Gastric Adenocarcinoma of the Fundic Gland Type

Update and Literature Review

Mark A. Benedict, DO,[1] *Gregory Y. Lauwers, MD,*[2] *and Dhanpat Jain, MD*[1]

From the [1]Department of Pathology, Yale University School of Medicine, New Haven, CT; and [2]Department of Pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL.

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ABSTRACT

Objectives: *Gastric adenocarcinoma of the fundic gland type (GA-FG) is a newly described entity with a lack of awareness amongst general surgical pathologists and this review highlights the key features and controversies associated with this uncommon neoplasm.*

Methods: *A literature search through PubMed using synonyms for GA-FG was conducted to obtain 111 cases.*

Results: *GA-FG is a well-differentiated neoplasm of oxyntic mucosa, that is comprised of chief cells and parietal cells. Chief cell differentiation is highlighted with Muc-6, RUNX3, and pepsinogen. Parietal cells are highlighted with H+/K+ ATPase and PDGFRA-α. Association with* Helicobacter *infection, chronic gastritis, intestinal metaplasia, or gastric atrophy is not seen. Most GA-FGs are confined to the mucosa. Deeper invasion, lymphovascular invasion, nodal metastasis, and extragastric spread are uncommon.*

Conclusions: *GA-FGs are rare lesions that typically follow a benign course. However, despite features of malignancy in some cases, complete surgical excision, sometimes with endoscopic mucosal resection, seems adequate treatment.*

Traditionally, gastric carcinoma has been grouped into two types: intestinal and diffuse (Lauren classification).[1] Evaluating the 54,099 stomach carcinomas reported during the 1978-2005 US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data set, 74% were of the intestinal type, 16% of the diffuse, while 10% were other epithelial carcinomas.[2] More relevant to our subject, a classification system devised by Nakamura et al[3] groups gastric carcinoma into differentiated and undifferentiated, based on the tumor's ability to form glands. However, with time it has become evident that gastric carcinomas can differentiate along several different epithelial lineages: surface foveolar lineage, pyloric gland lineage, chief cell lineage, and parietal (oxyntic) cell lineage. Our understanding of these multiple phenotypic facets of gastric neoplasms is in its early stages. The specific predisposing factors, demographics, and prognosis of these neoplasms, and how they vary from the conventional carcinomas, is unclear.

Gastric adenocarcinoma of the fundic gland type (GA-FG) is a novel entity first proposed in 2007 by Tsukamoto et al.[4] The characteristic oxyntic gland differentiation can be divided in three subcategories based on their composition: chief cell predominant (approximately 99% of reported cases), parietal cell predominant, and mixed phenotype. To date, the nature of this lesion is debated and there is a lack of awareness of GA-FG in the pathology community. This review aims to highlight our current understanding of gastric neoplasms with differentiation along elements of fundic glands.

Methodology

A literature search through PubMed using the phrases "gastric adenocarcinoma fundic gland type," "gastric adenocarcinoma chief cell predominant type," "gastric adenocarcinoma-mixed parietal and chief cell type," "gastric adenocarcinoma-parietal cell type," and "parietal cell carcinoma" revealed a total of 111 cases reported in the English language literature. A number of reports in older literature have described cases of oncocytic gastric neoplasms as "parietal cell" carcinoma; however, the evidence of parietal cell differentiation in most of these papers is not conclusive and they appear different from the GA-FG as we currently recognize them.[5,6] Hence, these cases were excluded from this review.

The clinical history and pathologic characteristics were examined for each case and summary data are tabulated in **Table 1**.[4-31]

Demographics

The majority of reports of GA-FG originate from East Asia (Japan and Korea), where the incidence appears to be still low. In the study by Tohda et al[7] only four (< 0.01%) patients with GA-FG were identified from the 30,182 individuals who underwent upper endoscopy (as part of a yearly check-up) between October 2010 and September 2014.

The patients are generally older adults and the average patient age is 66 years (range, 39-85 years). There seems to be a slight male predilection, with the M:F ratio being 2.2:1.

Etiopathogenesis

The carcinogenesis of gastric adenocarcinoma of the conventional type is multifactorial. However, chronic *Helicobacter pylori* infection with subsequent intestinal metaplasia and mucosal atrophy plays a major role and is associated in 80% of cases.[32] Autoimmune gastritis, which is also associated with increased risk for gastric adenocarcinoma, also has chronic inflammation that is followed by intestinal or other types of metaplasia and atrophy.

Of the 111 cases of GA-FG published, *H pylori* data were available in only 43 (39%) cases, of which 17 (40%) were positive for infection Table 1. In only one series did the percentage of *H pylori* positivity reach a rate that mirrored conventional gastric cancer, with 15 of 20 (75%) patients being *H pylori* positive with atrophy.[8] Yet, in the same study, the authors reported that the neoplasms developed in areas with no apparent atrophy observed endoscopically.[8] Additionally, independent histologic assessment found that in nearly all cases of GA-FG no surrounding atrophy was detected.[8]

Interestingly, some cases of GA-FG show dilated fundic glands with admixed foveolar type cells resembling fundic gland polyps (FGPs), thus raising the question as to whether there is any relationship with proton pump inhibitor (PPI) use and the development of these neoplasms.[5] Of note, in a series of 12 cases, of the eight patients with available history of medication, seven had used acid suppressive therapy (six PPI and one H_2 blocker).[9] However, in most of the reports, the history of medication use is not thoroughly investigated, especially PPI use.

Endoscopy and Gross Appearance

The overwhelming majority of GA-FG, that is 89 of 111 cases (80%), have occurred in the upper third of the stomach. Twenty out of 111 (18%) tumors developed in the middle third and only one tumor was seen in the lower third of the stomach (1%). Typically, GA-FGs are small, with an average size of 10 mm and the largest reported case measured 85 mm.[10] These lesions arise only in oxyntic mucosa. In one study, comprising 20 cases examined by endoscopy, the lesions appeared elevated in 12 (60%), flat in five (25%), and depressed in three (15%) cases, as per the Japanese classification of gastric carcinoma.[8] In another endoscopic study, the tumors were classified as "submucosal" in six of 10 (60%) or mucosal with a flat/depressed surface in four of 10 (40%) patients.[11] Some of the lesions mimic FGPs endoscopically.[7] These tend to have a white hue (70%) or yellow discoloration, with frequent complex and often branching dilated mucosal vessels, in a nonatrophic adjacent mucosa (90%).[8,11] Central depression noted by indigo carmine chromoendoscopy in one case is believed to be an evidence of submucosal involvement.[12] Interestingly, several cases documented a black pigmentation in the lesion, which aided in the early detection.[13,14] Narrow-band imaging, which enhances the visualization of the mucosal vessels, shows an irregular pattern, suggestive of the heterogeneity of the microvessels in GA-FG **Image 1A** and **Image 1B**.[15,22] The use of narrow-band imaging and endoscopic ultrasound enhances the opportunity for complete excision via endoscopic mucosal resection (EMR), which suffices in superficial tumors.[11]

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Table 1
Characteristics of Reported Gastric Adenocarcinomas-Fundic Gland Type

Author (Year)	No. of Cases	Age or Age Range (y)	Gender Distribution	Cell Type (Predominance)	Location: No. of Cases	*Helicobacter pylori*	Size (mm)	Invasion Depth	Lymphovascular Invasion	Outcome
Chan et al (2016)[9]	12	39-81	5 M 7 F	Chief cell	Upper third	—	2-20	Mucosa: 10 Submucosa: 2	No	Alive, no recurrence or metastasis
Sato et al (2016)[13]	1	77	F	Chief cell	Upper third	Neg	11	Submucosa	No	Alive, no recurrence or metastasis
Cha et al (2016)[23]	1	69	M	Chief cell	Upper third	—	25	Muscularis propria	No	Alive, no recurrence or metastasis
Chiba et al (2016)[8]	20 (9 cases with EMR)	44-85	16 M 4 F	Chief cell	Upper third: 14 Middle third: 6	Neg: 5 Pos: 15	3-20	Mucosal: 2 Submucosa: 7 No data: 11	No: 9 No data: 11	No morphological changes by endoscopic examination
Tohda et al (2016)[7]	4	42-62	2 M 2 F	Chief cell	Upper third: 3 Middle third: 1	Neg: 2 Pos: 2	2-5	Mucosal: 2 Submucosa: 2	No	Alive
Kawasaki et al (2016)[18]	1	62	M	Chief cell	Middle third	Neg	—	Submucosa	Yes	Alive
Kato et al (2015)[24]	1	80	M	Chief cell	Upper third	Neg	30	Submucosa	No	Alive
Takeda et al (2015)[14]	1	66	M	Chief cell	Upper third	—	—	—	—	—
Miyazawa et al (2015)[15]	5	67-78	3 M 2 F	Chief cell	Upper third	Neg	5-13	Submucosa	Yes: 1 No: 4	Alive, no recurrence or metastasis
Parikh et al (2015)[22]	1	66	M	Chief cell	Upper third	—	7	Submucosa	No	Alive, no recurrence or metastasis
Hori et al (2015)[25]	1	79	M	Chief cell	Middle third	—	—	Muscularis mucosae	No	Alive, no recurrence or metastasis
Fujii et al (2015)[11]	1	64	F	Chief cell	Upper third	Neg	—	Submucosa	No	—
Lewin et al (2015)[26]	1	49	M	NS	Upper third	—	11	Submucosa	No	—
Ueyama et al (2014)[16]	10	55-78	6 M 4 F	Chief cell	Upper third: 6 Middle third: 4	Neg: 7 No data: 3	3-31	Mucosal: 5 Submucosa: 5	Yes: 1 No: 9	Alive, no recurrence or metastasis
Ueo et al (2014)[19]	1	62	M	Chief cell	Middle third	Neg	44 × 35	Subserosa (venous invasion)	Yes (massive)	Gastrectomy with lymph node metastasis
Fujimoto et al (2014)[27]	1	50	M	Chief cell	—	—	5	—	—	—
Nomura et al (2014)[10]	26	49-79	22 M 4 F	NS	Upper third: 23 Middle third: 3	—	3-85	Submucosa	Yes: 3 No: 23	Alive, no recurrence or metastasis
Abe et al (2013)[28]	1	71	F	Chief cell	Upper third	Neg	—	Submucosa	No	Alive, no recurrence or metastasis

(cont)

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Table 1 (cont)

Author (Year)	No. of Cases	Age or Age Range (y)	Gender Distribution	Cell Type (Predominance)	Location: No. of Cases	*Helicobacter pylori*	Size (mm)	Invasion Depth	Lymphovascular Invasion	Outcome
Kushima et al (2013)[17]	3	56-78	1 M 2 F	Chief cell	Upper third	—	3-8	Submucosa	—	Alive, no recurrence or metastasis
Singhi et al (2012)[21]	10	44-79	4 M 6 F	Chief cell	Upper third	—	2-8	Mucosal	No	Alive, no recurrence or metastasis: 8 Persistence of disease: 1 No data: 1
Chen et al (2012)[29]	1	79	M	Chief cell	Upper third	Neg	—	Submucosa	No	Alive, no recurrence or metastasis
Park et al (2012)[5]	3	47-76	3 M	Chief cell	Upper third: 1 Middle third: 1 Lower third: 1	—	12-36	Mucosal: 1 Submucosa: 2	No	Alive, no recurrence or metastasis
Miyaoka et al (2011)[30]	1	59	F	Chief cell	Upper third	—	8	Submucosa	No	Alive, no recurrence or metastasis
Fukatsu et al (2011)[12]	1	56	M	Chief cell	Upper third	—	5	Submucosa	No	Alive, no recurrence or metastasis
Fujisawa et al (2011)[31]	1	50	M	Chief cell	Middle third	—	42	Submucosa	No	—
Terada (2011)[20]	1	78	M	Chief cell	Middle third	—	15 (ulcer)	—	—	Died of carcinomatosis
Tsukamoto et al (2007)[4]	1	82	F	Chief cell	Upper third	—	16	Mucosal	No	—
Total	111	39-85	75 M 36 F	Chief cell: 84 Not specified: 27	Upper third: 89 Middle third: 20 Lower third: 1 No data: 1	Pos: 17 Neg: 26 No data: 56	2-85	Mucosal: 31 Muscularis mucosae: 1 Submucosa: 63 Subserosal: 1 Muscularis propria: 1 No data: 14	Yes: 7 No: 87 No data: 17	Alive, no recurrence/metastasis: 81 Gastrectomy/nodal metastasis: 1 Carcinomatosis: 1 Disease persistence: 1 No morphological changes by endoscopic examination: 20 No data: 7

EMR, endoscopic mucosal resection; Neg, negative; NS, not specified; Pos, positive; —, no data.

Histology

The histologic appearance of GA-FG is often of a well-differentiated neoplasm, with the tumor bearing a resemblance to the fundic glands. Furthermore, at low magnification, GA-FG, especially of the mixed cell type, can mimic a fundic gland polyp or a pyloric gland neoplasm.[7]

The lesion is almost invariably lined on the surface by normal-appearing foveolar-type epithelium, while the deeper part shows a variable admixture of cell types normally present in oxyntic glands[7] **Image 2**. The deeper glandular structures, instead of a tubular architecture seen in normal oxyntic mucosa, form anastomosing cords, producing a so-called "endless glands" pattern[7] (Images 2C-2F). The glands may show a chief cell predominant pattern, parietal cell predominate pattern, or an even admixture of both cell types, parietal and chief cells (Images 2C-2F) **Image 3**. The distinction between the two cell types is usually easy because parietal cells are oval or triangular, and have a characteristic eosinophilic finely granular cytoplasm with central nuclei, while chief cells are columnar with a slightly basophilic cytoplasm and basal nuclei. The parietal cells are more common towards the surface or periphery of the neoplasm. Rarely, cribriforming and glandular infolding can be seen. Tumors with necrosis are rare. The neoplastic glands may show multilayering and nuclear stratification. Cytologic atypia is very mild in most cases, with the neoplastic chief and parietal cells showing slightly enlarged nuclei with opened up chromatin and small inconspicuous nucleoli. Mitotic figures are rare and the Ki67 index is low (< 5%).[7] The background stroma may appear normal, or show edema, myxoid changes, or desmoplasia (Images 2E and 2F). Even in submucosally invasive tumors, desmoplasia can be minimal (Images 2A and 2B). The tumors commonly merge imperceptibly with the adjacent mucosa (Image 2A) **Image 4**. Typically, the adjacent oxyntic mucosa is normal without any intestinal metaplasia or atrophy.[16]

As noted earlier, once a pathologist is aware of the entity, recognition of the parietal and chief cells in the well-differentiated mixed phenotypes is easy on H&E stains; however, their identification in the less-differentiated cases may require immunohistochemical (IHC) markers to confirm lineage differentiation **Image 5**.[7] A variety of IHC markers can be helpful and include MUC5AC, MUC6, CD10, pepsinogen-I, RUNX3, and H+/K+-ATPase **Table 2** (Images 5C and 5D). Of these, the markers for chief cell (pepsinogen-I) and parietal cell differentiation (RUNX3, H+/K+-ATPase, and PDFRA-α) are the most helpful, but are still not widely available.

Table 2
Cell Differentiation Markers

Marker	Cell Type Identified
MUC2	Goblet cell
MUC5AC	Gastric foveolar epithelium
MUC6	Mucous neck cell and pyloric gland
CD10	Brush border
Pepsinogen-I	Chief cell
H+/K+-ATPase	Parietal cell
Human milk fat globule-2 (HMFG-2) /platelet-derived growth factor receptor-α (PDGFRα)	Parietal cell
RUNX3	Chief cell

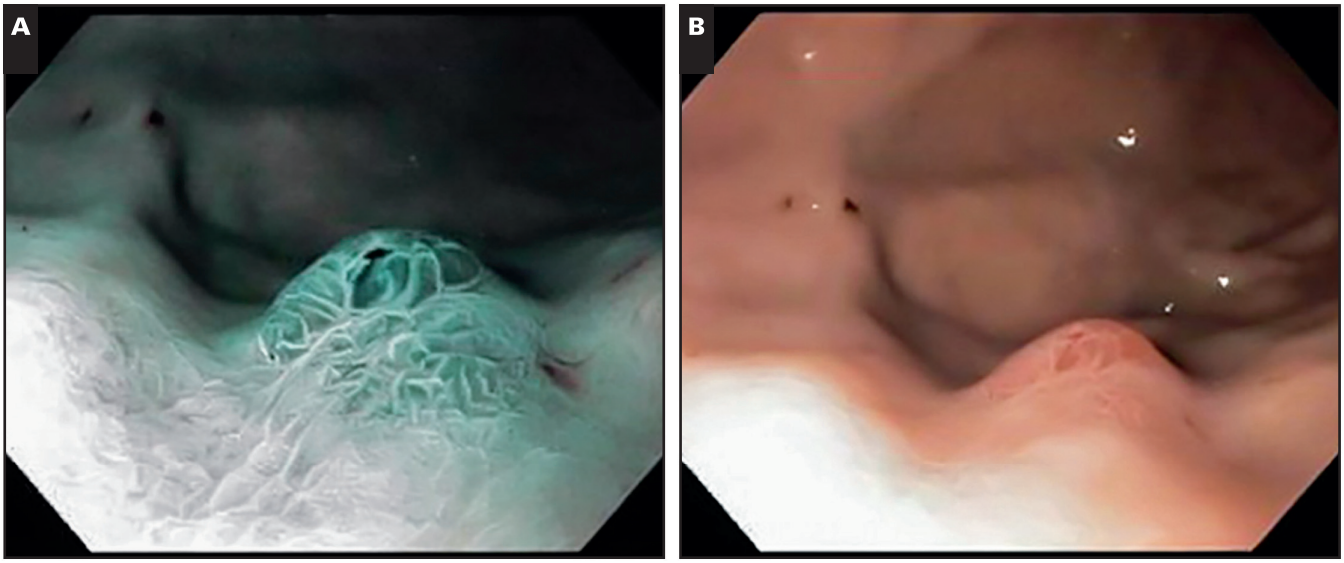

Image 1 **A**, Endoscopic narrow-band imaging is seen to enhance the visualization of the mucosal vessels. **B**, Endoscopic image revealing a small elevated lesion (from the same patient previously reported by Parikh et al[22]).

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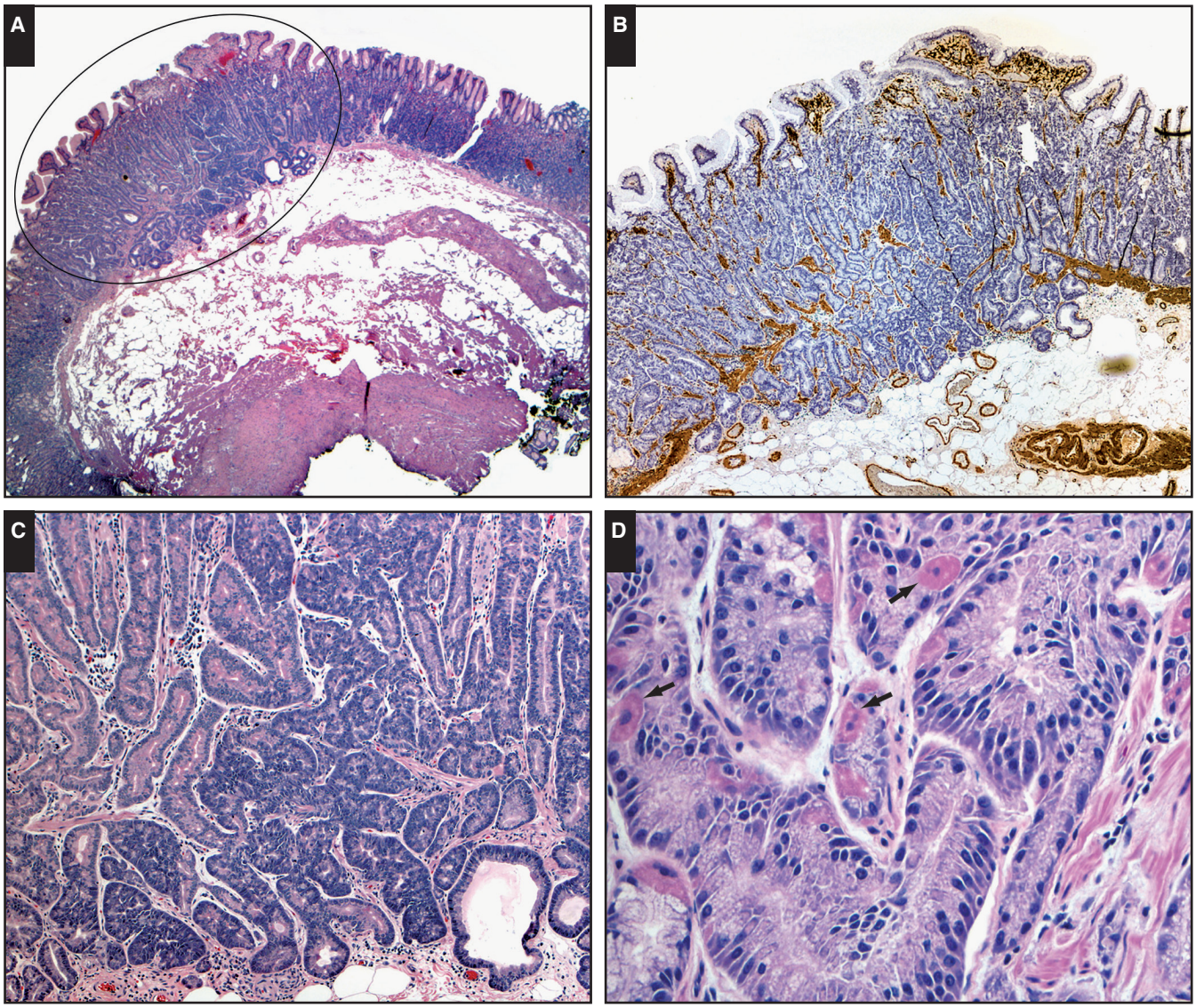

Image 2 **A**, Low magnification of gastric adenocarcinoma of the fundic gland type (GA-FG) (H&E, ×20) showing the tumor (within the circle) which blends imperceptibly with normal oxyntic glands (right portion of image). Note the submucosal invasion lacks any desmoplasia or myxoid change. Note occasional cystic glands in the lesion that may mimic a fundic gland polyp. The glands are visibly more complex than their normal oxyntic counterparts even at low magnification. **B**, Desmin immunostain (×40) highlights the breach of the muscularis mucosae by neoplastic glands invading into the superficial submucosa. **C**, The complex glandular architecture seen at higher magnification producing anastomosing and so-called "endless glands" pattern (H&E, ×100). **D**, Higher power of GA-FG showing an admixture of parietal cells (arrows) and chief cells (H&E, ×400) in the invasive component.

Most of the cases have been reported from Japan and Korea with only a few reports from the West, suggesting that either these tumors are uncommon in some part of the world or there is a lack of awareness. Almost all of the cases reported in the United States are of the well-differentiated mixed phenotype, as these are easy to recognize on routine histology. It is possible that less-differentiated neoplasms, especially along only one lineage, are underrecognized because of lack of appropriate immunohistochemical evaluation.

The superficial and the nonneoplastic foveolar cells tend to stain with Muc-5AC, while the chief and parietal cells are negative. In some cases, even foveolar type cells may also be seen within the tumor (Image 3C). The neoplastic cells are strongly positive for Muc 6. The chief cells express pepsinogen I and RUNX3, which seems to be a good marker for their identification. Pepsinogen II is less specific for identifying chief cells as the pyloric gland cells and mucus neck cells also tend to stain. The parietal cells stain positively for H+/K+-ATPase.

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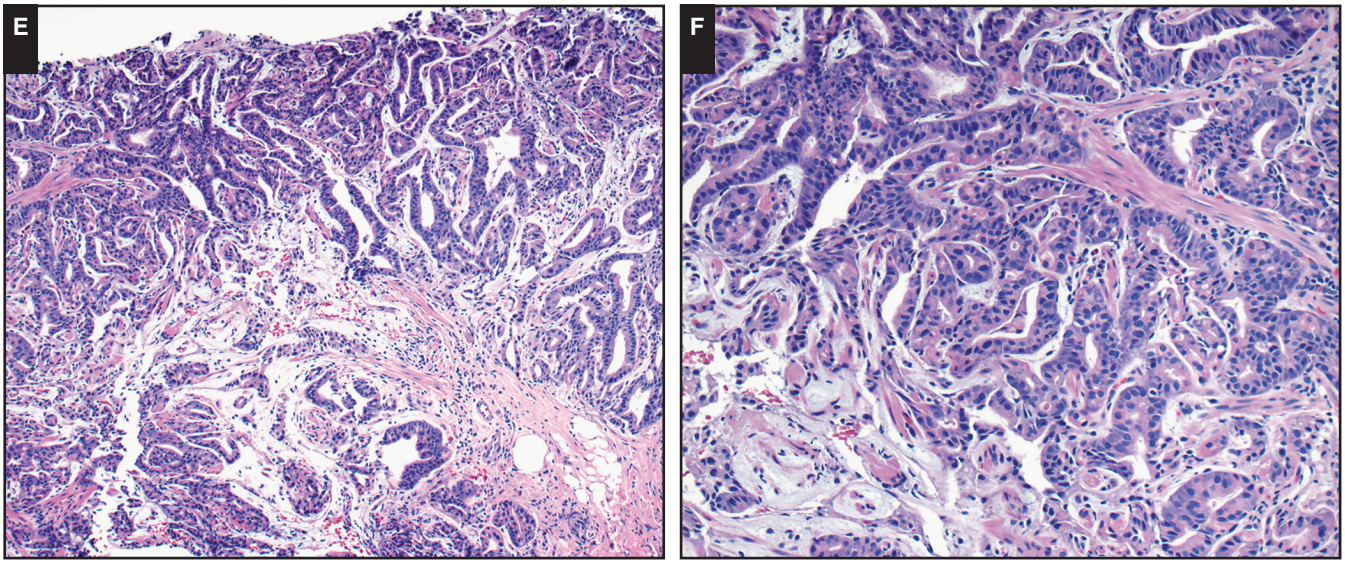

Image 2 (cont) **E**, Low-power view of another example of GA-FG with submucosal invasion with myxoid change in the stroma. In this example glands have more infiltrating architecture compared to previous example shown in **D** (H&E, ×40). **F**, The higher magnification showing the area of submucosal invasion (H&E, ×100). The admixture of parietal cells and chief cells in the infiltrating glands is also obvious at this magnification.

Endocrine cells are generally reported to be absent. In one study, staining for synaptophysin and CD56 showed diffuse positivity in the glands, while chromogranin was completely negative.[12] As the foregut-derived endocrine cells are invariably positive for chromogranin, we have concluded that there is no good evidence of endocrine differentiation.[5] Other studies also failed to show any endocrine cell component using chromogranin stain, although in our experience rare admixed endocrine cells can also be seen, especially at the periphery (Image 3D).

There are several reports of gastric carcinomas with parietal cell differentiation and oncocytic neoplasms in the literature that predate the first report of GA-FG, and may represent GA-FG with predominant parietal cells, although many of these lack conclusive evidence of parietal cell differentiation.[33,34] However, a couple of the recent examples have shown expression of H+-K+ ATPase, suggesting that some of these lesions may represent true parietal cell neoplasms or "GA-FG with predominant parietal cell differentiation."[33-36] As these tumors are very poorly characterized, at this time we have opted to keep them separate from GA-FG.

The differential diagnosis of GA-FG includes: pyloric gland adenoma and other well-differentiated GA, especially those with pyloric phenotypes, and less commonly dysplastic FGPs **Image 6**. The pyloric gland adenomas (PGA) show low columnar to cuboidal cells containing finely vacuolated and lightly eosinophilic or sometimes mildly granular eosinophilic cytoplasm (Images 6A and 6B).[37,38] These stain strongly with MUC6 and variably with MUC-5AC. However, one study showed similarities in the IHC profile and molecular phenotype, suggesting that these lesions may be closely related.[17] In this study, positivity for pepsinogen and MIST1 was present in 100% (3/3) of GA-FGT and 67% (8/12) of PGAs.[17]

Dysplastic fundic gland polyps are increasingly recognized and less likely to be confused with GA-FG. The dysplastic changes involve only the superficial foveolar epithelium (Images 6C and 6D), while the deeper part of the lesion lacks the architectural complexity, epithelial multilayering of the glands, anastomosing cord pattern, and stromal changes.[39] Rarely, large fundic gland polyps may undergo ischemia secondary to local trauma or torsion leading to intralesional hemorrhage, reactive epithelial atypia, and glandular cystic dilatation with sloughed epithelium, mimicking tumor necrosis (Images 6E and 6F). The very well-differentiated ("crawling") gastric adenocarcinoma with foveolar and pyloric phenotypes are in the differential diagnosis but are extremely rare. These differ from GA-FG largely by the morphology of tumor cells, which differentiate towards lightly eosinophilic foveolar MUC-5AC-positive epithelium or gastric pyloric (antral) gland lineages. Cytologic atypia may be mild and similar to GA-FG, but the cells lack the admixture of chief or parietal cells and have a clearly invasive growth pattern.[37,40]

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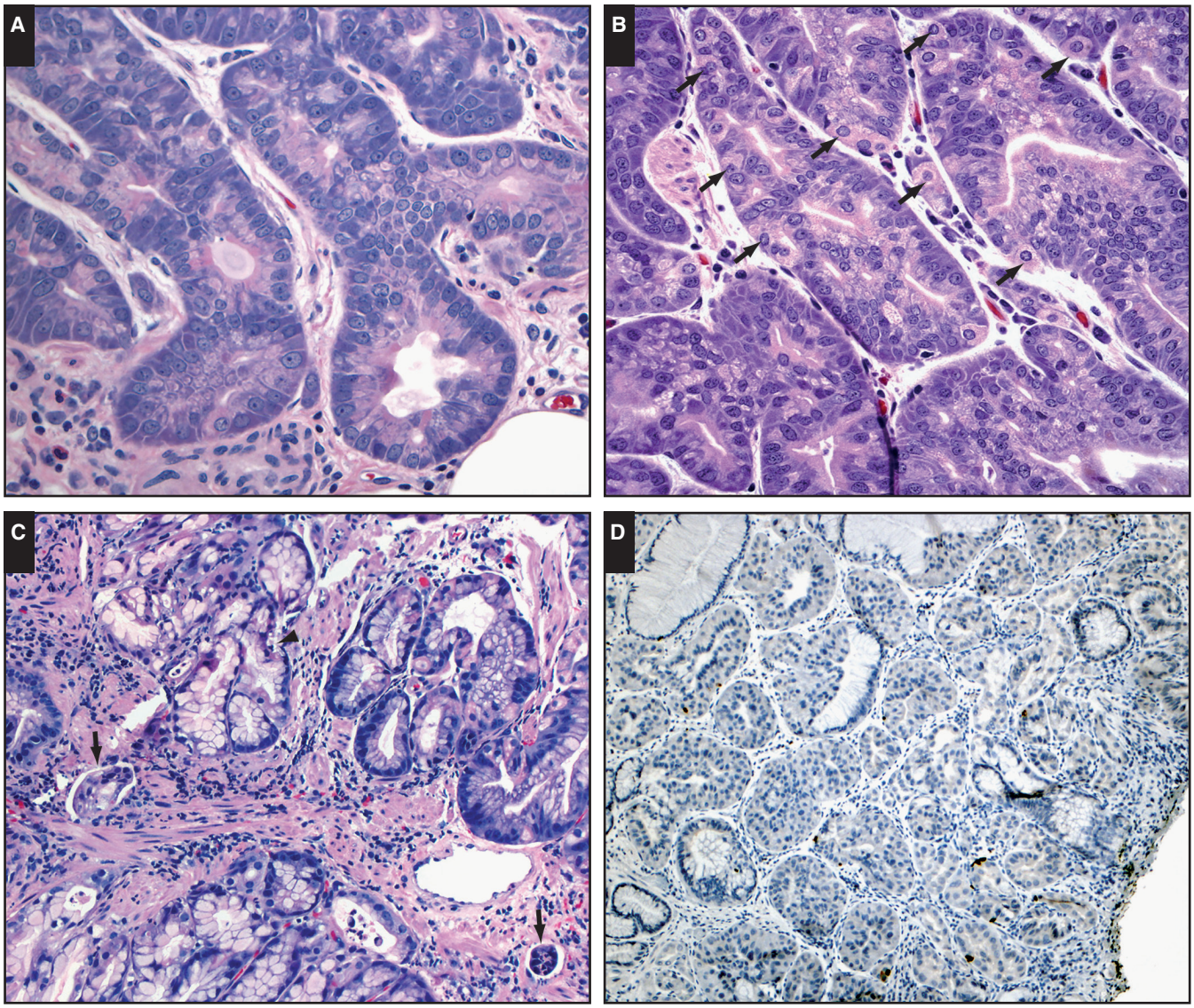

Image 3 **A**, Gastric adenocarcinoma of the fundic gland type (GA-FG) with glands showing predominantly chief cells (H&E, ×400). **B**, Example of GA-FG mixed type showing admixture of parietal cells (arrows) and chief cells in the infiltrating glands (H&E, ×400). **C**, Another example of invasive GA-FG mixed type that shows even foveolar cells (arrowhead) admixed with chief and parietal cells in the deeper part of the tumor (H&E, ×200). Several foci of lymphovascular invasion are also identified (arrows). **D**, GA-FG mixed type with scattered chromogranin-positive endocrine cells, especially at the periphery of the lesion (×200). Also note foveolar cells admixed with other cells types in the tumor.

Molecular Characteristics

The data on molecular alteration associated with GA-FG are limited. Activation of the WNT-β-catenin signaling pathway or the ERK1/2 MAPK pathway is believed to play a role in the tumorigenesis.[10] In a study by Nomura et al,[10] nuclear β-catenin positivity was found in 22 (80%) of 26 cases by IHC, and 13 cases (50%) harbored mutations in at least the *GNAS, CTNNB1, AXIN 1*or *2*, and *APC* genes.

In 11 of the 26 cases the mechanism of WNT signaling activation was unclear. In this study, five cases revealed *GNAS* mutations, at exons 8 and 9, of which two cases (7.7%) also revealed *KRAS* mutations.[10] Nuclear β-catenin expression coincided with *GNAS* mutations in four of five cases, three of which lacked mutations in *CTNNBl*, *APC*, or *AXIN*s, suggesting a role for *GNAS* activation in WNT signaling.[10] However, only membranous staining for β-catenin without any nuclear staining has been our own experience. Interestingly, sporadic fundic gland polyps also show activating mutations in β-catenin.[41]

Of note, *GNAS* mutations seemed to be associated with submucosal invasion and a larger tumor

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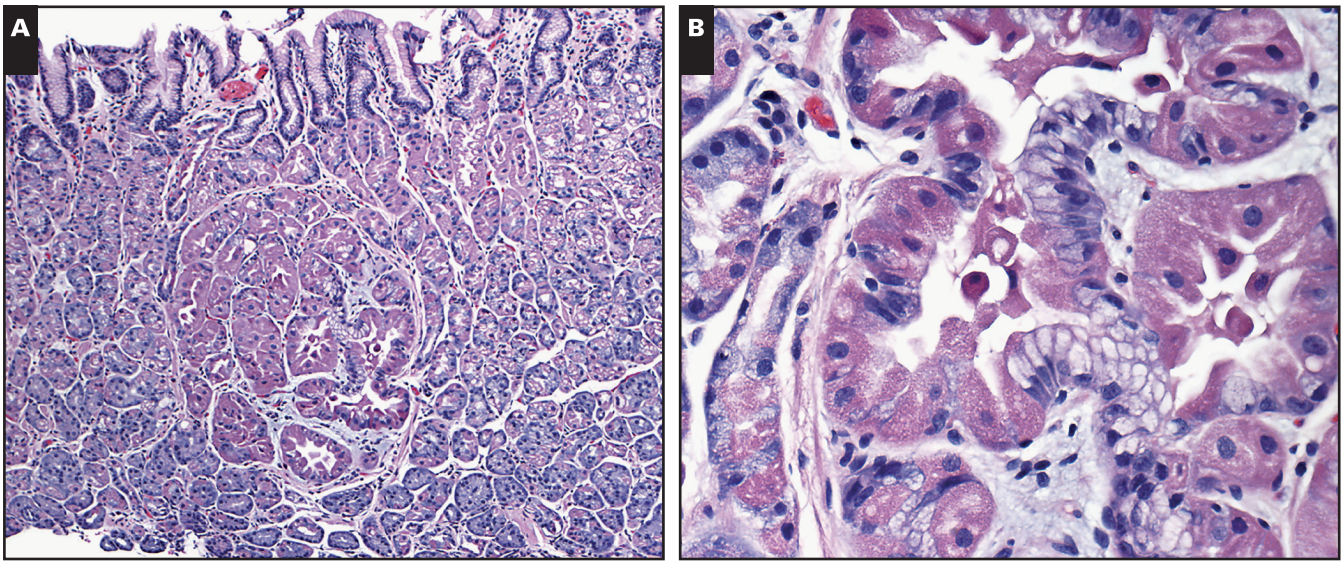

Image 4 **A**, An example of gastric adenocarcinoma of the fundic gland type (GA-FG) that was an incidental finding in a gastric biopsy. The lesion consists of only a few complex glands in a stroma with myxoid change (H&E, ×200). **B**, Higher-power image of (**A**) (×400) showing the lesion consists predominantly of parietal cells with mild nuclear atypia. The nuclei have open chromatin, occasional nucleoli, and are slightly larger compared to adjacent benign glands.

size; however, the findings were not statistically significant.[10] A second study comparing GA-FG with PGAs found frequent GNAS activating mutations in both lesions.[17] In contrast, *GNAS* mutations are either absent or infrequent in conventional gastric adenomas and adenocarcinomas.[42,43]

Behavior and Prognosis

At this time, of the total of 111 reported cases of GA-FG, 63 (57%) have shown submucosal invasion. Some have suggested that this may represent "prolapse-type" misplaced glands rather than true submucosal invasion. One case revealed subserosal invasion via lymphovascular spread, although lymphovascular invasion is infrequent, being reported in only seven (6%) of these 111 cases.[10,15,16,18,19] It should be noted that studies reporting lymphatic or vascular invasion did not report the use any special lymphatic/vascular markers of invasion, hence these are best classified as lymphovascular invasion. Of the cases with follow-up data, one patient died of carcinomatosis (histologic type was not confirmed and no autopsy was performed), a second required gastrectomy, and a third had persistent disease (noted likely to be due to incomplete resection).[19-21] In a rare example where a tumor was followed for 12 years, the tumor remained stable over a decade, suggesting that these are slow-growing neoplasms. In this example, the tumor was eventually removed by EMR and did show submucosal invasion; however, there was no nodal or distant metastasis and the patient did well during the limited follow-up.

The current evidence suggests that the majority of GA-FGs are limited to mucosa or superficial submucosa, are less aggressive than the conventional intestinal or diffuse types of gastric cancers, and follow a benign course. This appears to be especially true for well-differentiated cases with mixed phenotype. With that being said, there is evidence to suggest that rarely metastasis and death may ensue in deeply invasive tumors, especially with chief cell differentiation.[19,21] In light of these characteristics, it appears that tumors with superficial submucosal invasion can be treated with limited gastric resection or endoscopic mucosal resection, while extended gastrectomy with lymph nodes should be reserved for more deeply invasive lesions or those with suspected nodal metastasis.

Evolving Issues

Nomenclature remains a topic of controversy. As highlighted above, GA-FG with invasion limited to the mucosa are typically well-differentiated slowly progressive lesions with a seemingly good prognosis. Hence, some have suggested that these should be called "oxyntic gland adenomas," "fundic gland adenoma," or "fundic gland polyps with chief or parietal cell differentiation," and certainly for cases without any evidence of lymphovascular invasion these appellations appear appropriate.[9,21] It is equally reasonable to accept that intramucosal fundic

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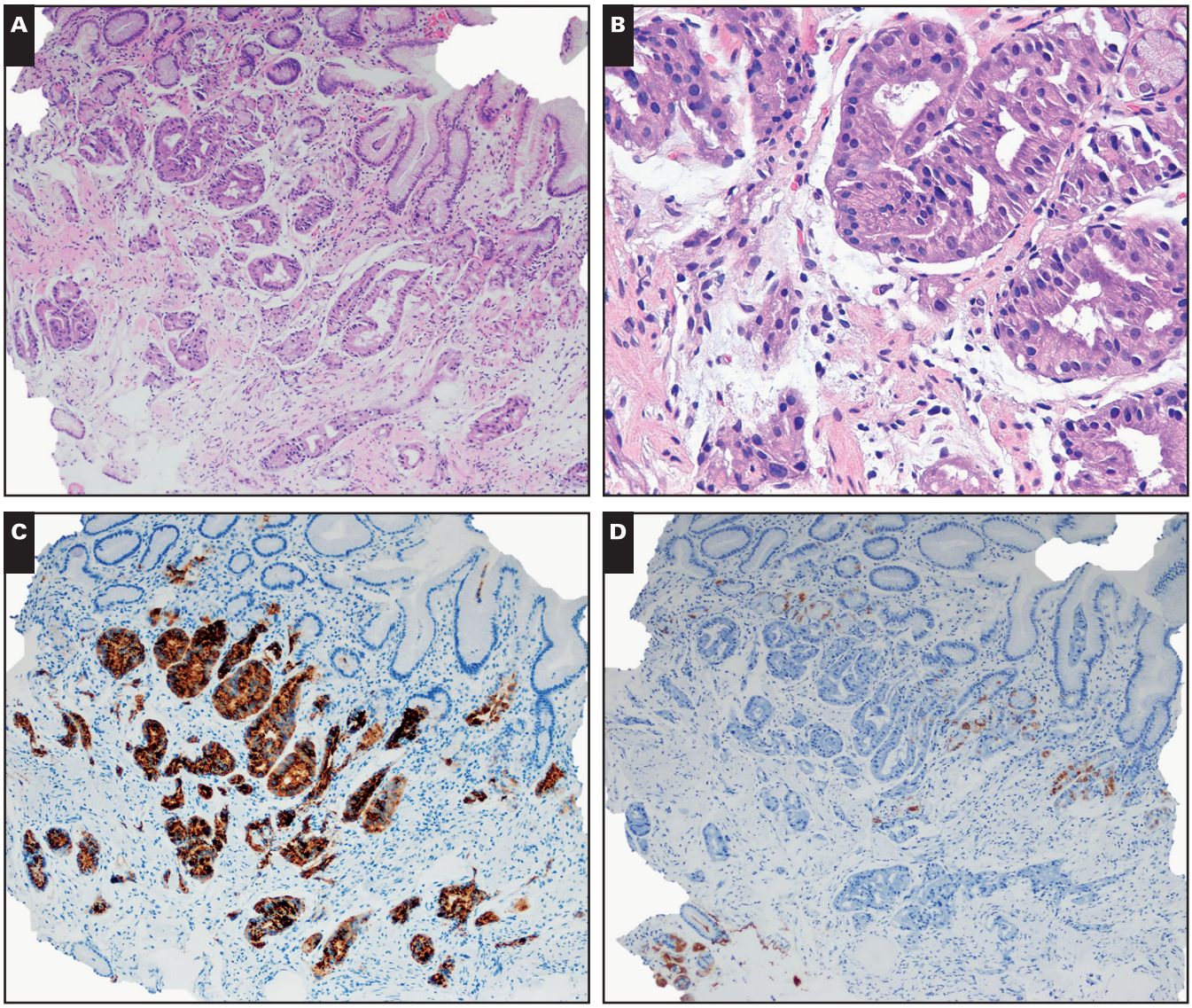

Image 5 **A**, An example of fundic gland carcinoma where the differentiation along parietal and chief cell lineages is not obvious on H&E (×10). **B**, Higher magnification of **A** to show when the lesions are less differentiated, the diagnosis is difficult solely based on H&E morphology (×40). **C**, Pepsinogen I stain is strongly positive within the tumor cells confirming chief cell differentiation (×10). **D**, H/K+-ATPase stain reveals patchy positivity within the tumor cells confirming parietal cell differentiation (×10).

gland adenocarcinoma has no metastatic potential. While both concepts appear justified, at this time there are insufficient data to make a more definitive recommendation. For lesions showing submucosal invasion the designation of "fundic gland carcinoma" should be used, until more data become available, with an understanding that in the absence of deep invasion or lymphovascular invasion the outcome is still likely to be benign.

The risk factors and etiopathogenesis of GA-FG appear different from conventional carcinoma. The use of PPI therapy has increased greatly over the years. It causes histologic changes, notably fundic gland polyps and parietal cell hyperplasia, and seems to coincide with the increasing recognition of GA-FG in practice. Concurrent detection of PPI-associated changes and use of acid suppressive therapy in some cases of GA-FG lend some support to this hypothesis. Moreover, PPI-related changes in the gastric microbiota and possible facilitation of more carcinogenic organisms also need to be investigated.[44,45]

The other issue is identification of GA-FG that are poorly differentiated. Because the IHC markers that identify parietal and chief cells are not widely used in practice, it is likely that some of the poorly differentiated adenocarcinomas of the stomach belonging to this category go

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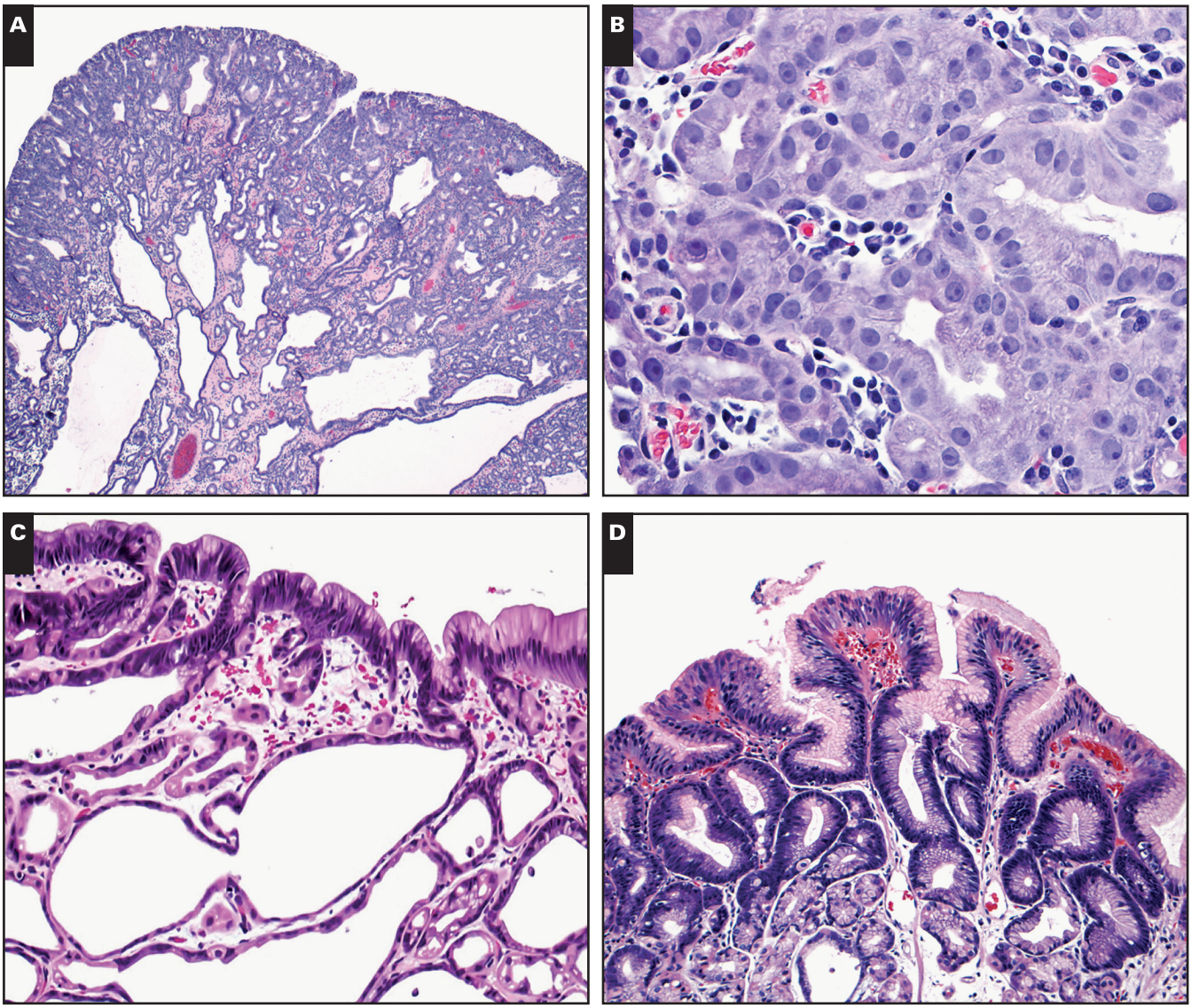

Image 6 **A**, Low-power view of a pyloric gland adenoma showing tightly packed glands lined by cuboidal or columnar cells with anastomosing structures similar to gastric adenocarcinoma of the fundic gland type (GA-FG). Many cystically dilated glands are also visible (H&E, ×20). **B**, Higher power of the same lesion showing slightly amphophilic finely vacuolated cytoplasm with round to oval nuclei and prominent nucleoli that can mimic chief cells (H&E, ×200). **C**, Fundic gland polyp with focal surface dysplasia (seen at the left of the image) (H&E, ×40). **D**, Dysplastic foveolar epithelium and normal-appearing chief and parietal cells (H&E, ×40).

unrecognized. Examples of some of the oncocytic neoplasms of the stomach may belong to the category of GA-FG with predominant parietal cell differentiation. It is also likely that some of the more advanced lesions may consist of only one cell phenotype. It is anticipated that as more cases are identified and gastric carcinoma classification evolves to include the various gastric phenotypes, our understanding of these lesions will also advance, leading to a better diagnostic criteria and nomenclature.

In summary, GA-FG is a well-differentiated neoplasm composed of cells normally occupying the oxyntic mucosa, that is, chief cells and parietal cells. The tumors may show predominance of either chief cells (overwhelming majority) or rarely parietal cells. The neoplasm appears very distinctive but with unclear etiopathogenesis. Whether a subset has no ability to invade or metastasize and can be truly called a "fundic gland adenoma" needs further studies. Some cases do show submucosal invasion, nodal metastasis, and rarely peritoneal dissemination. Despite clear features of malignancy in some cases, complete surgical excision, sometimes with EMR, seems adequate treatment and will afford a cure.

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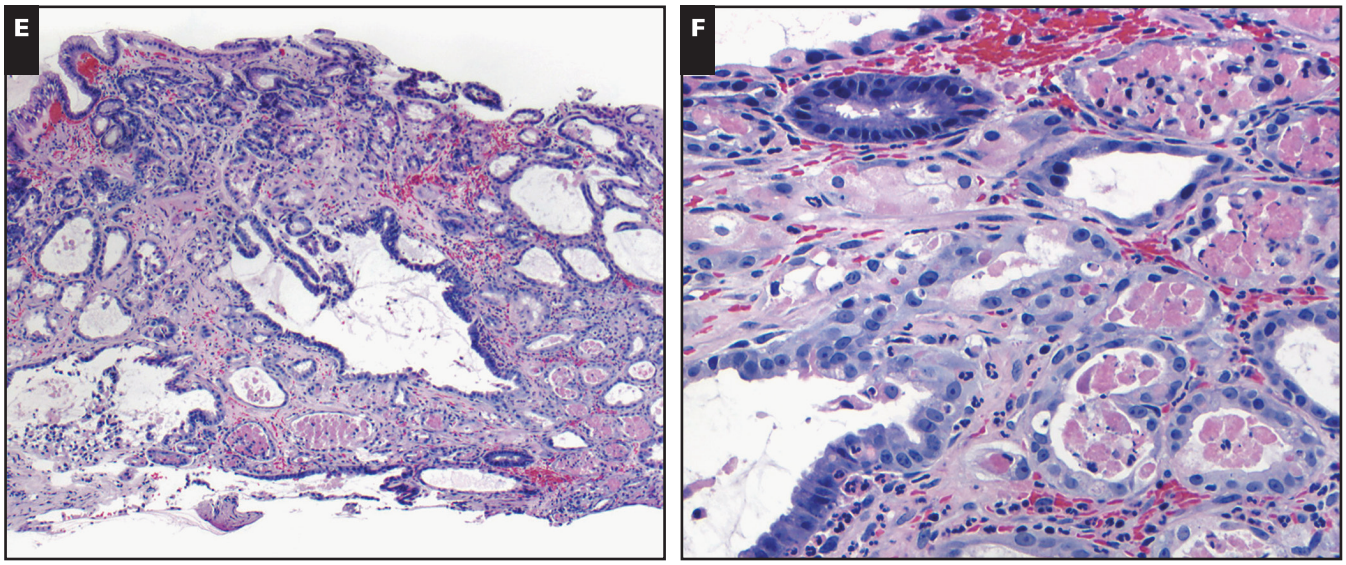

Image 6 (cont) **E**, Rare example of a fundic gland polyp with ischemic changes that shows somewhat distorted glands, but lacks the endless gland pattern of GA-FG (H&E, ×20). **F**, Higher magnification of the same lesion showing reactive atypia that may be confused with a GA-FG (H&E, ×40).

Corresponding author: Dhanpat Jain, MD, Dept of Pathology, Yale University School of Medicine, 310 Cedar St, New Haven, CT 06520-8023; Dhanpat.Jain@yale.edu.

References

1. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand*. 1965;64:31-49.
2. Wu H, Rusiecki JA, Zhu K, et al. Stomach carcinoma incidence patterns in the United States by histologic type and anatomic site. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1945-1952.
3. Nakamura K, Sugano H, Takagi K. Carcinoma of the stomach in incipient phase: its histogenesis and histological appearances. *Gan*. 1968;59:251-258.
4. Tsukamoto T, Yokoi T, Maruta S, et al. Gastric adenocarcinoma with chief cell differentiation. *Pathol Int*. 2007;57:517-522.
5. Park ES, Kim YE, Park CK, et al. Gastric adenocarcinoma of fundic gland type: report of three cases. *Korean J Pathol*. 2012;46:287-291.
6. Mardi K. Oncocytic adenocarcinoma of the stomach: parietal cell carcinoma. *J Cancer Res Ther*. 2013;9:162-163.
7. Tohda G, Osawa T, Asada Y, et al. Gastric adenocarcinoma of fundic gland type: endoscopic and clinicopathological features. *World J Gastrointest Endosc*. 2016;8:244-251.
8. Chiba T, Kato K, Masuda T, et al. Clinicopathological features of gastric adenocarcinoma of the fundic gland (chief cell predominant type) by retrospective and prospective analyses of endoscopic findings. *Dig Endosc*. 2016;28:722-730.
9. Chan K, Brown IS, Kyle T, et al. Chief cell-predominant gastric polyps: a series of 12 cases with literature review. *Histopathology*. 2016;68:825-833.
10. Nomura R, Saito T, Mitomi H, et al. *GNAS* mutation as an alternative mechanism of activation of the Wnt/β-catenin signaling pathway in gastric adenocarcinoma of the fundic gland type. *Hum Pathol*. 2014;45:2488-2496.
11. Fujii M, Uedo N, Ishihara R, et al. Endoscopic features of early stage gastric adenocarcinoma of fundic gland type (chief cell predominant type): a case report. *Case Rep Clin Pathol*. 2015;2:17-22.
12. Fukatsu H, Miyoshi H, Ishiki K, et al. Gastric adenocarcinoma of fundic gland type (chief cell predominant type) treated with endoscopic aspiration mucosectomy. *Dig Endosc*. 2011;23:244-246.
13. Sato Y, Fujino T, Kasagawa A, et al. Twelve-year natural history of a gastric adenocarcinoma of fundic gland type. *Clin J Gastroenterol*. 2016;9:345-351.
14. Takeda S, Mitoro A, Namisaki T, et al. Gastric adenocarcinoma of fundic gland type (chief cell predominant type) with unique endoscopic appearance curatively treated by endoscopic submucosal resection. *Acta Gastroenterol Belg*. 2015;78:340-343.
15. Miyazawa M, Matsuda M, Yano M, et al. Gastric adenocarcinoma of fundic gland type: five cases treated with endoscopic resection. *World J Gastroenterol*. 2015;21:8208-8214.
16. Ueyama H, Matsumoto K, Nagahara A, et al. Gastric adenocarcinoma of the fundic gland type (chief cell predominant type). *Endoscopy*. 2014;46:153-157.
17. Kushima R, Sekine S, Matsubara A, et al. Gastric adenocarcinoma of the fundic gland type shares common genetic and phenotypic features with pyloric gland adenoma. *Pathol Int*. 2013;63:318-325.
18. Kawasaki K, Kurahara K, Oshiro Y, et al. Depressed gastric adenocarcinoma of the fundic gland type. *Intern Med*. 2016;55:543-544.
19. Ueo T, Yonemasu H, Ishida T. Gastric adenocarcinoma of fundic gland type with unusual behavior. *Dig Endosc*. 2014;26:293-294.

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20. Terada T. Well differentiated adenocarcinoma of the stomach composed of chief cell-like cells and parietal cells (gastric adenocarcinoma of fundic gland type). *Int J Clin Exp Pathol*. 2011;4:797-798.
21. Singhi AD, Lazenby AJ, Montgomery EA. Gastric adenocarcinoma with chief cell differentiation: a proposal for reclassification as oxyntic gland polyp/adenoma. *Am J Surg Pathol*. 2012;36:1030-1035.
22. Parikh ND, Gibson J, Aslanian H. Gastric fundic gland adenocarcinoma with chief cell differentiation. *Clin Gastroenterol Hepatol*. 2015;13:A17-A18.
23. Cha HJ, Kim K, Kim M, et al. Concurrent gastric adenocarcinoma of fundic gland type and carcinoma with lymphoid stroma: a rare case report. *Case Rep Gastroenterol*. 2016;10:292-301.
24. Kato M, Uraoka T, Isobe Y, et al. A case of gastric adenocarcinoma of fundic gland type resected by combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique (CLEAN-NET). *Clin J Gastroenterol*. 2015;8:393-399.
25. Hori K, Ide YH, Hirota S, et al. Early gastric adenocarcinoma of the fundic gland type. *Endoscopy*. 2015;47(suppl 1 UCTN):E177-E178.
26. Lewin E, Daroca P, Sikka S, et al. Very well-differentiated gastric adenocarcinoma of the fundic gland type with intriguing morphologic features: a case report and review of the literature. *Am J Clin Pathol*. 2015;144:A391.
27. Fujimoto A, Horii J, Goto O, et al. A case of gastric adenocarcinoma of fundic gland type resected by ESD. *Prog Dig Endosc*. 2014;84:100-101.
28. Abe T, Nagai T, Fukunaga J, et al. Long-term follow-up of gastric adenocarcinoma with chief cell differentiation using upper gastrointestinal tract endoscopy. *Intern Med*. 2013;52:1585-1588.
29. Chen WC, Rodriguez-Waitkus PM, Barroso A, et al. A rare case of gastric fundic gland adenocarcinoma (chief cell predominant type). *J Gastrointest Cancer*. 2012;43(suppl 1):S262-S265.
30. Miyaoka Y, Izumi D, Mikami H, et al. A case report of an extremely well differentiated gastric adenocarcinoma of the fundic gland type successfully treated with ESD. *Gastroenterol Endosc*. 2011;53:1778-1785.
31. Fujisawa T, Ueyama S, Ouchi S, et al. Early gastric adenocarcinoma of the fundic gland type (chief cell predominant type) observed with magnifying endoscopy using narrow band imaging: report of a case. *Gastroenterol Endosc*. 2011;53:3769-3775.
32. Nagini S. Carcinoma of the stomach: a review of epidemiology, pathogenesis, molecular genetics and chemoprevention. *World J Gastrointest Oncol*. 2012;4:156-169.
33. Rychterova V, Hägerstrand I. Parietal cell carcinoma of the stomach. *Apmis*. 1991;99:1008-1012.
34. Gaffney EF. Favourable prognosis in gastric carcinoma with parietal cell differentiation. *Histopathology*. 1987;11:217-218.
35. Takubo K, Honma N, Sawabe M, et al. Oncocytic adenocarcinoma of the stomach: parietal cell carcinoma. *Am J Surg Pathol*. 2002;26:458-465.
36. Yang GY, Liao J, Cassai ND, et al. Parietal cell carcinoma of gastric cardia: immunophenotype and ultrastructure. *Ultrastruct Pathol*. 2003;27:87-94.
37. Joo M, Han SH. Gastric-type extremely well-differentiated adenocarcinoma of the stomach: a challenge for preoperative diagnosis. *J Pathol Transl Med*. 2016;50:71-74.
38. Mochizuki K, Kondo T, Tahara I, et al. Gastric adenocarcinoma of pyloric gland type with high-grade malignancy. *Pathol Int*. 2015;65:148-150.
39. Jalving M, Koornstra JJ, Boersma-van Ek W, et al. Dysplasia in fundic gland polyps is associated with nuclear beta-catenin expression and relatively high cell turnover rates. *Scand J Gastroenterol*. 2003;38:916-922.
40. Khor TS, Alfaro EE, Ooi EM, et al. Divergent expression of MUC5AC, MUC6, MUC2, CD10, and CDX-2 in dysplasia and intramucosal adenocarcinomas with intestinal and foveolar morphology: is this evidence of distinct gastric and intestinal pathways to carcinogenesis in Barrett esophagus? *Am J Surg Pathol*. 2012;36:331-342.
41. Torbenson M, Lee JH, Cruz-Correa M, et al. Sporadic fundic gland polyposis: a clinical, histological, and molecular analysis. *Mod Pathol*. 2002;15:718-723.
42. Matsubara A, Sekine S, Kushima R, et al. Frequent *GNAS* and *KRAS* mutations in pyloric gland adenoma of the stomach and duodenum. *J Pathol*. 2013;229:579-587.
43. Lee SH, Jeong EG, Soung YH, et al. Absence of GNAS and EGFL6 mutations in common human cancers. *Pathology*. 2008;40:95-97.
44. Paroni Sterbini F, Palladini A, Masucci L, et al. Effects of proton pump inhibitors on the gastric mucosa-associated microbiota in dyspeptic patients. *Appl Environ Microbiol*. 2016;82:6633-6644.
45. Zhang C, Powell SE, Betel D, et al. The gastric microbiome and its influence on gastric carcinogenesis: current knowledge and ongoing research. *Hematol Oncol Clin North Am*. 2017;31:389-408.

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