

**GASTRIC LUMPS AND BUMPS:
NO POLYP IS AN ISLAND**

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INTRODUCTION

Most specimens received in the pathology laboratory as “gastric polyp” have distinctive features that allow their easy categorization into one of the major established classes of epithelial (hyperplastic, inflammatory, fundic, or adenomatous) or stromal proliferations. Common wisdom, embraced even by many modern textbooks of gastrointestinal pathology, holds that while adenomas have a high cancer risk and are frequently associated with synchronous adenocarcinomas, the malignant potential in hyperplastic polyps is very low and it is virtually absent in sporadic fundic polyps. As a consequence, the histopathological diagnosis of gastric adenoma may result in the inclusion of the patient into an endoscopic surveillance program, whereas no further workup and often only a limited follow-up is the usual clinical response to a diagnosis of hyperplastic, inflammatory, or fundic polyp.

Several studies published in the last few years suggest that this may be an oversimplification. Other types of gastric polyps display molecular alterations that may lead to neoplastic pathways, and may carry unappreciated risks. More questions must be asked and more extensive investigations may be warranted in some patients with other types of gastric polyps. The objective of this presentation is to discuss the possible significance of this recent body of information, particularly from the viewpoint of the practicing surgical pathologist.

CLASSIFICATION AND KEY FEATURES OF GASTRIC POLYPS

To ensure a uniform understanding of the terminology used here, this section briefly outlines the main characteristics and the generally accepted views of the three entities considered. Potentially relevant diagnostic and management issues raised by more recent findings are discussed in the subsequent sections. For the complete classification of gastric polyps followed here the reader is referred to Odze’s 2004 Textbook of Surgical Pathology of the GI Tract ¹.

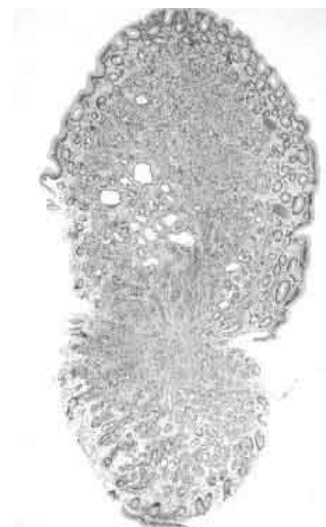
Hyperplastic polyps (Synonyms: Inflammatory, regenerative): they represent 70% to 80% of all gastric polyps, and arise most frequently on the background of an inflamed gastric mucosa. They are believed to originate as hyperproliferative responses to tissue injury; foveolar hyperplasia may be the elemental lesion. They are composed by elongated, grossly distorted, branching and dilated hyperplastic foveolae lying in an

edematous stroma rich in vasculature, and small, haphazardly distributed smooth muscle bundles; they contain varying degrees of chronic and active inflammation and granulation tissue. Hyperplastic polyps are usually small, measuring 0.5 - 1.5 cm in diameter, but may occasionally reach much larger dimensions. They are often multiple. Frequently, areas of the surface epithelium are eroded; this may result in chronic blood loss and iron-deficiency anemia, one of the most common clinical manifestations of hyperplastic polyps of the stomach. The prevalence of dysplasia has been reported to range from 1% to 20%, generally, but not in all series, more frequent in larger polyps². The overall malignant potential of hyperplastic polyps has been estimated to be less than 2%. Polypoid foveolar hyperplasia, gastric foveolar polyps and gastritis cystica polyposa (characteristic of post-Billroth I and II gastric stumps) may be considered variants of the same basic hyperproliferative foveolar lesion.



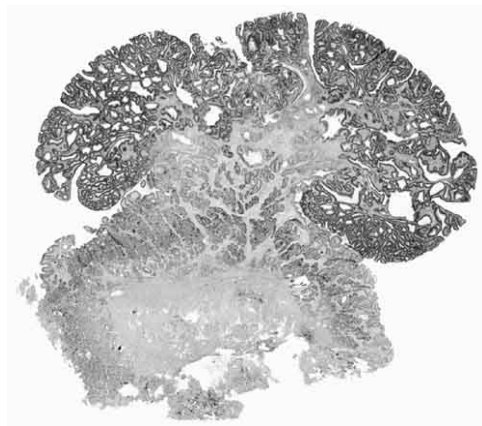
Gastrosopic view of an antral bleeding hyperplastic polyp

Fundic gland polyps: often classified as hamartomatous lesions, fundic gland polyps (generally referred to as “fundic polyps”) consist of smooth sessile circumscribed elevations (usually measuring < 0.5 cm) in the oxyntic mucosa. The basic lesion is one or more cystically dilated oxyntic gland. They may occur sporadically, in association with long-term use of proton-pump inhibitors (PPI), and in the familial adenomatous polyposis (FAP) syndrome. Although dissenting opinions have been published, sporadic and PPI-associated fundic polyps are traditionally believed to have neither malignant potential nor ominous associations; a “minimal” cancer risk is often mentioned for FAP-associated fundic polyps.



Low-power view of a fundic gland polyp, showing a few dilated oxyntic glands

Adenomas: gastric adenomas may occur sporadically and in association with FAP. Only the former are discussed here.



Pedunculated gastric adenoma

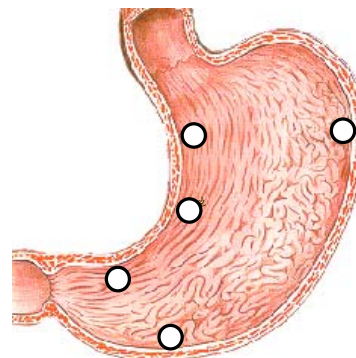
Adenomas are defined here as circumscribed, pedunculated or sessile proliferations of dysplastic epithelium without detectable invasion of the lamina propria. For the controversies that have arisen between Japanese and Western pathologists with regards to the distinction between adenoma and adenocarcinoma, the reader is referred to the

Padova³ and Vienna Classifications⁴ and to a historical accounts of the issue⁵. Sporadic gastric adenomas may be viewed as one of the possible steps in the development of adenocarcinoma: both arise most often on a background of chronic atrophic metaplastic gastritis; they share a common epidemiological pattern; the larger an adenomatous polyp the greater the probability that it contains foci of adenocarcinoma; and a synchronous adenocarcinoma in another area of the stomach has been found in up to 30% of patients with an adenoma. Most adenomas occur in the antrum and they are detected when they are solitary (~80%) and measure less than 2 cm.

CLINICO-PATHOLOGICAL CORRELATIONS

To paraphrase somewhat blasphemously John Donne, no polyp is an island. Gastric polyps (like gastric cancer) rarely if ever arise in a normal stomach. Although most gastroenterologists are aware of this, a thorough search for the background on which gastric polyps arise is uncommonly performed at the time the polyp is discovered. A few years ago, when *H. pylori* was suspected to be the cause of almost every possible gastric and extra-gastric ailment, a colleague and I designed a simple retrospective study aimed at determining the type of gastritis found at the time a gastric polyp was removed. Being in a large medical center with a digestive diseases division that was very active in clinical research and had been the foster home to the Updated Sydney System (the real home being in Pathology!), we assumed that virtually every polyp would be accompanied by a set of representative biopsy specimens from the rest of the stomach. Although the exact figures are now forgotten, no more than one third of the one hundred-something polyps removed in the previous five years had any synchronous biopsy specimens, and in less than 10% of the cases was a topographically defined set of specimens available.

Clearly, the study could not be carried out. I suspect that the situation is not very different in most other centers, and it is perhaps our responsibility as pathologists to deliver the message to our clinical colleagues: for an accurate and perhaps even predictive diagnosis of gastric polyps, let us have a good look at the rest of the gastric mucosa.



The five biopsy mapping sites recommended by the Updated Sydney System

Hyperplastic polyps

H. PYLORI, AND CHEMICAL INJURY

Foveolar hyperplasia is a compensatory response to increased cellular exfoliation from the surface epithelium that can be viewed as a visual surrogate for increased epithelial cell turnover^{6,7}. While greatly hyperplastic foveolae are easily recognized, lesser degrees of foveolar elongation and increased tortuosity may not be apparent. As an empirical tool, it has been suggested that if more than four cross sections of the same pit are seen in a well-oriented gastric biopsy specimen, one can confidently diagnose foveolar hyperplasia⁸. The diagnosis of hyperplasia is also facilitated by the finding of

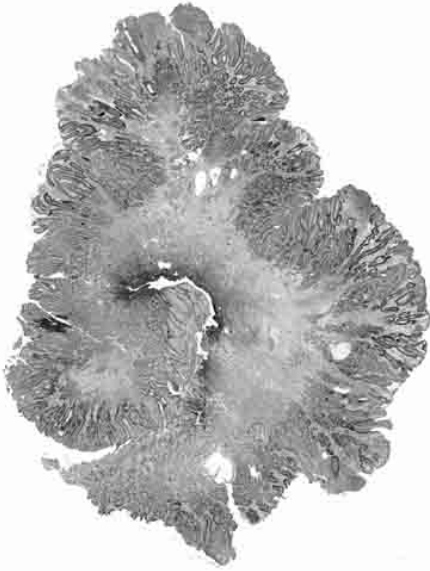
hyperchromatic nuclei and mitotic activity reaching an increased height of the pit, and by signs of cellular immaturity (mucin depletion, a cuboidal shape, and a high nucleocytoplasmic ratio). Foveolar hyperplasia has long been recognized as a prominent feature of bile reflux gastritis⁶. More recently, hyperplasia it has been emphasized as a key feature of the gastropathy associated with long-term NSAIDs treatment⁸. Lesser degrees of hyperplasia are commonly seen in *H. pylori* gastritis, but when hyperplasia is marked and diffuse it suggests co-existent chemical injury⁹.

These two broad categories of conditions (chronic active gastritis caused by *H. pylori* and chemical injury) are the ones most commonly associated with hyperplastic polyps. In *H. pylori* gastritis (or in patients who may have had a long-standing *H. pylori* gastritis that progressed to atrophy with neither activity nor detectable bacteria) extreme focal foveolar hyperplasia, perhaps in response to a localized more severe injury (erosion, superficial ulcer) may evolve into an agglomerate of highly hypertrophic foveolae, and the long-standing processes of inflammation, repair, and proliferation result into the features of a hyperplastic polyp: grossly distorted, long, dilated pits, inflammation, granulation tissue and erosions. Removal of the injury (*i.e.*, eradication of *H. pylori*) has been shown to cause the regression of hyperplastic polyps in a high proportion of patients (up to 70% in one study)¹⁰.

A histologically similar picture, but usually associated with larger and more expansive lesions, can be found in areas adjacent to gastrojejunostomy stomas. The initial step is likely foveolar hyperplasia in response to pancreaticoduodenal secretions as well as acids, bile salts, and lysolecithin, the last being produced by the action of phospholipase in pancreatic juice on the lecithin in bile. Duodenogastric reflux results in disruption of the mucus barrier and the direct action of chemicals on the surface epithelium. Loss of the mucous barrier allows back-diffusion of hydrogen ions and secondary injurious effects¹¹. The combined injury leads to accelerated exfoliation of surface epithelial cells and a histamine-mediated vascular response that manifests as edema and hyperemia. Repetitive injury may lead to the release of other pro-inflammatory agents, such as platelet-derived growth factor, which among its many actions stimulates smooth muscle and, later on, fibroblastic proliferation⁷. The first macroscopically visible lesion is polypoid foveolar hyperplasia, which may evolve into the large masses of hyperplastic polyps found in some patients at the gastrectomy site.

FROM HYPERPLASIA TO CARCINOMA

Both isolated hyperplastic polyps and the polypoid aggregates found at gastrectomy sites have a low but definite potential for the development of malignancy. Between 1% and 20% of hyperplastic polyps have been found to harbor foci of dysplasia; furthermore, mutations of the *p53* gene, chromosomal aberrations, and microsatellite instability have been detected in these polyps¹²⁻¹⁶. In the presence of such a wide array of evidence supporting the biological plausibility of a neoplastic evolution, what should the pathologist's attitude be?



Hyperplastic polyp

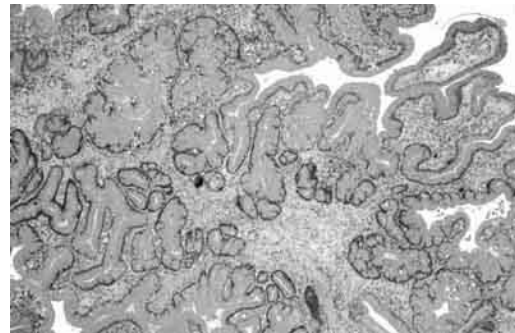
A PRACTICAL APPROACH TO HYPERPLASTIC POLYPS

Two considerations may help put these potentially worrisome findings into perspective. First, the polyp under examination is no longer in the patient; if dysplasia, or even non-invasive carcinoma, is present, it has been removed and cured. Second, the molecular studies carried out so far were designed to acquire insights into possible neoplastic mechanisms, not to develop predictive tests: thus, in the clinical setting the performance of immunostains to detect p53 accumulation or microsatellite instability (both easily available and accurate) or gene arrays, would yield results that can neither be interpreted nor used.

More important, in my view, is to be able to evaluate the stomach in which the polyp has arisen. When a hyperplastic polyp of any size with or without dysplasia (by far the more

common occurrence) is diagnosed, the gastroenterologist should be personally informed and, unless one has been done recently, a full set of topographically defined biopsy specimens (“gastric mapping”) needs to be obtained. If *H. pylori*-gastritis is present, eradication is warranted, with a follow-up endoscopy after a few months to monitor not only the successful eradication of *H. pylori*, but also the possible recurrence of polyps. If extensive atrophy and metaplasia are found, the patient should be considered at risk for gastric cancer, the polyp could be viewed as an alarming lesion, and an individualized surveillance plan (for which guidelines do not exist as yet) should be implemented¹⁷. If the polyp is obtained from a gastrectomy site, in the absence of dysplasia, the optimal management remains uncertain.

Although the European literature has emphasized a high risk for gastric stump cancer, particularly after Billroth I operations¹⁸, a landmark study conducted in the Netherlands revealed a 0.2% overall incidence of adenocarcinoma in post-gastrectomy patients followed for 15 to 46 years. In North America, although case reports and calls for surveillance are occasionally published, a low incidence of cancer has generally been found^{19,20}.



Dilated convoluted glands characteristic of hyperplastic polyps

Fundic polyps: a distant connection

The dilated oxyntic glands that form the small mucosal bumps in the mucosa of the gastric corpus are unlikely candidates for the development of malignancy. The epithelium is that of a mixture of flattened oxyntic, chief, and mucous cells. Dysplastic changes are virtually never seen, although some authors have insistently disputed the entirely benign nature of these polyps²¹.

An association of FAP-associated fundic polyps with colonic neoplasia is not unexpected, since in that nosological context the two are expressions of the same inherited condition.

In the last few years, there have been several reports of patients with sporadic fundic polyps and a colorectal neoplasia (adenomas or carcinomas), and a number of investigators have conducted both retrospective and prospective studies to better define the strength of the association. The conclusions of the most recent of these studies¹⁵ are astonishing: 29 of 64 patients (45.3%) with sporadic fundic polyps had colorectal neoplasia (including 8 adenocarcinomas, 3 adenomas with intraepithelial neoplasia, and 18 tubular adenomas). In the control group, similar in size and demographic characteristics, only 6 patients (9.3%) had adenomas. Although there may be considerable methodological problems with the study (judging from the information available in the article), the authors' conclusions ("Our results suggest that it is necessary to conduct a careful diagnostic work-up of the colon in patients with gastric fundic gland polyps") should be taken seriously. It is certainly worthwhile to carry out larger rigorously designed studies in different populations to explore this puzzling association.

Another interesting and potentially important finding is the recent discovery that a significant proportion of sporadic fundic polyps (even those arising in apparent response to long-term PPI use) of have genetic alterations involving beta-catenin stabilization, as do those associated with FAP^{22,23}. Abnormal expression of the E-cadherin/catenin membrane complex is common in esophageal adenocarcinoma (as well as in other tumors) and occurs early in the dysplasia/carcinoma sequence in Barrett's esophagus, indicating that disturbances in this cell adhesion complex might be important in tumorigenesis and tumor progression in this disorder²⁴. The significance of these findings in fundic polyps may not yet be apparent, but the view that these polyps are completely devoid of malignant potential may deserve a second look.

The pathologist's role in after the diagnosis of a fundic polyp is limited. No specific studies are warranted on the polyps themselves. However, particularly in the case of multiple polyps, alerting clinicians about the possibility of FAP and reminding them about the possible connection with colorectal neoplasia may be appropriate. If other biopsy specimens from the corpus are available, the telltale signs of chronic PPI use (dilated oxyntic glands, protruding hyperplastic oxyntic cells, and *H. pylori* located in the lower portions of the glands as well as within the oxyntic cell canaliculi) should also be reported, suggesting that the fundic polyps may be related to pharmacological acid suppression.

Adenomas and the goblet of mucus

The approach to gastric adenomas has not been changed significantly by molecular studies that have confirmed its neoplastic nature. One of the most interesting recent studies reports that the distinction of the type (“intestinal” versus “gastric”) may further define the cancer risk (greater in the former)²⁵. In the presence of adenomas, however, irrespective of their cellular make up, a complete gastric bioptic mapping is necessary to determine the phenotype of gastritis on which the adenoma arises. As stated above, metaplastic atrophic gastritis with an adenoma is an indication for an aggressive surveillance program.

SUMMARY

No published guidelines exist for the managements of most types of gastric polyps. Since cancer risk in these heterogeneous patients has not been quantified, the pathologist can influence clinicians’ attitudes and ultimately benefit their patients by suggesting extensive biopsy protocols that elucidate the status of the gastric mucosa and help make informed decisions on the design of individualized follow-up protocols.

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