Sporadic Fundic Gland Polyps With Low-Grade Dysplasia

A Large Case Series Evaluating Pathologic and Immunohistochemical Findings and Clinical Behavior

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ABSTRACT

Objectives: Fundic gland polyps (FGPs) occur in two clinical settings, sporadic and syndromic. Epithelial dysplasia is rare in sporadic FGPs, and progression data from large series are lacking. The aim of this study was to evaluate the clinical, morphologic, and immunohistochemical features in a large series of sporadic FGPs with epithelial dysplasia.

Methods: We studied 85 patients with FGPs with low-grade dysplasia (FGPD), including 62 patients with sporadic and 23 with syndromic FGPDs.

Results: Sixty-two patients with sporadic FGPD comprised 29 men and 33 women with a median age of 56 years. The indications for endoscopy were heartburn and follow-up of Barrett esophagus, and 49 patients had a history of proton pump inhibitor use. Morphologically, sporadic and syndromic FGPDs were similar. Immunohistochemical staining for p53 was normal (weak 1+) in all polyps, Ki-67 immunohistochemistry showed staining in the mucus neck and surface epithelium, and nuclear accumulation of β-catenin was observed in 9 of 40 sporadic FGPDs. Twenty-six (42%) patients with sporadic FGPDs had follow-up esophagogastroduodenoscopies with biopsies after a mean period of 14.8 months (nine with more than one follow-up): nine (35%) had no additional polyps, 13 (50%) had nondysplastic sporadic FGPs, and four (15%) had sporadic FGPDs.

Conclusions: Sporadic FGPDs were seen primarily in middle-aged patients with gastroesophageal reflux. Follow-up data support the indolent nature of these polyps.

Fundic gland polyps (FGPs) are the most common type of gastric polyp.¹ ² They typically occur in the body and fundus of the stomach and are composed of cystically dilated oxyntic glands lined by attenuated chief, parietal, and mucous neck cells. The polyp surface is lined by gastric foveolar epithelium. FGPs occur in two different clinical settings, sporadic and syndromic (familial adenomatous polyposis, or FAP).

Sporadic FGPs have been reported in 0.8% to 1.9% of patients who undergo upper endoscopy.³ ⁴ They are slightly more common in women than in men, and their occurrence has been associated with prolonged use of proton pump inhibitors (PPIs).³ ⁴ In sporadic FGPs, low-grade epithelial dysplasia has been described, but its prevalence is extremely rare (approximately 1%).⁵ Syndromic FGPs arise in patients with FAP, have been reported in 12.5% to 84% of patients with FAP, occur in a younger age group, and equally affect men and women.⁶-¹³ Epithelial dysplasia is more common.
in this group, seen in 25% to 62% of cases, and is typically low grade, and only rare cases of high-grade dysplasia have been reported.\textsuperscript{5,12-16}

Although sporadic and syndromic FGPs are histologically and histochemically indistinguishable,\textsuperscript{17-19} they differ with respect to their genetic and molecular backgrounds. Sporadic FGPs show a very high frequency of activating mutations in the $\beta$-catenin gene,\textsuperscript{20,21} whereas syndromic FGPs occur through an inherited germline mutation in the $APC$ gene (adenomatous polyposis coli) coupled with additional somatic mutations, leading to complete inactivation of both copies of the $APC$ tumor suppressor gene.\textsuperscript{22} It has been shown that when low-grade dysplasia is present in either sporadic or syndromic FGPs, truncating mutations in the $APC$ tumor suppressor gene occur in both settings. This is different from the nondysplastic sporadic FGPs, which only harbor activating mutations in the $\beta$-catenin gene.\textsuperscript{21-23}

Possibly because of the rarity of sporadic FGPs with dysplasia, to our knowledge, no large series evaluating the clinicopathologic findings and clinical outcome associated with these polyps have been published. Consequently, the clinical significance of this finding remains unclear with no evidence-based data to guide the management of these patients.

In an attempt to provide useful information, we designed a study to evaluate the clinical, morphologic, and immunohistochemical features of a relatively large series of sporadic FGPs with low-grade dysplasia (FGPD). We also reviewed clinical and endoscopic follow-up in all cases for which it was available.

**Materials and Methods**

**Study Setting**

This study was conducted at Miraca Life Sciences Division of Gastrointestinal Pathology, a specialized laboratory receiving specimens from gastroenterologists operating in outpatient endoscopy centers across the United States. Biopsy specimens are interpreted by a group of gastrointestinal pathologists who share a common approach to biopsy evaluation and maintain a relative uniformity through internally standardized specimen handling, diagnostic criteria, and terminology. This study was based on the retrospective analysis of deidentified patient electronic records. The study was approved by the Miraca Life Sciences Institutional Review Board.

**Patient and Tissue Samples**

We used the Miraca Life Sciences Database to extract all patients who had a histopathologic diagnosis of FGPD between January 2008 and December 2011. Demographic, clinical (which included PPI history), and endoscopic information was collected. Each case was evaluated for subsequent esophagogastroduodenoscopy (EGD) and biopsy results. We also recorded all histopathologic diagnoses made on any other gastrointestinal biopsy specimens obtained at the same time as the index biopsy of the FGPD. FGPD cases were categorized as sporadic when there was no clinical or endoscopic evidence of FAP, attenuated FAP, concurrent or prior evidence or history of gastric adenomas, duodenal adenomas, or multiple colonic adenomas. Patients with a history of idiopathic inflammatory bowel disease, gastrointestinal malignancy, or upper gastrointestinal surgery were excluded from the analysis.

Our database search yielded 108 patients with a diagnosis of gastric FGPD, of whom 23 had syndromic FGPD. Of the remaining 85, the consensus diagnosis by the authors (M.D.L. and B.B.) was as follows: 63 cases from 62 patients had sporadic FGPD. The remaining 22 cases were not included due to erosions and regenerative epithelial changes, lack of surface for evaluation of dysplasia, and suboptimal tissue/processing artifact. In addition, two cases of likely pyloric gland adenoma were excluded. This process yielded a total of 85 patients, which constituted the study group. These included 62 sporadic and 23 syndromic FGPDs.

**Histopathologic Criteria**

The slides of all biopsy specimens diagnosed as FGPD (fixed in formalin and stained with H&E) were reviewed by the authors. Histologic criteria for inclusion required the typical features of FGPs (characterized by cystically dilated oxyntic glands lined by attenuated chief and parietal cells) with dysplasia in the surface/foveolar epithelium and mucous neck cells. Dysplasia was defined as nuclear enlargement, hyperchromasia, pseudostratification, and loss of cytoplasmic mucin as described by Wu et al.\textsuperscript{5} A representative case of sporadic FGPD is depicted in Image II. All specimens were stained with an anti-*Helicobacter* immunohistochemical stain (monoclonal antibody; Cell Marque, Rockville, CA).

**Immunohistochemistry**

We performed immunohistochemical staining for p53, $\beta$-catenin, and Ki-67 on 4-µm tissue sections using a panel of commercial antibodies: p53 (mouse antibody; Ventana Medical Systems, Tucson, AZ), Ki-67 (rabbit antibody; Ventana Medical Systems), and $\beta$-catenin (monoclonal mouse; Cell Marque). Appropriate positive and negative controls were included for each run of immunostains. p53 stain was interpreted as either “normal” (weak 1+ nuclear staining) or “overexpressed” (3+ strong nuclear staining). $\beta$-Catenin was considered “negative,” when there was
membranous staining, vs “positive,” when there was nuclear staining.

For Ki-67 immunolabeling, the following categories were applied:

1. Increased staining pattern: nuclear staining in more than 10% of surface epithelium and mucus neck cells
2. Normal pattern: rare scattered mucus neck cells and glands, with absence of surface staining
3. Reactive pattern: rare nuclear staining at the surface (<2%) with increased staining in the mucus neck regenerative region

Immunohistochemical staining for p53, Ki-67, and β-catenin was performed on 40 of the sporadic FGPDs, 15 of the FAP-associated FGPDs, and 40 controls (consecutive cases of sporadic FGPs without dysplasia). Ki-67 immunohistochemistry (IHC) was also done on 13 cases of FGP with reactive changes, mostly related to erosions.

**Statistical Analysis**

Analysis was performed using SigmaStat Version 3.5 (Systat Software, Point Richmond, CA). Median, mean, and standard deviation were calculated for continuous variables (age in years), and comparisons between groups were made by the Fisher test. Simple odds ratios (ORs) were calculated using an online OR calculator.

**Results**

During the study period, there were 624,209 EGDs from 577,739 unique patients (median age, 57 years; range, 3 months to 98 years; 60.0% female). A total of 35,372 unique patients had a histopathologic diagnosis of FGP (median age, 59 years; range, 10-98 years; 68.6% female), with heartburn and hiatal hernia being the most common indication for EGD. Patients with FGPs were slightly but significantly older compared with our EGD population ($P < .001$) and significantly more likely to be female (OR, 1.49; 95% confidence interval [CI], 1.46-1.53; $P < .0001$).

**Patients With Dysplasia in FGP**

The prevalence of dysplasia in FGPs in our study population was 0.3%. None of the polyps were diagnosed as having high-grade dysplasia. Of the 23 patients with syndromic FGPDs, 20 had FAP syndrome. An additional three were likely to have an attenuated polyposis based on multiple colonic adenomas and younger age at presentation. The demographic and clinical information comparing the 62 patients with sporadic FGPDs and 23 patients with syndromic FGPDs is summarized in Table I.

**Sporadic FGP With Dysplasia**

The median age of patients with sporadic FGPDs was 56 years (range, 24-88 years); 33 (53.2%) were women and 29 (46.8%) were men. Compared with all sporadic FGPs without dysplasia, patients with sporadic FGPDs were younger (56 vs 59 years; $P < .0001$) and almost twice as likely to be male (OR, 1.91; 95% CI, 1.16-3.16; $P < .01$).

The most common indications for endoscopy included heartburn/reflux (53%), epigastric pain (22%), and follow-up of Barrett esophagus (21%). Other indications included gastroesophageal reflux disease (GERD) refractory to PPIs, dyspepsia, dysphagia, nausea, vomiting, and anemia. Of 52 patients for whom medication history was available, 49 had
a history of PPI use, and three patients were not taking PPIs. Endoscopy showed a single polyp in 33 cases and multiple polyps in 30 cases. The polyp size ranged from 0.1 to 2.0 cm, with a mean ± SD size of 0.5 ± 0.38 cm.

**Syndromic FGP With Dysplasia**

The median age of patients with syndromic FGPDs was 51 years (range, 13-75 years); 16 (69.6%) were women and 7 (30.4%) were men. The indications for endoscopy included a history of FAP and/or a history of a malignant gastrointestinal neoplasm. Only two patients had heartburn and/or esophagitis. The three patients with possible attenuated FAP were 36, 66, and 75 years old and had duodenal adenomas and multiple colon adenomas. The size of the gastric FGPD ranged from 0.2 to 1.3 cm, with a mean ± SD size of 0.43 ± 0.23 cm.

**Morphologic Features of Sporadic and Syndromic FGPDs**

The histologic features of both sporadic (illustrated in Image 1) and syndromic FGPDs were similar, with dysplasia limited to surface epithelium and to the mucus neck cells. The dysplasia resembled adenomatous change with nuclear hyperchromasia, stratification, and mucin depletion. Typical features of FGPs with cystically dilated glands were present in the polyp body. None of the cases showed features of either high-grade dysplasia or malignancy. The gastric mucosa on which FGPDs arose was normal in the oxyntic region and either normal or reactive (“mild reactive gastropathy”) in the antrum. All cases were negative for *Helicobacter pylori* by IHC. None of the cases demonstrated atrophy, significant chronic or active inflammation, or intestinal metaplasia.

**Immunohistochemical Stain Results for Sporadic and Syndromic FGPDs**

The immunohistochemical findings for p53, Ki-67, and β-catenin (illustrated in Image 2) were similar in sporadic and syndromic FGPDs. Ki-67 highlighted nuclei along the surface and mucus neck region in all cases. The surface epithelial staining pattern was either patchy or diffuse in the area of dysplasia. Immunolabeling for p53 demonstrated weak 1+ staining pattern in all cases, with no evidence of overexpression. β-Catenin exhibited membranous staining. The β-catenin stain accentuated the cell membranes, and a cytoplasmic blush was seen as well. However, nine (22.5%) of the 40 sporadic FGPDs and two (13.3%) of the 15 FAP-associated FGPDs displayed nuclear staining for β-catenin (Image 3), but the difference was not statistically significant due to the small number of positive cases (P = .7).

**Immunohistochemical Stain Results for Sporadic FGPs Without Dysplasia**

Ki-67 highlighted rare nuclei within cells in the mucous neck region, but there was no staining in the nuclei lining the surface. Immunolabeling for p53 demonstrated weak 1+ staining pattern in all cases, β-Catenin exhibited the normal staining pattern, with membranous staining, but no nuclear staining (Image 2).

Upon comparing sporadic and FAP-associated FGPD with sporadic FGP without dysplasia, the results of the Ki-67 surface staining (P < .0001) and β-catenin nuclear staining (P = .006) were statistically significant.

**Morphological and Immunohistochemical Stain Results for Sporadic FGPs With Reactive Changes**

The 13 cases of FGPs with reactive changes exhibited mucosal erosions, attenuated surface epithelium, or loss of cytoplasmic mucin with active inflammation. As expected, Ki-67 IHC staining highlighted a markedly increased regenerative zone in the mucus neck area with either absent or reduced surface staining (Image 4).

**Follow-up Data of Sporadic FGPD**

Follow-up endoscopies were available in 26 (42%) of 62 patients, with nine having more than one EGD with a history of PPI use, and three patients were not taking PPIs. Endoscopy showed a single polyp in 33 cases and multiple polyps in 30 cases. The polyp size ranged from 0.1 to 2.0 cm, with a mean ± SD size of 0.5 ± 0.38 cm.

**Table 1**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sporadic FGPD Cases</th>
<th>Syndromic FGPD Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>62</td>
<td>23</td>
</tr>
<tr>
<td>Age, median (range), y</td>
<td>56 (24-88)</td>
<td>51 (13-75)</td>
</tr>
<tr>
<td>Sex, M/F, No.</td>
<td>29/33</td>
<td>7/16</td>
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<td>Most common indications for endoscopy, %</td>
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<td>Screening and surveillance due to history of FAP</td>
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<tr>
<td>GERD</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Follow-up Barrett esophagus</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>PPI use, No.</td>
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<td>NA</td>
</tr>
<tr>
<td>Polyp number, single/multiple</td>
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<td>Multiple in all</td>
</tr>
<tr>
<td>Polyp size, mean ± SD, cm</td>
<td>0.5 ± 0.38</td>
<td>0.43 ± 0.23</td>
</tr>
</tbody>
</table>

FAP, familial adenomatous polyposis; FGPD, fundic gland polyp with low-grade dysplasia; GERD, gastroesophageal reflux disease; NA, not applicable; PPI, proton pump inhibitor.
biopsies. The mean interval was 14.8 months (range, 1 month to 4 years). Nine of the 26 patients had no additional polyps, 13 had FGP without dysplasia, and four had FGPD. The four patients with repeat FGPD were as follows: a 49-year-old woman with normal colon and duodenum, a 69-year-old man with normal duodenum (no colon biopsy), a 48-year-old man with no colon or duodenum biopsy, and a 47-year-old woman with a normal duodenum and ileum, as well as colonoscopy with one tubular adenoma and a hyperplastic polyp.

**Discussion**

To date, the studies regarding sporadic FGPD have all been small series consisting of one to 15 cases. The
**Image 3** A and B, Sporadic fundic gland polyp with low-grade dysplasia showing H&E stain and corresponding β-catenin immunohistochemistry highlighting scattered positive nuclear stain (arrows) (×100).

**Image 4** H&E stain (A, ×40; and B, ×100) with corresponding Ki-67 immunohistochemistry (C, ×100) of fundic gland polyp with reactive epithelial changes. Note the expanded proliferative zone in the mucus neck and reduced surface staining (×40).
rare nature of these polyps has made it difficult to determine the clinical behavior and progression, which are important parameters to guide patient management. When pathologists make a diagnosis of sporadic FGPD, clinicians often inquire how these polyps should be followed up. Our population of 62 patients with sporadic FGPDs showed minimal and possibly clinically insignificant differences from the much larger group of patients with nondysplastic FGPs: the former were almost twice as likely to be men and were slightly younger than the latter. The indications for the index EGD were essentially identical in the two groups, with GERD by far the most common reported condition and a strong association between PPI use and FGPs. The 20 patients with FAP-associated FGPD were slightly younger, and as expected, the main reason for EGD was surveillance for the development of upper gastrointestinal neoplasia and not reflux.

In another large study from our institution, Genta et al26 studied 6,081 patients with sporadic FGPs without dysplasia; 67.8% were women with a median age of 59 years, with GERD being the main indication for EGD, similar to our population of sporadic FGPD.

Like the study by Genta et al26 that showed an inverse relationship between sporadic FGPs and Helicobacter infection, none of our patients with FGPD had Helicobacter gastritis. Similar to the surrounding gastric mucosa in sporadic FGPs without dysplasia, the background gastric mucosa of the sporadic FGPD cases was normal or showed reactive gastropathy, and none of the cases had atrophy or intestinal metaplasia. Thus, paradoxically, it would appear that all FGPs, irrespective of the presence of dysplasia, tend to arise in essentially healthy stomachs.

The prevalence of sporadic FGPDs in our patient population was very low, representing 0.3% of all FGPs, less than the approximately 1% stated in other studies.5 One explanation could be because of the surging use of PPIs in the past decade, FGPs are becoming increasingly common, while the yet unknown factors that promote dysplasia may have remained constant. Thus, dysplastic FGPs become more diluted in the ever increasing numbers of nondysplastic FGPs. Second, the low prevalence rate in our study may be the result of the large number of cases of FGPs in our institution, the rare nature of this entity, and the strict diagnostic criteria, with reevaluation of the cases in consensus conferences. We also excluded 22 cases due to erosions and reactive and regenerative epithelial changes that can mimic dysplasia.

The morphology of sporadic FGPD was the same as that of FAP-associated FGPD. Both displayed dysplasia limited to the surface foveolar epithelium and mucus neck, with underlying typical fundic polyps with cystically dilated glands. The
underlying presence of dilated fundic cysts lined by parietal and chief cells is an important contrast from gastric adenomas. This distinction is very important in preventing us from overcalling a sporadic FGPD as a gastric adenoma. Correct diagnosis is important as the behavior and management of gastric adenomas are different. Also, the lack of atrophy and intestinal metaplasia in the surrounding gastric mucosa of these polyps should be an important clue to their diagnosis.

Immunolabeling of p53, β-catenin, and Ki-67 showed similar results in sporadic and syndromic FGPDs. p53 showed weak 1+ staining (normal) in all cases, which is similar to the results by Jalving et al. and Hassan et al. β-Catenin showed nuclear staining in a small proportion of cases of sporadic FGPD (22.5%). Jalving et al. demonstrated nuclear β-catenin staining in three of five FGPDs (two syndromic and one sporadic). No nuclear β-catenin staining was observed in the cases studied by Hassan et al. The lower nuclear β-catenin in our cases could be attributed to lack of high-grade dysplasia, the IHC having low sensitivity to detect nuclear translocation, or dysplasia developing before nuclear β-catenin translocation. Interestingly, when we compared the FGPD cases with nuclear β-catenin stain with those with normal membranous staining, the morphology was similar. Proliferation marker Ki-67 showed an increased nuclear staining in the surface epithelium and mucus neck stem cell region in the area of dysplasia. This is in contrast to the expanded regenerative zone of reactive cases without significant surface staining. The sporadic FGPs without dysplasia showed weak 1+ p53 staining, membranous β-catenin staining, and negative Ki-67 staining on the surface and mucus neck. Based on our study, p53 is not helpful in distinguishing dysplasia from nondysplastic sporadic FGPs. Ki-67 appears to be a more promising discriminator, the caveat being that increased Ki-67 nuclear staining was noted on the surface in a limited number of reactive cases. The β-catenin nuclear immunohistochemical staining in the sporadic FGPD cases along with the increased Ki-67 staining in the surface and mucus neck does further support the neoplastic nature of these polyps.

Follow-up EGD data were available in 26 (42%) of 62 cases with a time interval ranging from 1 month to 4 years (mean, 14.8 months). Nine patients had no additional polyps, 13 had sporadic FGP without dysplasia, and four patients had sporadic FGPD. None of the cases progressed to high-grade dysplasia or adenocarcinoma. Similar results were shown in a recent study by Arnason et al. with none of their 15 cases of sporadic FGPD progressing to a higher grade lesion. This supports the currently held view that sporadic FGPDs are indolent lesions with no malignant potential.

This study had both strengths and limitations. The retrospective nature of the study and the relatively short follow-up in a number of cases were unavoidable shortcomings of the study. On the other hand, the large patient population with EGD in our database, which allowed the analysis of a substantial group of patients with FGPDs, is one of the strengths of this work. In addition, the fact that all pathology reports were issued from a single group of gastrointestinal pathologists provided an additional guarantee that interobserver variability was minimized. This was further integrated by the authors’ consensus review of all cases initially suspected of having dysplasia and their application of rigorous criteria.

Conclusion

This is the largest series to date regarding sporadic FGPDs. Similar to sporadic FGPs without dysplasia, patients with sporadic FGPDs are more likely to be middle-aged patients with reflux and taking PPIs. Follow-up EGD in 42% of our cases supports the prevailing notion that these polyps do not progress. The lack of p53 overexpression in the sporadic FGPDs may explain why these polyps do not develop high-grade dysplasia or adenocarcinoma. Although these polyps are rare, correctly distinguishing these from gastric adenomas is very important given the lack of progression in sporadic FGPDs. In summary, recognition of the morphology and the presence or absence of dysplasia, coupled with the knowledge of clinical presentation, allows for accurate diagnosis and classification of these polyps and for proper follow-up of patients who are diagnosed with them.

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