels; pathology reports; upper endoscopy results; and pertinent imaging, including endoscopic ultrasound findings.

H&E slides and immunohistochemistry stains (chromogranin, synaptophysin, Ki-67) were reviewed to confirm the diagnosis and evaluate tumor features. In addition, background mucosa, including peritumoral (overlying or immediately adjacent) mucosa, oxyntic mucosa away from the tumors, and gastric antral mucosa (if available), were examined for tumor-associated ulcer, loss of oxyntic glands, foveolar hyperplasia, intestinal metaplasia, significant PPI effect, fundic gland polyp, neuroendocrine dysplasia in the oxyntic mucosa, and antral neuroendocrine cell hyperplasia. Gastric neuroendocrine dysplasia is defined as enlarged, adenomatous or fused micronodules; microinfiltration; or nodular growth of ECL cells.[11] Antral neuroendocrine cell hyperplasia is defined as the predominance of neuroendocrine cells in the neck of antral glands. Tumors were graded based on the 2019 edition of the World Health Organization *Digestive System Tumors*.[2] The 8th edition of the American Joint Committee on Cancer staging system for G-NETs was used to stage the tumors.[12]

Statistical analysis was performed using GraphPad Prism, version 9.00 (GraphPad Software). Unpaired *t* test and the 2-sided Fisher exact test were used for analysis of continuous and categorical data, respectively. $P < .05$ was considered statistically significant.
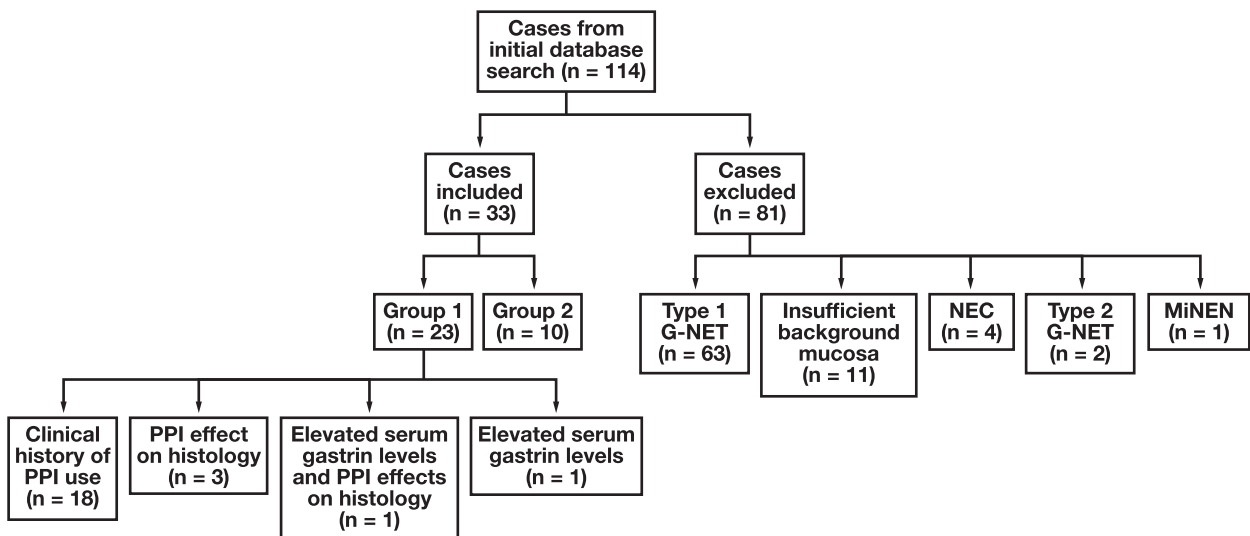
FIGURE 1 Flow diagram of exclusion and inclusion criteria. G-NET, gastric neuroendocrine tumor; NEC, neuroendocrine carcinoma; MiNEN, mixed neuroendocrine–nonneuroendocrine neoplasm; PPI, proton pump inhibitor.

TABLE 1 Demographics and Clinicopathologic Features of Non–Type 1/2 Gastric Neuroendocrine Tumor

	Total	Group 1 (n = 23)	Group 2 (n = 10)
Sex, No.			
M	20	12	8
F	13	11	2
Age, mean (SD), y	58.7 (13.6)	61.2 (10.0)	53.0 (19.1)
Indication, No.			
Abdominal pain/dyspepsia	13	11	2
GI bleed/anemia	10	5	5
Emesis	2	2	0
Other	8	5	3
Location, No.			
Fundus/body	31	23	8
Antrum/pylorus	2	0	2
Size[a]			
Mean (SD), cm	1.26 (0.88)	0.97 (0.67)	1.94 (1.0)
Range, cm	0.2-3.5	0.2-2.5	0.7-3.5
Gross description, No.			
Mass	7	2	5
Polyp/papule/nodule	21	18	3
Ulceration/erosion	2	0	2
Focality, No.			
Unifocal	25	16	9
Multifocal	8	7	1
Grade, No.			
G1	11	9	2
G2	13	10	3
G3	1	0	1
Unknown	8	4	4
Depth of invasion,[b] No.			
Mucosa/submucosa	28	23	5
Muscularis propria	2	0	2
Subserosa/serosa	2	0	2
Unknown	1	0	1
TNM stage,[c] No.			
I-II	28	22	6
III	2	1	1
IV	3	0	3
Treatment,[d] No.			
Endoscopic biopsy	8	4	4
Endoscopic mucosal resection or polypectomy	18	17	1
Partial gastrectomy	7	2	5

GI, gastrointestinal.
[a]$P < .01$ when comparing size between groups 1 and 2.
[b]$P < .01$ when comparing mucosa/submucosa and muscularis propria/subserosa/serosa between the 2 groups.
[c]$P < .05$ when comparing stage I-II and stage III-IV between the 2 groups.
[d]$P < .01$ when comparing endoscopic resection/polypectomy and surgical resection between the 2 groups.

RESULTS

Overall Demographics and Clinicopathologic Features

Forty specimens of G-NET from 33 patients were analyzed in this retrospective study. Demographics and clinicopathologic features are summarized in **TABLE 1**. Among the patients included, 20 were men and 13 were women, with a mean (SD) age of 58.7 (13.6) years. The most common presentation was abdominal pain, followed by GI bleeding and anemia. Three patients had lymph node metastasis,

and 3 had distant metastasis. Two of the 33 patients died from the disease.

PPI/Gastrin-Associated vs Other Non—Type 1/2 G-NETs

Based on clinical history, laboratory studies, and background mucosal changes, each patient was assigned to group 1 or group 2. Group 1 (n = 23) included patients with a documented history of at least 6 months of PPI use before disease diagnosis, increased serum gastrin levels, or significant PPI effect on H&E slides (designated as PPI/gastrin-associated non—type 1/2 G-NETs). In group 1, PPI use was documented in 18 cases. A history of PPI use was not provided in the remaining 5 cases. Among these 5 cases, 2 showed elevated gastrin levels, and 3 had prominent PPI effect in background oxyntic mucosa without documented gastrin levels FIGURE 1 . One of the 2 cases with documented gastrin levels had a high gastrin level (>3,500 pg/mL), and extensive imaging studies did not reveal additional tumors in the duodenum, pancreas, or other sites. This patient had no history of MEN-1 syndrome or clinical features of Zollinger-Ellison syndrome, such as gastric/duodenal ulcers. This patient's gastrin levels returned to normal following a distal gastrectomy. All other patients were assigned to group 2 (n = 10), which might represent patients with typical type 3 G-NETs.

There was no significant difference in sex (52% vs 80% male; $P = .25$) and age (mean age, 61 vs 53 years; $P = .11$) between group 1 and group 2 TABLE 1 . The most common known indication for upper endoscopy was abdominal pain or dyspepsia for group 1 and GI bleeding or anemia for group 2. Group 2 tumors were significantly larger (mean, 1.94 cm vs 0.97 cm; $P = .002$). Approximately 30% of group 1 cases were multifocal. Interestingly, 1 of 10 cases in group 2 was also multifocal. All group 1 tumors were located in the fundus/body mucosa, whereas 2 group 2 tumors were located in the gastric antrum/pylorus. Most group 1 lesions presented as a polyp, papule, or nodule FIGURE 2A ; most group 2 cases were mass lesions FIGURE 3A . Most tumors were either grade 1 or 2 in both
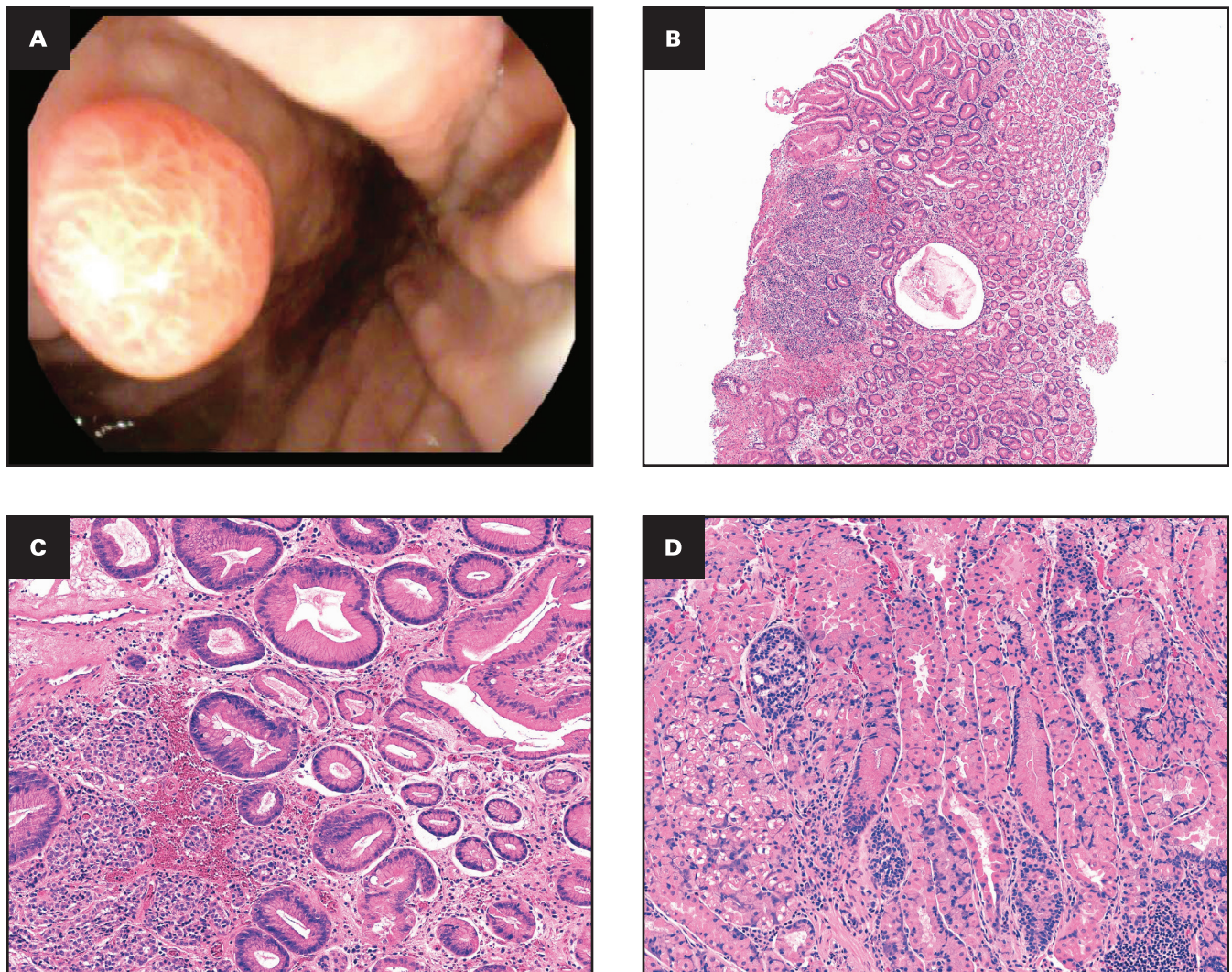
FIGURE 2 Proton pump inhibitor (PPI)/gastrin associated non–type 1/2 gastric neuroendocrine tumor. **A**, Polypoid lesion endoscopically. **B**, Neuroendocrine tumor involves mucosa. **C**, Peritumoral mucosa showing loss of oxyntic glands, foveolar hyperplasia, and focal intestinal metaplasia. **D**, Background gastric body mucosa showing neuroendocrine cell dysplasia and prominent PPI effect.

groups. Grade 3 was rare and seen only in group 2 (1/10 [3%]). Tumors in group 1 were all confined to the mucosa or submucosa. In contrast, 4 of 9 patients with known tumor invasion depth in group 2 had tumor extending to muscularis propria or deeper. Only 1 of 23 group 1 patients had stage III disease, whereas 4 of 10 in group 2 had either stage III (n = 1) or stage IV disease (n = 3; 4% vs 40%, P = .02). Patients were treated by endoscopic biopsy only (n = 8), endoscopic polypectomy or mucosal resection (n = 18), or partial gastrectomy (n = 7). Patients in group 1 were significantly more likely to be treated by local resection (endoscopic polypectomy or mucosal resection) than surgical resection (partial gastrectomy) compared with patients in group 2 (P < .01) TABLE 1.

Associated Mucosal Changes

Peritumoral mucosa was defined as the mucosa overlying a tumor or immediately adjacent to a tumor. Peritumoral mucosal change includes mucosal ulceration/erosion in 3 patients (9%),

loss of oxyntic glands in 22 patients (67%), foveolar hyperplasia in 22 patients (67%), and intestinal metaplasia in 8 patients (24%) FIGURES 2B, 2C, 3B, and 3C. In 4 patients, tumors were intermixed with oxyntic glands (12%). Background oxyntic mucosa showed significant PPI effect in 17 patients (52%) and neuroendocrine dysplasia in 5 patients (15%) FIGURE 2D. Antral mucosa was available in 10 cases, with 3 of them showing prominent neuroendocrine cell hyperplasia.

Loss of oxyntic glands, foveolar hyperplasia, intestinal metaplasia, and intermixed tumor with oxyntic glands were observed in the peritumoral mucosa of both groups TABLE 2. Intestinal metaplasia was more common in group 2 (50% vs 13%; P = .04), as was erosion/ulceration of the peritumoral mucosa (30% vs 0%; P = .02). No other associated mucosal changes were significantly different between the 2 groups. Peritumoral mucosal changes were seen in tumors as small as 0.22 cm. Median tumor size in cases with loss of oxyntic glands, foveolar hyperplasia, or intestinal metaplasia was 1.1 cm
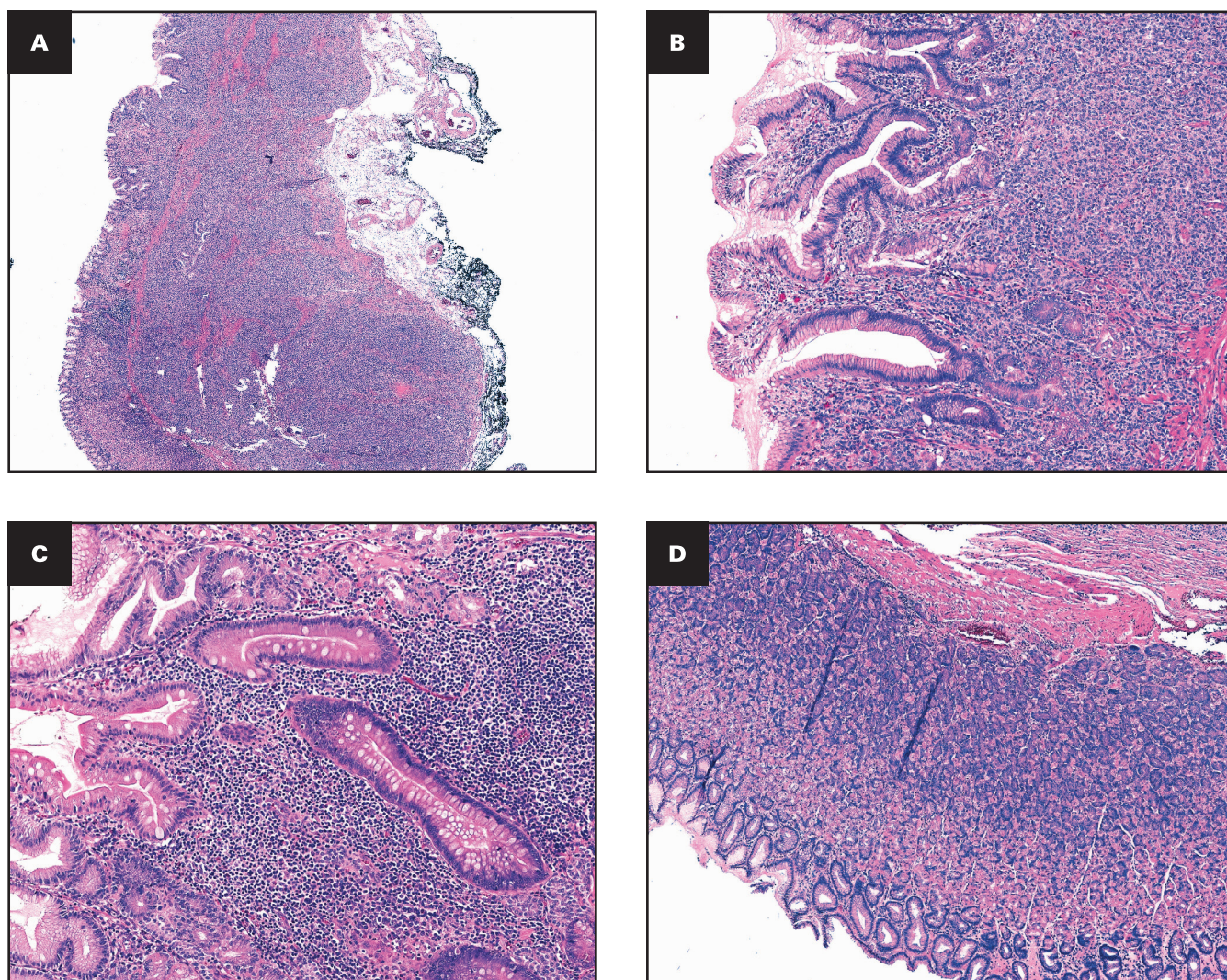
FIGURE 3 An example of typical type 3 gastric neuroendocrine tumor. **A,** A cross-section of the entire mass lesion. **B,** Peritumoral mucosa showing loss of parietal cells and foveolar hyperplasia. **C,** Peritumoral mucosa showing chronic inflammation (lymphoid aggregate) and intestinal metaplasia. **D,** Normal gastric body mucosa away from the mass.

TABLE 2 Peritumoral and Background Mucosal Changes of Non–Type 1/2 Gastric Neuroendocrine Tumor

Mucosal Changes	Patients, No. (%) (n = 33)	Group 1, No. (%) (n = 23)	Group 2, No. (%) (n = 10)
Peritumoral			
Erosion/ulceration[a]	3 (9)	0 (0)	3 (30)
Loss of oxyntic glands	22 (67)	16 (70)	6 (60)
Intestinal metaplasia[a]	8 (24)	3 (13)	5 (50)
Foveolar hyperplasia	22 (67)	15 (65)	7 (70)
Tumor intermixes with oxyntic glands	4 (12)	3 (13)	1 (10)
Background			
PPI effect[a]	17 (52)	17 (74)	0 (0)
Neuroendocrine dysplasia	5 (15)	5 (22)	0 (0)

PPI, proton pump inhibitor.
[a]$P < .05$ when comparing groups 1 and 2.

(range, 0.22-3.5 cm), 1.5 cm (range, 0.22-3.5 cm), and 1.4 cm (range, 0.3-3.5 cm), respectively. Neuroendocrine dysplasia in oxyntic glands was seen in 5 of 23 cases in group 1 and was notably absent in all group 2 cases FIGURE 3D. In addition, 3 of 10 cases in group 1 with antral biopsy available for review showed neuroendocrine cell hyperplasia in the antrum.

G-NET in Patients With Cirrhosis

Notably, 3 patients in this series had documented liver cirrhosis, all of whom were in group 1 (3/23 [13%]). When patients in group 1 were stratified by the presence or absence of liver cirrhosis, mean (SD) tumor size tended to be larger in patients with cirrhosis than in those without cirrhosis (1.63 [0.32] cm vs 0.87 [0.65] cm; $P = .06$). All cirrhotic group 1 tumors were unifocal and grade 1 or 2. All lesions were polypoid, with tumor invasion to the submucosa. All were larger than 1 cm (T2) but with no lymph node or distant metastases.

DISCUSSION

Historically, G-NETs have been classified as type 1 in the setting of chronic atrophic gastritis, type 2 if associated with gastrinoma and MEN-1 syndrome, and type 3 if there is no evidence of chronic atrophic gastritis or gastrinoma. Recently, provisional type 4 and type 5 tumors have been proposed. Patients with provisional type 4 G-NETs demonstrate multiple NETs and grossly elevated serum gastrin because of hypochlorhydria from a hereditary dysfunction of gastric acid production caused by alterations in a potassium channel encoded by the *KCNQ1* gene or the gastric H+/K+ ATPase α subunit.[9] Patients with provisional type 4 G-NETs frequently present with iron-deficient anemia, and tumors are more aggressive than type 1 G-NETs, with frequent lymph node metastases.[13] In this series, there was 1 case with high gastrin levels and no reported history of gastrinoma or MEN-1 syndrome. This patient presented with iron-deficient anemia. Numerous G-NETs confined to the gastric fundus/body were identified with prominent parietal cell hyperplasia and multifocal neuroendocrine dysplasia in the background oxyntic mucosa. Subsequent gastrin levels returned to normal after distal partial gastrectomy. This was the only case in group 1 to demonstrate a lymph node metastasis; therefore, it may represent a provisional type 4 G-NET case. Unfortunately, gastric acid levels and genetic information were not obtained in this case. Provisional type 5 G-NETs are seen in patients with long-term PPI use associated with elevated gastrin levels. Recently, we reported that G-NETs associated with long-term PPI use had an indolent clinical course similar to type 1 G-NETs.[10] This study further confirmed our previous findings: Tumors in patients with a history of long-term PPI use were mostly smaller than 1 cm, G1 or G2, T1 or T2, and not typically associated with lymph node or distant metastases. It is important to note that patients with a history of PPI use are more likely to receive an upper endoscopy for evaluation of esophageal reflux, which may result in earlier detection of G-NET and may partially contribute to the more indolent course of these tumors. Large-scale studies with long-term follow-up may be needed to confirm the indolent behavior of PPI-associated G-NETs.

Treatment of G-NETs differs by subtype. Surgical intervention is often necessary for type 3 G-NETs, whereas polypectomy and surveillance are commonly used for other subtypes.[14] Therefore, differentiating the subtype of G-NET clinically or through histologic evaluation is important for patient care. Once type 1 and type 2 G-NETs have been excluded, clinical history for an elevated serum gastrin level or long-term PPI use is important for further subtyping. In addition, background mucosal changes, such as significant PPI effect and neuroendocrine hyperplasia, may help elucidate the subtype. The PPI effect consists of cystic dilation of the fundic glands and parietal cell hyperplasia with or without cytoplasmic vacuolization.[15] These microscopic features may correspond to gastric "cobblestone lesions" on endoscopy.[16] In this study, 74% of group 1 cases demonstrated significant PPI effect. Gastric neuroendocrine hyperplasia may not be specific to type 4 or type 5 G-NETs but may suggest a hormone-dependent etiology because high gastrin levels lead to ECL cell hyperplasia.[17] Finally, type 3 G-NETs are more aggressive tumors. Type 3 G-NETs should be suspected if the background mucosa is normal and prognostic features seem poor, which includes large tumor size, deep depth of invasion, grade 3 histology, and advanced stage.[18,19] Taken together, assessing the clinical and pathologic features may assist in subtyping a G-NET.

Although both type 1 and provisional type 5 G-NETs have similar biological behavior, management of these neoplasms may be different because of their unique underlying mechanisms. For example,

discontinuation of PPI treatment may be effective in preventing new lesions in patients with provisional type 5 G-NETs. Likewise, tumor regression was reported by Jianu et al[20] after cessation of PPI use. Our cohort demonstrated that peritumoral mucosal changes were common in PPI/gastrin-associated G-NETs. Loss of oxyntic glands was seen in 70% of group 1 cases, and intestinal metaplasia was seen in 13% of group 1 cases; these findings can mimic chronic atrophic gastritis. Therefore, to differentiate type 1 and provisional type 5 G-NETs, a biopsy of the background oxyntic mucosa away from the tumor may be necessary; as observed in this study, even small tumors can have loss of oxyntic glands in the peritumoral mucosa. In addition, differentiating aggressive type 3 G-NETs from type 1 G-NETs is even more important. We found that peritumoral mucosa in type 3 G-NETs was also frequently associated with loss of oxyntic glands (60%) and intestinal metaplasia (50%). Misclassification of a G-NET may result if a mucosal biopsy away from the tumor is not provided. Therefore, gastroenterologists should be encouraged to obtain a biopsy of the background gastric mucosa away from the tumor.

Interestingly, our cohort contained 3 patients with liver cirrhosis, all of whom were in group 1. In these patients, G-NETs tended to be larger than in those without cirrhosis. Hypergastrinemia is common in patients with cirrhosis,[21] which may contribute to tumor development. Human studies have demonstrated reduced gastric acid secretion in patients with cirrhosis because of an excessive amount of circulating acid–inhibiting intestinal peptides rather than gastric mucosal atrophy.[21,22] Hypoacidity, in turn, leads to hypergastrinemia. Use of PPIs in patients with cirrhosis may further increase gastrin levels. Unfortunately, gastrin levels were not obtained in all 3 group 1 cirrhotic cases. Although the trophic effects of gastrin may be a necessary factor in the development of some G-NETs, however, it may not be the sole factor. For example, there are reports that chronic PPI use and *Helicobacter* infection synergize to induce G-NETs.[23,24] In patients with cirrhosis, capillary ectasia and reactive gastric mucosal changes are common, which may be an additional contributory factor.

In conclusion, PPI/gastrin-associated non–type 1/2 G-NETs present at an early stage and have an indolent clinical behavior. Peritumoral mucosal changes in non–type 1/2 G-NETs can mimic atrophic gastritis, which could lead to misclassification of G-NETs. In addition, G-NETs in patients with cirrhosis may be more aggressive than in other patients.

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