Published in final edited form as:

Am J Surg Pathol. 2014 March ; 38(3): 389–393. doi:10.1097/PAS.0000000000000146.

Upper GI Tract Lesions in Familial Adenomatous Polyposis (FAP):

Enrichment of Pyloric Gland Adenomas and Other Gastric and Duodenal Neoplasms

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Abstract

Patients with familial adenomatous polyposis (FAP), an autosomal dominant cancer predisposition syndrome caused by mutations in the *APC* gene, develop neoplasms in both the upper and lower gastrointestinal (GI) tract. To clarify the upper GI tract lesions in FAP patients in a tertiary care setting, we reviewed specimens from 321 endoscopies in 66 patients with FAP. Tubular adenomas in the small bowel were the most common neoplasms (present in 89% of patients), although only 1 patient developed invasive carcinoma of the small bowel. Several types of gastric neoplasms were identified—65% of patients had at least 1 fundic gland polyp, and 23% of patients had at least 1 gastric foveolar-type gastric adenoma. Pyloric gland adenomas were also enriched, occurring in 6% of patients—this is a novel finding in FAP patients. Despite the high frequency of gastric neoplasms, only 1 patient developed carcinoma in the stomach. The very low frequency of carcinoma in these patients suggests that current screening procedures prevent the vast majority of upper GI tract carcinomas in patients with FAP, at least in the tertiary care setting.

Keywords

familial adenomatous polyposis; cancer screening; fundic gland polyp; pyloric gland adenoma

Familial adenomatous polyposis (FAP) is an autosomal dominant cancer predisposition syndrome caused by germline mutations in the adenomatous polyposis coli (*APC*) gene.^{1–3} Patients with FAP develop numerous adenomas of the colon and invariably develop carcinoma unless a colectomy is performed. In addition, patients with FAP also develop neoplasms of the upper gastrointestinal (GI) tract,^{3,4} but these lesions are less well characterized than those in the colon.

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Conflicts of Interest: The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

After the colorectum, the duodenum is the second most common site of polyps in FAP. Duodenal adenomas arise in most patients with FAP, and the lifetime risk of these adenomas is estimated at 100%.⁵ Consequently, FAP patients have a relatively high risk for duodenal adenocarcinomas.^{3,5}

Gastric lesions are also common in patients with FAP and consist mostly of fundic gland polyps (FGPs); however, approximately 10% of gastric polyps in FAP are reported to be gastric adenomas.⁶ As a result, all observers recommend upper tract surveillance in patients with FAP, although there are no uniform guidelines for implementation.⁶ As our institution has had a hereditary colorectal cancer registry since 1973, we have followed a large number of patients with FAP and thus have a large number of samples from FAP patients in our archives.

In the current study, we review our experience with upper tract polyps in FAP patients; as additional types of gastric polyps have been described since previous large histologic surveys of FAP patients, we evaluated whether our material contained types of upper tract polyps not previously known to arise in FAP patients.

MATERIALS AND METHODS

All upper GI biopsy specimens were obtained from patients in the Johns Hopkins Polyposis Registry. This registry was initially gathered in 1973 from a 6-state area of the mid-Atlantic and now contains >400 pedigrees with FAP. Patients with FAP treated at The Johns Hopkins Hospital over a 25-year period were identified by a computer search of the Department of Pathology archives. Specimens without neoplasms, polyps, or mass lesions were excluded as were patients with only a single biopsy at our institution. The remaining biopsy specimens were examined histologically to characterize the spectrum of neoplasms in the upper GI tract in patients with FAP.

RESULTS

Specimens from 321 endoscopies in 66 patients with FAP were identified and reviewed. These 66 patients were followed at our institution for an average of 10.8 years, and 15% of the patients were followed for >20 years (Table 1). These endoscopies identified 633 lesions that were examined histologically, and each patient had an average of 9.6 lesions over the course of their surveillance. The most common neoplasms were tubular adenomas of the small bowel—we identified 371 tubular adenomas, and at least 1 tubular adenoma was present in 59 of 66 patients (89%). Although tubular adenomas were common in the small bowel, only 1 case with high-grade dysplasia and 1 case with invasive carcinoma (in patients aged 61 and 37 y, respectively) were identified.

Gastric polyps occurred in the majority of patients in our cohort (Table 2). Gastric FGPs were the most common gastric polyp, with 203 total polyps and 43 of 66 patients (65%) with at least 1 FGP (Figs. 1, 2). The majority of the FGPs (66%) lacked dysplasia, and high-grade dysplasia was exceedingly rare (< 1%). In addition, several gastric foveolar-type gastric adenomas⁷ were also identified—43 adenomas were identified, affecting 15 of 66 patients (23%) (Fig. 3). Pyloric gland adenomas (PGAs) were also enriched in FAP patients—7

PGAs were identified in 4 patients (Fig. 4). Although PGAs were still uncommon in patients with FAP, they occurred at a higher frequency (6%) than in autoimmune gastritis, a condition previously reported to be enriched for PGAs⁸ ($P = 0.02$, χ^2 test). Other uncommon gastric polyps in our FAP cohort included gastric hyperplastic polyps (6 polyps in 4 patients) and intestinal-type gastric adenomas (1 polyp in 1 patient). Despite the variety of gastric neoplasms reported in this series of FAP patients, only 1 patient developed invasive gastric carcinoma at 39 years. The carcinoma in this patient was located at the gastroesophageal junction and was not associated with a precursor lesion; therefore, the relationship of the carcinoma to an FAP-related neoplasm cannot be determined.

DISCUSSION

In addition to the predicted frequent duodenal adenomas, our study of upper tract lesions in FAP identified several types of gastric polyps. As reported by others, we identified frequent FGPs and gastric foveolar type gastric adenomas. In addition, we also report the novel finding of increased frequency of PGAs in patients with FAP. Still, despite frequent gastric polyps, invasive gastric adenocarcinoma was rare in our cohort, with only 1 case of ambiguous etiology. This study allows us to examine the prevalence and natural history of gastric neoplasms in FAP, and the paucity of advanced lesions indicates that current screening procedures with removal of early lesions is sufficient to prevent progression to adenocarcinoma in these patients.

Fundic Gland Polyps

FGPs associated with FAP syndrome differ from sporadic FGPs in their epidemiologic, clinicopathologic, and genetic features. For example, FAP-associated FGPs occur in a majority of patients with FAP and show a more equal sex distribution than sporadic FGPs. They are also 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, whereas FGPs are rare in the non-FAP pediatric population. In addition, approximately 25% of FAP-associated FGPs demonstrate low-grade epithelial dysplasia.⁹ Although dysplasia in sporadic FGPs can occur, it is distinctly unusual.¹⁰ A retrospective histologic evaluation of several hundred sporadic FGPs at our hospital revealed <1% with low-grade dysplasia, and 1 of these cases was subsequently determined to be a member of an attenuated FAP family.⁹ Syndromic and sporadic FGPs differ genetically in alterations in genes of the Wnt signaling pathway, specifically *APC* and *CTNNB1* (which encodes β -catenin). Somatic, second-hit *APC* alterations precede morphologic dysplasia in many FAP-associated FGPs, indicating that FGPs arising in the setting of FAP are neoplastic lesions.¹¹ In contrast, sporadic FGPs without dysplasia have mutations in the gene encoding β -catenin (*CTNNB1*) but lack *APC* alterations,¹² whereas sporadic FGPs with low-grade dysplasia display *APC* alterations but usually lack mutations in *CTNNB1*.¹³

Despite the above differences, the natural history of sporadic and syndromic FGPs is surprisingly similar. 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 in fundic gland polyposis, have never been

reported to progress to gastric adenocarcinoma.^{10,12,13} Similarly, adenocarcinoma associated with fundic gland polypsis in patients with FAP is rare enough to be a reportable occurrence.^{14,15} Currently, upper endoscopic surveillance in patients with FAP is performed mainly to address the increased risk for duodenal adenocarcinoma (> 300-fold).³ The presence of dysplastic or nondysplastic FGPs is regarded as an incidental finding and virtually never requires surgical resection. Even surveillance of dysplastic FGPs remains controversial.

In the current study, we identified frequent FGPs, with at least 1 FGP occurring in 65% of patients. Intriguingly, patients with dysplastic FGPs were younger on average than those with nondysplastic FGPs. This argues against the possibility that dysplastic FGPs arise directly from nondysplastic FGPs and instead suggests that dysplastic and nondysplastic FGPs may arise through unique pathways in FAP patients.

Gastric Foveolar-type Gastric Adenoma

After fundic gland gastric polyps, the next most common type of stomach polyp in our cohort of FAP patients was gastric foveolar-type gastric adenoma. Abraham et al⁷ classified gastric adenomas as intestinal type, containing at least focal goblet cells and/or Paneth cells, and gastric foveolar type, lined entirely by gastric mucin cells, as shown on periodic acid-Schiff/Alcian blue staining. Intestinal-type adenomas are significantly more likely than gastric foveolar-type adenomas to show high-grade dysplasia, adenocarcinoma within the polyp, intestinal metaplasia in the surrounding stomach, and gastritis. Patients with intestinal-type adenomas are also more likely to have separate gastric adenocarcinomas. However, there is confusion in the literature regarding the natural history of these gastric polyps because essentially the same term (foveolar-type gastric dysplasia) has been used to describe a different type of polyp.¹⁶ In a Korean study, intestinal metaplasia was identified in the background mucosa in all cases of so-called “foveolar,” “hybrid,” and “adenomatous” dysplasia, and these polyps were all gastritis associated. Rather than using the previously discussed morphologic criteria, the authors of this study performed immunolabeling for mucins and found that their “hybrid” polyps with both intestinal and gastric foveolar differentiation were more aggressive than those with only intestinal-type differentiation.¹⁶ For pathologists practicing in the West, the Abraham criteria are most applicable and allow the pathologist to assign risk categories for gastric adenomas. As the “gastric foveolar-type adenoma” is rare, associated with *APC* alterations,¹⁷ unassociated with background pathology, and appears as an isolated sporadic lesion akin to a colonic sporadic adenoma, the patients are at low risk for progression to a more advanced lesion.¹⁸ In agreement with previous studies, patients with FAP in our institution (Western) tend to have the gastric foveolar type of gastric adenoma. It can be regarded as analogous to colorectal adenomas found in uninfamed mucosa and is presumably associated with biallelic inactivation of *APC*.

Because the diagnosis of both polyps relies on the presence of dysplastic foveolar epithelium, the distinction between FGPs with low-grade dysplasia and gastric foveolar-type gastric adenomas can be challenging. In the current study, we required the presence of dilated fundic glands underlying dysplastic foveolar epithelium to diagnose an FGP with

low-grade dysplasia. In the absence of dilated fundic glands, we considered dysplastic foveolar epithelium to be indicative of a gastric foveolar-type gastric adenoma. Although this method of distinction is not perfect, as it would incorrectly classify FGPs in which the dilated fundic glands were not sampled, we note that the distinction actually carries little clinical significance, as both lesions carry low risk for more advanced lesions.

Pyloric Gland Adenomas

The most interesting observation in this study is that gastric PGAs were more common in FAP than in autoimmune gastritis,⁸ although they were previously not appreciated in patients with FAP. These lesions were fully characterized in 2003 by Vieth et al¹⁹ and confirmed by our group.¹⁸ As most histologic studies of upper tract lesions in FAP patients were published before the recognition of PGAs, these lesions were presumably classified as other types of polyps in previous reports. PGAs are neoplastic polyps known to occur in the stomach, gallbladder, duodenum, and main pancreatic duct, essentially in any site in which pyloric metaplasia can arise. These polyps show a preference for the gastric body, and gastric examples show a remarkable female predominance. This female predominance occurs because many PGAs arise in patients with autoimmune metaplastic atrophic gastritis,^{18,19} which characteristically has ample pyloric metaplasia. In one study of gastric polyps in 461 patients with autoimmune gastritis, 143 patients had endoscopically identifiable lesions. The lesions (n = 240) consisted of 179 polyps (138 hyperplastic polyps, 20 oxyntic mucosa pseudopolyps, 18 intestinal-type gastric adenomas, and only 3 PGAs).⁸ As such, even in the setting of autoimmune gastritis, PGAs are rare.

Histologically, PGAs are composed of closely packed pyloric-type glands with cuboidal to low columnar epithelium showing pale or eosinophilic, “ground-glass” cytoplasm. Nuclei are round without prominent nucleoli. Foci of dysplasia/carcinoma are commonly encountered. High-grade dysplasia is seen in some cases, and invasive carcinoma is associated with 12% to 47% of the lesions, depending on the authors’ criteria for carcinoma. Using our criteria, the figure is probably closer to 10% to 15%. PGAs show coexpression of MUC6 (marker of pyloric gland mucin) and some MUC5AC (marker of foveolar mucin), and, in their pure form, they lack expression of MUC2 (marker of intestinal mucin) and CDX2. Although foveolar-type gastric adenomas show MUC5AC expression, they lack expression of MUC6 and MUC2.¹⁸ Some PGAs, however, show areas of transition from gastric to intestinal differentiation, and these foci may show immunolabeling with MUC2 and CD10.²⁰ As with other types of adenomas, complete excision of PGA with biopsy of the background flat mucosa is appropriate in these patients, as PGAs often arise in the setting of chronic mucosal injury. Of interest in patients with FAP, their PGAs arose in pristine rather than damaged oxyntic mucosa in our study. In the cases in which information about the polyp site was available, the PGAs in FAP patients arose in the gastric body and fundus, in keeping with the locations of both sporadic PGAs and those associated with autoimmune gastritis. In FAP patients, PGAs frequently co-occurred with FGPs and gastric foveolar-type gastric adenomas. As these other polyps occurred in previous, concurrent, and subsequent biopsies, there is no way to definitively exclude the possibility that the PGAs arose from another type of gastric polyp. Still, although their natural history cannot be definitely

determined from the data in this study, PGAs clearly represent distinct lesions, as pyloric differentiation is not seen in any other type of gastric polyp.

We investigated the clinical history to determine *APC* mutation status in all of the patients with PGAs and gastric foveolar-type gastric adenomas in the current study. Of these 17 patients, data on *APC* mutation were available for 10 patients. The mutations in *APC* did not cluster in any specific region of the gene in either lesion.

Gastric Adenocarcinoma

Despite the increased frequency of dysplastic FGPs and gastric adenomas in FAP, the risk for gastric adenocarcinoma is not significantly increased in Western FAP patients.³ This contrasts with studies of Asian patients with FAP, among whom the risk of gastric adenocarcinoma is increased approximately 3-fold.²¹ This low risk in Western FAP patients also contrasts with the much higher risk for gastric adenocarcinoma in non-FAP patients who have gastric 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, a major risk factor for sporadic gastric cancer. Most Western patients with FAP have normal gastric mucosa outside of any antral adenomas or body FGPs. In contrast, most patients with sporadic gastric adenomas have chronic atrophic gastritis (particularly *Helicobacter pylori*-mediated) that predisposes to gastric adenocarcinoma in the intestinalized gastric mucosa outside of the adenomas.

Although patients with FAP frequently develop neoplasms in the upper GI tract, on the basis of our data, current screening procedures with removal of suspicious lesions prevent the vast majority of carcinomas in these patients, supporting the importance of early screening and polyp removal in FAP patients. Our findings also confirm those of others: patients with FAP are likely to manifest small-bowel adenomas, gastric FGPs, and gastric foveolar-type gastric adenomas. However, in addition to FGPs and gastric foveolar-type gastric adenomas, patients with FAP are also predisposed to gastric PGAs, a novel finding in this study of upper GI tract lesions in FAP.

Acknowledgments

Source of Funding: Supported by NIH grant P50 CA 62924.

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FIGURE 1.
FGP. Like sporadic FGPs, syndromic ones display cystically dilated oxyntic glands.

FIGURE 2.

FGP with low-grade dysplasia. This syndromic FGP shows surface low-grade dysplasia in foveolar epithelium at the upper left of the field. Note the dilated gland in the center of the field.

FIGURE 3.

A gastric adenoma with pure gastric foveolar differentiation. Each cell has a crisply delineated apical mucin cap.

FIGURE 4.

PGA. Gastric pyloric adenomas often arise in damaged gastric mucosa in patients with autoimmune gastritis and gastric pyloric metaplasia. Those associated with FAP arose in normal oxyntic mucosa. These lesions show compact tubules, each containing a monolayer of round nuclei and ground-glass cytoplasm.

TABLE 1

Demographics and Follow-up of FAP Patients (n = 66)

	N (%)
Sex	
Male	26 (39)
Female	40 (61)
Race	
White	48 (73)
Black	12 (18)
Other/unknown	6 (9)
	Average (Range)
Age at first pathology specimen (y)	32 (10-62)
Age at last pathology specimen (y)	43 (16-73)
Total pathology follow-up (y)	10.8 (0-49)
Age at first upper endoscopy specimen (y)	37 (13-68)
Age at last upper endoscopy specimen (y)	42 (14-71)
Total upper endoscopy follow-up (y)	5.2 (0-22)

TABLE 2**Gastric Neoplasms in Patients With FAP**

Gastric Neoplasm	No. Polyps (n=261)	No. Patients (n=66) (N [%])	Mean Age at Diagnosis (y)	% Female	% Male
FGP	203	43 (65)	40	78	22
FGP, negative for dysplasia	134	38 (58)	43	76	24
FGP, low-grade dysplasia	67	24 (36)	35	82	18
FGP, high-grade dysplasia	2	2 (3)	32	100	0
Gastric foveolar-type gastric adenoma	43	15 (23)	34	81	19
PGA	7	4 (6)	47	81	19
Gastric hyperplastic polyp	6	4 (6)	52	100	0
Intestinal-type gastric adenoma	1	1 (2)	25	100	0
Carcinoma	1	1 (2)	39	0	100