Fundic Gland Polyps

Fundic gland polyps (FGPs) occur in two forms: sporadic and those associated with familial adenomatous polyposis (FAP). FGPs were originally described in patients with FAP (eFig. 2.35) and were believed to be a manifestation of that syndrome, but they are now recognized to be one of the most common gastric polyps (along with hyperplastic polyps) in individuals without FAP. Sporadic FGPs are found in 1% to 2% of routine upper endoscopic examinations, and are most common in middle-aged females. They are typically small (a few millimeters and only rarely >1 cm), sessile, and dome-shaped. Sporadic FGPs may be single but are commonly multiple (usually a few polyps). Rarely, patients without FAP have carpeting of the body and fundus by numerous FGPs, in a manner that resembles a polyposis syndrome. Unlike hyperplastic polyps, though, FGPs are not particularly associated with any type of inflammatory or atrophic background mucosal pathology. Their presence is inversely correlated with H. pylori infection(1). They are usually an incidental finding. No symptoms or clinical manifestations (e.g., gastrointestinal bleeding) can be ascribed to them. However, some studies do indicate a temporal association between use of proton pump inhibitors and the development of FGPs (2). This potential link is controversial and has not been demonstrated in any controlled prospective trial (3).

The morphology of both fundic gland polyps and proton pump inhibitor effects overlaps considerably. An endoscopic nodule correlates with dilated oxyntic glands, some of which contain cells with apocrine-like snouts. Because it is sometimes difficult to distinguish between these two processes, correlation relies chiefly on the presence of an endoscopic lesion.

FGPs associated with FAP syndrome differ from sporadic FGPs on several epidemiologic and clinicopathologic points. For example, FAP-associated FGPs occur in a majority of patients with FAP (reported frequencies range from 12.5% to 84% of FAP patients, depending on their age at endoscopy) and show a more equal gender distribution. They are more numerous than sporadic FGPs, and hence patients with FAP are more likely to have fundic gland “polyposis.” FAP-associated FGPs also occur at younger ages, including children (FGPs are vanishingly rare in the non-FAP pediatric population; a retrospective search for all FGPs biopsied in children without FAP using a computerized pathology database spanning 16 years revealed only three examples at our hospital). In addition, approximately 25% of FAP-associated FGPs demonstrate low-grade epithelial dysplasia. Dysplasia in sporadic FGPs can occur but is distinctly unusual and has never been associated with progression to carcinoma(1). A retrospective histologic evaluation of several hundred sporadic FGPs at our hospital revealed <1% with low-grade dysplasia, and one of these cases was subsequently determined to be a member of an attenuated FAP family (4).

The natural history of FGPs is interesting because both sporadic and FAP-associated FGPs can increase, decrease, or remain constant in number, as seen when patients are followed-up with serial upper endoscopic examinations. Sporadic FGPs, even fundic gland polyposis, have never been reported to progress to gastric adenocarcinoma. Several cases of adenocarcinoma associated with fundic gland polyposis in patients with FAP exist, but this is a reportable occurrence (5, 6). Currently, upper endoscopic surveillance in patients with FAP is performed mainly to address the increased risk for duodenal polyposis (>300-fold) and particularly periampullary adenomas and adenocarcinomas (7). The presence of dysplastic or nondysplastic FGPs is regarded as an
incidental finding and would virtually never require surgical resection. Even surveillance of dysplastic FGPs remains controversial.

As their name implies, fundic gland polyps develop only in the gastric body and fundus; they do not arise in the antrum. In patients with FAP, FGPs are more common than gastric adenomas, despite the fact that the colorectal and duodenal polyps in these patients are adenomas. When gastric adenomas do develop in the FAP setting, they are usually antral. Despite the increased frequency of dysplastic FGPs and gastric adenomas in FAP, the risk of gastric adenocarcinoma is only slightly increased (approximately twofold in one study) and is not significantly increased statistically in Western FAP patients (7). This contrasts with studies of Asian patients with FAP, among whom the risk of gastric adenocarcinoma is increased approximately tenfold. This low risk in Western FAP patients also contrasts with the much higher risk of gastric adenocarcinoma in non-FAP patients who have adenomas. This most likely reflects the fact that germline mutations in the APC gene on chromosome 5q21 leading to FAP do not predispose patients to background gastritis or gastric atrophy. Most Western patients with FAP have normal gastric mucosa outside of any antral adenomas or body FGPs. Most patients with sporadic gastric adenomas, in contrast, have chronic atrophic gastritis (particularly *Helicobacter pylori*-mediated) that predisposes to gastric adenocarcinoma in the intestinalized background gastric mucosa outside of the adenomas.

**GASTRIC ADENOMAS AND GASTRIC DYSPLASIA**

**Intestinal and Gastric Foveolar Type Gastric Adenomas**

Much literature in this area has been difficult to interpret. Although there is massive experience with gastric cancer and its precursors in Japan, pathologists there have used different diagnostic criteria from Western pathologists, as pointed out by Lauwers et al. in 1999 (8). The observation that Japanese pathologists did not require invasion to diagnose carcinoma (and “invasion” was not listed as a criterion in the 1990 World Health Organization [WHO] classification) presumably has informed their far better cure rates for early carcinomas, compared to results in Western countries. Based on these observations, an international panel convened in Vienna published consensus definitions of gastric epithelial neoplasia in 2000 (9), which distinguished between noninvasive lesions and invasive ones.

Currently, if such a lesion produces a polyp, it is referred to as an adenoma and the dysplasia is graded, whereas flat lesions are termed “dysplasia” and are graded using criteria similar to those in the esophagus. This is not particularly scientific, but is a convention that has worked. Both types of lesions confer risk, and both require sampling of the entire stomach to exclude invasive carcinoma. As in the case of gastric hyperplastic polyps, the background pathology is important. To illustrate this, Abraham et al. studied 61 gastric adenomas from 51 patients between 1985 and 2001 (10). The adenomas were classified as intestinal-type, containing at least focal goblet cells and/or Paneth cells; gastric foveolar type, lined entirely by gastric mucin cells, as shown on periodic acid Schiff/Alcian blue staining (PAS/AB); or indeterminate. The histologic features of both the adenomas (location, multiplicity, degree of dysplasia, and presence of adenocarcinoma within the polyp) and the surrounding gastric mucosa (presence of gastritis, intestinal metaplasia, and adenocarcinoma) were evaluated. Gastric adenomas were distributed equally throughout the stomach, were most frequently solitary (82%), and contained adenocarcinoma in nine cases (14.8%). There were 34 intestinal-type adenomas (56%) in 31 patients, 25 gastric foveolar-type adenomas (41%) in 18 patients (including 10 patients with familial adenomatous polyposis), and two indeterminate type (3%). Intestinal-type adenomas were significantly more likely than gastric foveolar-type adenomas to show high-
grade dysplasia ($p < 0.0001$), adenocarcinoma within the polyp ($p = 0.016$), intestinal metaplasia in the surrounding stomach ($p < 0.000001$), and gastritis ($p = 0.002$). Patients with intestinal-type adenomas were also more likely to have separate adenocarcinomas, as seen in five cases (100%), although this did not reach statistical significance. Youn Park et al. found that foveolar-type gastric dysplasia is more commonly associated with an endoscopically flat lesion compared to adenomatous-type dysplasia in a study that included 69 cases (31 adenomatous, 23 hybrid [adenomatous and foveolar], and 15 foveolar type). In the same study adenomatous-type dysplasia was more often located in the gastric body/fundus, were larger, and were more likely to be multifocal. These differences, however, were not statistically significant. In contrast to the work of Abraham and colleagues, the same group found that foveolar and hybrid-type dysplasia (defined by at least 10% of a second phenotype) were significantly more likely to display high-grade morphology than the adenomatous-type ($p=0.046$ and 0.008, respectively). In addition, intestinal metaplasia was identified in the background mucosa in all cases of foveolar, hybrid, and adenomatous dysplasia. Furthermore, foveolar-type dysplasia showed more recurrence than the hybrid or adenomatous types (11). These dissimilar findings between the two studies are probably best explained by differences in the populations studied (USA vs. Korean) and exclusion criteria. In the Abraham study, for example, the patients with gastric foveolar type gastric adenomas lacked intestinal metaplasia in their background flat mucosa. Regardless of the type of dysplasia, complete removal of the adenoma should be performed as a fraction of these progress to high-grade dysplasia or invasive cancer. A retrospective study of 27 gastric adenomas found 8 lesions with progression: 1 adenoma with high grade dysplasia and 3 with low grade dysplasia progressed to invasive cancer and 4 with low grade dysplasia progressed to non-invasive high-grade dysplasia (12). For pathologists practicing in the United States, the Abraham criteria are most applicable and allow the pathologist to assign risk categories for gastric adenomas; since the “gastric foveolar type adenoma” is rare, unassociated with background pathology and appears as an isolated sporadic lesion akin to a colonic sporadic adenoma, the patients are at low risk (10, 13).

Since gastric adenomas are rarely truly “sporadic” lesions (the vast majority in daily practice in the United States are of the intestinal type and associated with background intestinal metaplasia), thorough sampling of the surrounding gastric mucosa is essential to understand the clinicopathologic context of the adenoma. A Korean study also found increased risk of colorectal adenomas (48.3% vs 33.3% in control group, $p=0.022$) in patients with gastric adenomas, arguing for screening colonoscopies in patients with this type of gastric polyp (14).

Flat dysplasia is typically encountered incidentally also in the setting of atrophy as a result of long-standing injury due to *Helicobacter* infection or autoimmune atrophic gastritis. There are no guidelines regarding patient management in this situation as the issue of flat dysplasia is difficult to address since these are endoscopically undetectable lesions. Low-grade dysplasia has been reported to “regress”, persist, and progress to a higher grade dysplastic lesion/adenocarcinoma in 53.3%, 31.1%, and 6.6%/8.8% of cases, respectively. High grade lesions, however, are unlikely to regress and are associated with a significant risk of progression to invasive carcinoma, reported at 69% (11/16 patients) by Rugge et al. (in this study however, it was unclear if the studied cases represented flat or polypoid lesions) (15). Of course, “regression” in the setting of flat low-grade dysplasia is a term that must be used with caution as these lesions are not grossly evident and are unlikely to be “spotted” endoscopically. In the study by Rugge et al. “regression” required 1) at least two “negative” endoscopic examinations and 2) follow up of at least 12 months after the first negative biopsy. As a result of its low
likelihood of progression, it is difficult to justify surgical intervention in a patient with low-grade dysplasia. These patients are typically followed endoscopically and their stomachs mapped with multiple biopsies. High-grade dysplastic lesions are typically managed with endoscopic mucosal resection (EMR) or surgical resection.

Pyloric Gland Adenoma

These lesions have been mentioned briefly over the years and in the 1990 WHO classification of gastric neoplasms but were fully characterized in 2003 by Vieth et al. (16) Pyloric gland adenoma (PGA) is a neoplastic polyp known to occur in the stomach, gallbladder, duodenum, and main pancreatic duct. These polyps show a preference for the gastric corpus, account for 2.7% of all gastric polyps, are typically seen in older patients (median age 73 years), and gastric examples show a remarkable female predominance (13, 16). More than 1/3 occur in patients with autoimmune metaplastic atrophic gastritis (AMAG) (13, 16) and account for 10% of polyps found in patients with AMAG (17). H. pylori or chemical gastritis may also be present in the background mucosa (16). Histologically, these polyps are composed of closely packed pyloric-type glands with cuboidal to low columnar epithelium showing pale or eosinophilic, “ground glass” cytoplasm (Fig. 2.17, 2.18, eFig. 2.70, 2.71). Nuclei are round without prominent nucleoli. Foci of dysplasia/carcinoma are commonly encountered. Low grade and high grade dysplasia are seen in 12% and 39% of the cases, respectively (13) while invasive carcinoma is associated with 12-47% of the lesions, depending on the authors’ criteria for carcinoma; using Western criteria, the figure is probably closer to 10-15% (13, 16). PGA’s show coexpression of MUC6 (marker of pyloric gland mucin) and MUC5AC (marker of foveolar mucin) and lack expression of MUC2 (marker of intestinal mucin) and CDX2. While foveolar-type gastric adenomas show MUC5AC expression, they lack expression of MUC6 and MUC2(13). Some cases, however, show areas of transition from gastric to intestinal differentiation and these foci may show immunolabeling with MUC2 and CD10 (18). As with other types of adenomas, complete excision of PGA with biopsy of the background flat mucosa is appropriate in these patients.

Oxyntic Gland Polyp/Adenoma

Encountered in the literature as “chief cell hyperplasia with structural and nuclear atypia” and “chief cell proliferation of the gastric mucosa”, this peculiar lesion was initially described in 2003 by Müller-Höcker and Rellecke and later in 2005 by Matsukawa et al. as an unusual variant of fundic gland polyp occurring in the cardia/corpus(19, 20). Initial reports described anastomosing cords of irregularly branched tubules composed of monotonous epithelial cells with central, round nuclei and amphophilic cytoplasm associated with oxyntic and foveolar microcysts. The case described by Matsukawa et al. reports nuclear atypia in the form of nuclear stratification, suggestive of a tubular carcinoma. However, mitotic figures and Ki67 labeling index were low in both reports. Chief cell origin for these proliferations is supported by ultrastructural findings and positive immunohistochemical staining for pepsinogen-I. However, scattered parietal cells were observed within these proliferations. In both of these reports an adjacent fundic gland polyp could be identified (19, 20). More recently, Ueyama et al. described similar lesions with the term “gastric adenocarcinoma of fundic gland type”. In their report of 10 cases, the Ki67 labeling index was also low and none of the patients died or suffered recurrences during the 10-70 month follow-up period (21). We have encountered similar polyps and diagnosed them as “oxyntic gland polyp/adenoma”(22). Because of their rarity and lack of long-term studies we suggest endoscopic follow-up to assure that the lesion has been completely
HER2 TESTING IN GASTRIC CARCINOMA

HER2 status evaluation is routinely requested in cases of gastric carcinoma as a result of findings from the ToGA trial, an international phase III multicenter study, which showed that addition of Trastuzumab (an anti-Her2 monoclonal antibody) to a chemotherapy treatment regimen prolongs survival by a few months in patients with HER2-positive gastric carcinoma (23). HER2 overexpression is found in just over 20% of gastric cancers and most of these are of the intestinal type (24). Approximately 7% of diffuse-type carcinomas express HER2 overexpression (25). Correlation between HER2 amplification by fluorescence in situ hybridization (FISH) and immunohistochemistry is less rigorous than for breast carcinoma as more than 20% of cases may carry low-level HER2 amplification by FISH without immunohistochemical reactivity. These patients do not benefit from treatment with Trastuzumab and, as a result, HER2 immunohistochemistry is the first line of evaluation for HER2 overexpression. Fluorescence in situ hybridization should be performed in equivocal (2+) cases. Criteria for HER2 evaluation are different from those in breast carcinoma (Table).

Table. Immunohistochemistry scoring for HER2 in gastric and gastro-esophageal junction cancer in biopsy and resection specimens.

<table>
<thead>
<tr>
<th>Biopsy specimen staining pattern</th>
<th>Resection staining pattern</th>
<th>HER2 overexpression assessment</th>
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<tbody>
<tr>
<td>No reactivity or no membranous reactivity in any tumor cell</td>
<td>No reactivity or membranous reactivity in &lt;10% of tumor cells</td>
<td>Negative (0)</td>
</tr>
<tr>
<td>Tumor cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of tumor cells stained</td>
<td>Tumor cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of tumor cells stained</td>
<td>Negative (1+)</td>
</tr>
<tr>
<td>Tumor cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained</td>
<td>Tumor cell cluster with a weak to moderate complete, basolateral or lateral membranous reactivity irrespective of percentage of tumor cells stained</td>
<td>Equivocal (2+)</td>
</tr>
<tr>
<td>Tumor cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of</td>
<td>Tumor cell cluster with a strong complete, basolateral or lateral membranous reactivity irrespective of</td>
<td>Positive (3+)</td>
</tr>
<tr>
<td>percentage of tumor cells stained</td>
<td>percentage of tumor cells stained</td>
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Adapted from Bang et al (23).

References


