

Gastric Lumps and Bumps: A tale of two polyps
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General Comments

The stomach is far less rich in polyps than is the colon. As a result, we know much less about gastric polyps than colonic polyps, and the literature tends to be much more recent and sparser. About 5 to 10% of biopsies of endoscopic gastric polyps are normal mucosa. The reasons for this include the biopsy forceps missing the lesion, an intramural lesion that is not available to endoscopic biopsy, normal mucosa that somehow turned into an endoscopic bump and finally the pathologist doesn't know a polyp when he or she sees one. There are about 10 named gastric polyps involving the mucosa including two surface adenomas, a deep adenoma, two heterotopias, juvenile and Peutz-Jeghers polyps, polyps with no names and no literatures and finally the two that will be discussed here, fundic gland polyps and hyperplastic polyps. From a clinician's standpoint, the main issue is whether the polyp is neoplastic, and if it is, then whether it is benign or malignant. If it is not neoplastic, then in general, there does not seem to be a great interest in polyp type, but we type it anyway. There are a few exceptions to this. It appears from our practice that there is so little interest on the part of the endoscopists in the mucosa adjacent to a polyp or in the mucosa in the rest of the stomach, that it is only biopsied infrequently.

The two common polyps, hyperplastic and fundic gland, have not been rigidly defined in the literature or in the textbooks, and as a result, we do not know their histologic limits.

Hyperplastic polyps

Historical perspective: During the 1960's and 1970's, the most common gastric polyp had three names from 3 different years, regenerative polyp in 1965¹, hyperplastic polyp in 1971² and hyperplaseogenous in 1973⁴. The hyperplastic designation won over the other two. In the early literature, these polyps were described as mainly single, although a few patients made multiples. Histologically, they had a complex surface architecture, deep cysts, and excess stroma. The architecture included coarse villiform changes on the surface, ulcers both in the flat and villiform areas, an edematous inflamed lamina propria, striking distortion of the pits, and glands did not participate. There were a variety of different types of epithelium including normal pit or foveolar epithelium, hypertrophic pit epithelium with huge distended goblet cells, and regenerative epithelium with the typical syncytial undifferentiated cytoplasm and vesicular nuclei that characterize regenerative epithelium everywhere. In some polyps, the epithelium is more atypical with elongated stratified nuclei, more frequent mitoses, and less cytoplasmic mucin. Intestinal metaplasia occurs, but is not a dominant component, and in one study from Japan, it was mentioned that the likelihood of finding intestinal metaplasia in the polyp was less than

finding it in the surrounding mucosa¹¹. Of course this comment was based on Japanese stomachs which commonly have intestinal metaplasia. I cannot find comparable information on intestinal metaplasia in United States stomachs with these polyps.

Hyperplastic polyps are said to occur in three settings. The first, the sporadic polyp is the most common. The second and third settings are based on the findings of somewhat similar changes in polypoid mucosa on the gastric side of a gastroenteric anastomosis, and on the top of the proximal-most gastric folds, originally described in refluxers, but also found in non-refluxers. It turns out that the anastomosis and proximal fold polyps never quite achieve the distortion, exuberance and stroma of the sporadic polyps, so it is questionable whether they are all the same.

Elster in 1976 stated that “hyperplastic polyps of the stomach have no counterpart in other parts of the gastrointestinal tract and are thereby organotypical”⁴. This was reemphasized by Hattori from Japan nine years later, and it is clear that this is a true analysis¹¹. We see occasional polyps in other sites, especially the colon, that have somewhat similar architecture and stroma, but they never quite look the same.

Is there a universally accepted, clear-cut definition of the hyperplastic polyp? In the literature and in the textbooks it becomes hardly any author ever actually defines it, but the authors do describe it, although the descriptions are not necessarily comparable. In one description from Stolte et al from Germany in 1995¹², a hyperplastic polyp was characterized by lengthening, tortuosity, and variable cystic dilatation of foveolae, widening of the stroma and edema, increased numbers and dilatation of the capillaries and apical erosions. However, this is a description and not a definition, and it does not tell us what features are required for the diagnosis of hyperplastic polyp and to what extent they must be present. As a result, whenever a study on hyperplastic polyps was published, it was not clear if the authors of those studies actually analyzed the same lesions. We also have no idea how the full-blown polyp develops. Does it start from a localized focus of pit expansion and stromal edema and inflammation or simply from a small polyp containing only elongated foveolae, a lesion which has been designated as focal or polypoid foveolar hyperplasia? Not only don't we know how this lesion evolves, but we have no clue as to what is the stimulus for its development. We don't know if it is inflammatory or neoplastic or a mixture. If we look at small lesions that have all of the architectural and stromal features, they appear to arise in the pit or foveolar compartment and look like they are tacked onto the surface. We must be aware of the possibility that since there are no minimal requirements for the diagnosis of hyperplastic polyp, a lot of things are thrown into that category that may not belong there, and some of these are presumably included in published studies of hyperplastic polyps. This is a common situation throughout not just pathology but medicine in general, namely a tendency to try to fit everything into existing categories, rather than separating them into categories that currently are not named.

There is a fact (or rumor) that hyperplastic polyps occur in inflamed stomachs^{13, 14}, as much as 40% with *Helicobacter pylori*, and others with atrophic gastritis including the autoimmune type. Reports also indicate that there may be additional chemical or reactive gastropathy, but this is so common in stomachs these days, that its significance is questionable. Data such as this suggests that these are inflammatory lesions, but we don't know that for a fact.

It is also stated that dysplasia occurs in anywhere from 1 to 20% of hyperplastic polyps, and this is size related with more dysplasia in larger lesions. Cancers have even been described in a very, very few polyps. There is clearly something wrong with data that puts anything between 1 and 20%. The inflammatory and dysplastic data had been based on studies of a polyp that had and still has no minimal diagnostic criteria and also on publications some of which are based on studies including only whole intact polyps and on other studies that included biopsies as well which potentially introduced sampling problems.

What separates low-grade dysplasia from regenerative epithelium in these polyps is exactly the same thing that separates low-grade dysplasia from regenerative epithelium everywhere else in the gastrointestinal tract. It is sometimes impossible to tell which kind of epithelium is present. These polyps are sitting in stomachs that contain a lot of solid material and which have churning and mixing motility activities, so these polyps are probably banged around a lot. Therefore, whatever the authors call this epithelium is what it gets published as, and perhaps this accounts for the dysplasia rate that varies from 1 to 20%. Furthermore, is there anything that separates a hyperplastic polyp with dysplasia from an adenoma with secondary hyperplastic polyp changes? We have seen some adenomas in which fairly extensive hyperplastic polyp-like changes involve the surface. Biopsies may exacerbate this distinction because of sampling.

The neoplastic associations, regardless of how we interpret the data, color surveillance recommendations. For instance, the American Society for Gastrointestinal Endoscopy has published guidelines in 2006 that are available on its website (www.ASGE.org). These guidelines state that the polyps should be endoscopically excised wherever feasible and clinically appropriate. No surveillance endoscopy is necessary after adequate sampling (there is no definition of adequate sampling) or removal of nondysplastic polyps. Topographical biopsy “mapping” may be useful to detect the presence of gastritis and intestinal metaplasia.

Topographical biopsy mapping is not done at our institution. I am sure that there are institutions where it is the rule, but I don't even know that for a fact.

Summary: we do not know what hyperplastic polyps are, what causes them, what their precursors are, and there are no minimal criteria for diagnosis. It is not clear that all hyperplastic polyp studies have actually studied the same polyps, so the results of these studied probably should not be pooled for analysis. The dysplasia/carcinoma risk is not settled. Nevertheless, we will keep trying!

Fundic gland polyps

General Comments: Beginning in the 1970's we started seeing another gastric polyp which also had little published information. This is what we now call a fundic gland polyp (FGP). These days it is the most common of all gastric polyps, probably 7 to 1 over its closest competitor, the hyperplastic polyp. Sometimes these are part of a syndrome, familial adenomatous polyposis, that includes cancers, but cancers for all intents and purposes don't occur in fundic gland polyps. They also tend to carpet the fundus in the body, especially in the patients with FAP. As with hyperplastic polyps, they also appear to be tacked onto the top of the normal oxyntic mucosa indicating that they have developed within the pit compartment.

Historical perspective: It appears that the first recognition or name for fundic gland polyp was by Elster in 1976. He referred to these as “cysts of gastric glands”, and then a year later he changes the name to “fundic gland cysts”^{4,15}. These were described as “fundic glandular cysts in otherwise normal gastric mucosa”. However, an analysis of the illustrations in his papers indicates that this otherwise normal gastric mucosa is really not normal but the superficial glands are disorganized, clustered, often budding and branching. Watanabe from Japan in an analysis of gastric lesions in FAP may have been the first to use the fundic gland polyp designation¹⁶. In his paper, there was no definition of fundic gland polyp, just many illustrations and descriptions such as “simple hyperplasia of fundic glands”. Actually, it is difficult to recognize any hyperplasia, since there are fewer glands per unit area in FGPs than in normal oxyntic mucosa. What was mentioned in Watanabe’s paper was the fact that the glands were irregular, tortuous, sometimes branching; that is, they were disorganized. Before the Elster and Watanabe papers, we only recognized two types of gastric polyps, adenomas and hyperplastic polyps. Fundic gland polyps were probably included in the mix. We did not recognize them as separate, so we probably called them hyperplastic, since they did not look like adenomas. They don’t have adenoma-like dysplasia.

Diagnostic criteria: In the twelve months from August, 2005 through July, 2006, four pathologists in the gastrointestinal subspecialty sign-out service at the University of Michigan made the diagnosis of fundic gland polyps in 306 patients, 16 of whom had familial adenomatous polyposis. The age distribution of patients with these polyps corresponds to the age of the patients who were biopsied during upper endoscopy. There were twice as many women as men, but this has been found in other studies. Regardless, when I asked my colleagues, and even myself how to define a fundic gland polyp and to list the minimal diagnostic criteria, there was no consensus. Nevertheless, I showed them several polyps which had a variety of changes including short pits, long pits, clusters of glands beneath the surface that varied from area to area, cysts, some of which were gland cysts, some pit cysts and some mixed cysts, and expanded lamina propria which often had a lot of smooth muscle. Everybody diagnosed them as fundic gland polyps, and the basic reasons for diagnosis boiled down to “because they look like it”. I showed the same polyps to a bunch of our house officers and they came up with the same diagnosis for the same reason. Therefore, we seem to know what a fundic gland polyp looks like, and we can teach other people how to recognize it, but we have a great deal of difficulty defining what it is leads us to that diagnosis.

As was true for hyperplastic polyps, there are no published minimal criteria that will allow a bump in the gastric oxyntic mucosa to be called a FGP. A look at the literature and in the textbooks and even in the World Health Organization Classification of Tumors published in 2000, the definitions are anything but uniform.

The Appelman Approach: FGPs for dummies (for what it is worth): FGPs are architecturally complex but cytologically simple lesions. They are architecturally complex in that the entire mucosa is structurally altered when compared to normal, and they are cytologically simple because all cells are mature gastric epithelial cells. Perhaps because of this combination, they have been referred to as hamartomas. There are two sets of architectural abnormalities, epithelial and stromal. The intensity of these changes varies greatly from one polyp to another. The epithelial architectural alterations involve both the pits and the glands. The pit changes involve length. In most areas of these

polyps, the pits are shorter than normal, but in some polyps, they are longer. Pits also extend deeply into the mucosa and form cysts. The gland changes are more complex and include clusters of glands beneath the surface, parietal cells in the upper parts of the pits or even on the surface, glands with irregular branches and buds, and cystic glands toward the middle and deeper parts of the polyps. Actually, there are many cysts that have a mixture of pit and gland epithelium. The stromal changes include an increase in the amount of lamina propria when compared to normal oxyntic mucosa. This bonus stroma may be edematous, may have inflammation, and often has smooth muscle bundles, probably not extending from the muscularis mucosae, considering that these polyps are tacked onto the surface. The bigger the polyp, the larger the number and size of the cysts. This suggests that these polyps enlarge by an increase in number and size of cysts.

Fundic gland polyps are said to occur in three settings. First are those that are associated with familial adenomatous polyposis, in other words in patients with a germline mutation in the FAP gene. Second are sporadic polyps, that is, not in FAP patients, but occurring in people who are not taking proton pump inhibitors. Third are sporadic polyps occurring in patients who have been treated with proton pump inhibitors.

Genetic Changes: The polyps in different patients with FAP do not look the same, but neither do the polyps from single FAP patients. However, they all have variations on the same abnormalities including pit and gland architecture and lamina propria changes. In one study on FAP patients with known germline APC gene mutations, APC gene alterations were found in at least one polyp in 9 of these 11 patients, but not all polyps from individual patients had the detectable gene alterations²³. Conceivably, this variation may be due to the fact that this is a 9-year-old study, and there may be better detection systems now. Furthermore, no individual patient had more than one APC gene alteration in the polyps.

Genetic changes were also analyzed in sporadic fundic gland polyps that have no APC gene defects. In one study from the USA, 52 of 57 polyps from 40 patients have beta-catenin mutations²⁴. In this study, there was no mention if the patients were taking proton pump inhibitors. In another study from Japan, 29 of 45 such polyps from 35 patients had the beta-catenin mutation, and none of these patients were on long term proton pump inhibitors²⁵. In both these studies, the mutations were found in both the pit epithelium and in the gland cyst epithelium in almost all polyps, and different mutations were found in different polyps from the same patients, in contrast to the findings of the FAP patients. In another study of patients taking proton pump inhibitors, CpG island methylation was found to be more common in sporadic polyps, but we have not had any data since the publication of that study 6 years ago²⁸.

Do proton pump inhibitors cause FGPs? Twenty years ago these polyps were curiosities, but there has been a striking increase in incidence that seems to coincide with the increased use of PPIs. The data regarding cause and effect are conflicting. In one study from the USA, two groups of patients were compared, a larger group not taking proton pump inhibitors who only had a single upper endoscopy, and a smaller group taking PPIs who had both an initial exam and a follow-up exam if they had no polyps at the first exam²⁰. Comparing these two groups, FGPs were much more common in the PPI group, but so were other polyps, and in this study, there was no second endoscopy for the group not taking PPIs. Also, FGPs were described simply as composed of cystic fundic glands, nothing more and nothing less.

The second study from Germany compared over 28,000 patients not taking PPIs with over 2200 patients on the drugs, and the prevalence of FGPs was identical²². We do know that PPIs induce hypertrophy of parietal cells with formation of apical snouts, and they also induce fundic gland cysts. Both of these changes appear to increase with increasing length of time the patients are taking PPIs. Both of these changes appear to be secondary to the hypergastrinemia that results from inhibition of gastric acid production by the drugs.

FGPs contain many parietal cells. The parietal cells in the polyps seem to respond to PPIs as do the native parietal cells, namely they undergo hypertrophy and develop snouts. Perhaps PPIs do not cause FGPs, but they may make tiny ones bigger and endoscopically apparent as a result of the parietal cell hypertrophy and increase in gland cysts²¹.

Finally, there is some literature suggesting that in patients with fundic gland polyps, there is an increased risk for colonic adenomas and carcinomas. However, the studies do not all come to the same conclusion^{9, 30}. In a recent study, FGPs were associated with increased prevalence of hyperplastic colonic polyps in men and colonic adenomas in women mainly over 60 years of age, but there was no increased association with adenocarcinoma.

Summary: Fundic gland polyps occur in familial adenomatous polyposis but also spontaneously, and their incidence has increased at the same time as has the use of proton pump inhibitors. They are architecturally complex and cytologically simple polyps. There is no proof that PPIs induce polyps with the same architectural complexity that occurs in FAP patients. The parietal cells in FGPs respond to PPIs exactly like parietal cells in flat mucosa. This may make some tiny FGPs enlarge and become endoscopic polyps. Genetic abnormalities have been found in both FAP and sporadic FGPs, and there may be some alteration in PPI associated polyps. The association between FGPs and colonic neoplasia is not clearly established. Finally, until we have a rigid definition of the minimal criteria for a fundic gland polyp, we will have no clue as to whether PPIs or anything else cause them.

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