Management of Gastric Polyps: An Endoscopy-Based Approach

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The endoscopic finding of a gastric polyp and the histopathologic report that follows may leave clinicians with questions that have not been addressed in formal guidelines: do all polyps need to be excised, or can they just be sampled for biopsy? If so, which ones and how many should be sampled? What follow-up evaluation is needed, if any? This review relies on the existing literature and our collective experience to provide practical answers to these questions. Fundic gland polyps, now the most frequent gastric polyps in Western countries because of widespread use of proton pump inhibitors, and hyperplastic polyps, the second most common polyps notable for their association with gastritis and their low but important potential for harboring dysplastic or neoplastic foci, are discussed in greater detail. Adenomas have had their name changed to raised intraepithelial neoplasia and are decreasing in parallel with Helicobacter pylori infection; however, they do retain their importance as harbingers of gastric cancer, particularly in East Asia. Gastrointestinal stromal tumors have low incidence and no known associations, but their malignant potential is high; early diagnosis and proper management are crucial. Although rare and benign, inflammatory fibroid polyps need to be recognized, particularly by pathologists, to avoid misdiagnosis. Gastric neuroendocrine tumors (carcinoids) are important because of their association with either atrophic gastritis or the multiple endocrine neoplasia syndromes; those that do not arise in these backgrounds have high malignant potential and require aggressive management. The review concludes with some practical suggestions on how to approach gastric polyps detected at endoscopy.

Keywords: Gastric Polyps; Endoscopic Management.

A gastric polyp is an abnormal growth of tissue projecting from the gastric mucosal membrane. Encountering a polyp in the stomach prompts concerns regarding its histology, cause, natural history, and whether specific therapy is required. During the past few decades, North America and much of the world have experienced a marked decrease of Helicobacter pylori–related gastroduodenal diseases; during the same period, the use of proton pump inhibitors (PPIs) has become widespread. Furthermore, the indications for esophagogastroduodenoscopy (EGD) have undergone a shift, with a greater emphasis on the evaluation of gastroesophageal reflux disease and the prevention of esophageal adenocarcinoma related to Barrett’s esophagus. As a result of these new paradigms, the findings encountered at EGD have changed substantially.

In North America and the industrialized West these changes have affected both the incidence and the types of gastric polyps. The overall incidence of polyps appears to have increased, as indicated by a higher prevalence in large series. There also has been a shift in the relative proportion of the different types of polyps: the clinically inconsequential fundic gland polyps have become the dominant type, while growths traditionally associated with H pylori gastritis (eg, hyperplastic and adenomatous polyps) have become less common. In contrast, in East Asian, Latin American, and possibly African populations, where H pylori infection and chronic gastritis remain common, larger proportions of gastric polyps are related to the underlying inflammatory process and are either hyperplastic or neoplastic. Despite these geographic differences, the finding of gastric polyps, particularly when numerous, will make clinicians in all regions face similar quandaries: which polyps need to be excised? Which ones and how many should be sampled for histologic evaluation? Also, what follow-up evaluation is needed?

This review attempts to provide practical answers to these questions. Although it relies largely on prevalence data derived from North American and European populations, its recommendations regarding natural history, clinical approach, and follow-up evaluation are based on the natural history of each type of polyp, which is determined largely by its histology and the gastric mucosal background on which it arises. Such features are independent of prevalence and, therefore, have universal validity.

Polyps that reveal a malignancy upon histopathologic examination lose their polyp status, irrespective of their initial endoscopic appearance, and we have excluded them from this review. Furthermore, because it is impossible to be simultaneously practical and comprehensive, we also had to neglect...
lesions (eg, lipomas, heterotopias, and leiomyomas) because they are unlikely to cause clinical dilemmas.

**Fundic Gland Polyps**

Fundic gland polyps are the most common type of polyps detected at EGD in Western countries. In a large recent pathologic study, fundic gland polyps were diagnosed in approximately 6% of patients who had an EGD and represented 74% of all gastric polyps submitted for histopathologic evaluation. Endoscopically, fundic gland polyps are usually multiple, small (<1 cm), and appear smooth, glassy, and sessile. By narrow band imaging they have a honeycomb appearance with dense vasculature, a nonspecific pattern that also can be seen in hyperplastic polyps.

When first discovered, fundic gland polyps were believed to be hamartomatous. However, their association with PPI use, confirmed in a number of studies, suggests that mechanisms related to the suppression of acid secretion by proton pump inhibition may be involved in their pathogenesis.

**Histopathologic Features and Diagnostic Criteria**

Histologically, fundic gland polyps consist of one or more dilated oxyntic glands, lined by flattened parietal and mucous cells (Figure 1). Fundic gland polyps are among the most characteristic lesions of the stomach: the recognition of the dilated oxyntic glands with flattened parietal and mucous cells in slides stained with H&E is immediate and unequivocal (Figure 1B and C). One caveat is that when the surface of a polyp is eroded the regenerative appearance may be misinterpreted as dysplasia. True dysplasia, particularly high grade, is exceedingly rare and is virtually limited to fundic gland polyps found in patients with polyposis syndromes. No special stains or molecular studies are warranted.

**Clinical Approach**

The finding of multiple characteristic polyps in the oxyntic portion of the stomach in a patient taking PPIs is essentially diagnostic of fundic gland polyps. Generally, when first encountered, one or more representative polyps should undergo a biopsy examination to confirm the diagnosis. Large polyps (>1 cm in diameter) should be removed entirely to confirm the diagnosis because fundic gland polyps rarely exceed this size. A biopsy specimen from the polyp in these cases is not adequate because if the polyp is not of the fundic gland type, biopsy sampling may not include crucial areas of possible dysplasia or neoplasia. In addition, a thorough visual inspection of the remaining polyps should be made; any lesion that appears significantly different from the others should be undergo a biopsy examination, or, if possible, be removed. Specifically, size larger than 1 cm, ulceration, and unusual location such as the antrum should prompt a more aggressive approach. When fundic gland polyps are found in a young patient, especially if numerous (eg, ≥20), the possibility of a polyposis syndrome should be considered. Individuals with familial polyposis syndromes typically are younger than the average patient with fundic gland polyps (mean age, 40 y), and occasionally have polyps in the antrum. When gastric polyps are associated with duodenal adenomas a familial polyposis syndrome strongly should be considered and colonoscopy should be recommended.

Fundic gland polyps rarely are found in stomachs affected by H pylori infection and, therefore, in the absence of a familial polyposis syndrome, concerns about gastric cancer are moot. Nonetheless, when polyps are innumerable or large (>1 cm)
there may be cause for concern regarding eventual outcome. Although no guidelines exist, we suggest that when either more than 20 polyps are present or their size is larger than 1 cm one should consider reducing or preferably stopping the medication to assess whether this will result in regression of the polyps. If regression occurs, it is unknown whether PPIs can be re instituted. Practically, if surgical therapy is not an option, one might consider a different PPI and at the minimally effective dose. Although there does not seem to be a correlation between serum gastrin levels and the presence of fundic gland polyps, it may be worthwhile to measure gastrin levels in these patients. A high level (>400 pg/mL) suggests profound acid suppression. If the patient is not an intrinsic hypersecretor and does not have a gastrinoma or Zollinger–Ellison syndrome, PPIs should be withdrawn, and, if gastroesophageal reflux disease symptoms persist, replaced with an H2-receptor antagonist. Recent reports of gastric carcinoids associated with profound PPI-induced acid suppression and the increasing awareness of other potential adverse effects (eg, interference with the absorption of a variety of other medications, possible hip fracture, and Clostridium difficile infection) have provided further impetus to using PPIs less often and at the minimal effective dose.

Hyperplastic Polyps

Hyperplastic polyps are inflammatory proliferations of the gastric foveolar cells (the mucin-producing epithelial cells that line the gastric surface and the gastric pits). When the inflammatory infiltrates are prominent, they may be referred to as inflammatory polyps. When hyperproliferation of foveolar cells is the most salient characteristic, gastric pits (also known as foveolae, from the Latin word for “small pit”) become elongated, tortuous, and generate elevations of the mucosa; these lesions are known as polypoid foveolar hyperplasia. In patients with post-Billroth I and II gastric stumps the gastric mucosa adjacent to the anastomosis continuously is exposed to bile reflux and significant degrees of foveolar hyperplasia may occur. In some cases there also may be cystic dilatation of the foveolae, with a resulting polypoid lesion consisting of cysts, tortuous pits, and often an eroded surface epithelium. This is sometimes referred to as gastritis cystica polyposa. Because all these are expressions of the same basic lesion we suggest that confusion be avoided by referring to all variants as hyperplastic polyps.

The classic association of gastric hyperplastic polyps has been with mucosal atrophy, whether caused by H pylori infection or autoimmune gastritis. Hyperplastic polyps have slipped from being the most common type of gastric polyp encountered at endoscopy to less than 20% of them. Hyperplastic polyps are equally common in men and women and typically occur in the sixth and seventh decades (median age, 66 y). Endoscopically, they are found most frequently in the antrum and often are multiple. They are usually smooth, dome-shaped, and measure between 0.5 and 1.5 cm in diameter (Figure 2), although they may be much larger. Large hyperplastic polyps often become lobulated and pedunculated, and the surface epithelium typically is eroded (Figure 2), which may result in chronic blood loss and iron-deficiency anemia. Rarely, patients with large hyperplastic polyps present with gastric outlet obstruction because the polyp may obstruct or prolapse through the pylorus. Hyperplastic polyps are believed to arise as a hyperproliferative response to tissue injury (erosions or ulcers) accompanied by increased cellular exfoliation. The resulting foveolar hyperplasia, long recognized as a prominent feature in chemical gastropathy and, to a lesser extent in H pylori gastritis, may be the initial step in

Figure 2. Hyperplastic polyp. (A) Endoscopic view of a hyperplastic polyp on a stalk in the antrum. Histologically, (B) hyperplastic polyps are characterized by marked foveolar hyperplasia, and (C) a mixoid stroma are characterized with dilated tortuous glands lined by normal or reactive foveolar epithelium. (D) Larger polyps have prominent erosions covered with fibrinopurulent material with underlying granulation tissue, (E) often with areas of edematous stroma and oddly shaped glands.
their genesis. This could explain why they increasingly are seen arising in a background of reactive gastropathy.

**Histopathologic Features and Diagnostic Criteria**

The typical features of hyperplastic polyps include elongated, grossly distorted, branching, and dilated hyperplastic foveolae lying in an edematous stroma rich in vasculature, and small haphazardly distributed smooth muscle bundles with varying degrees of chronic and active inflammation (Figure 2). Between 1% and 20% of hyperplastic polyps have been reported to harbor foci of dysplasia (Figure 3). This wide range is more likely a reflection of the different criteria used in the assessment of dysplasia than because of real geographic or biological variability. Mutations of the p53 gene, chromosomal aberrations, and microsatellite instability all have been detected in these polyps. The overall prevalence of carcinoma in hyperplastic polyps is less than 2%, and it is more frequent in polyps larger than 2 cm.

When foci of dysplasia or carcinoma are diagnosed within a hyperplastic polyp, clinicians often inquire whether the lesion was in fact an adenoma or a carcinoma erroneously identified as a hyperplastic polyp. This is almost never the case. Adenomas (as detailed later) consist entirely of dysplastic epithelium; in contrast, hyperplastic polyps with dysplastic foci are inflammatory lesions formed by long distorted branching, and dilated hyperplastic foveolae lying in a vascular edematous stroma. Finding foci of dysplastic (ie, neoplastic) epithelium within these lesions does not call for a reconsideration of their original pathogenesis or classification, although it does change their management.

The histopathologic diagnosis rests on the detection of the earlier-mentioned features in traditional H&E-stained slides. Because erosions, ulcerations, and inflammation, even extensive, are expected features of these polyps, pathologists are encouraged to avoid adding the word “inflammatory” to the diagnostic line. This invariably results in calls from puzzled clinicians who want to know whether hyperplastic and inflammatory gastric polyps are different or, as one put it, one and the same. They are one and the same.

When inflammatory polyps measure less than 1 cm, the routine examination of representative sections from each polyp is considered adequate. Larger polyps (>1 cm) may harbor dysplasia and even carcinoma. Therefore, they should be sectioned in 2- to 3-mm slices, and sections should be prepared from each slice. This practice will allow the detection of otherwise easily missed dysplastic or neoplastic lesions (Figure 3). Outside the research arena, no special stains or molecular studies are necessary. If no specimens from other parts of the stomach are included, an immunohistochemical stain for *H. pylori* can be helpful.

**Clinical Approach**

In view of the potential cancer risk, all hyperplastic polyps larger than 1 cm should be excised completely. If dysplasia or intramucosal carcinoma is found, but the stalk is not affected, the lesion can be considered completely removed and most likely cured. The excision of the polypoid lesion always should be accompanied by additional sampling of the unaffected mucosa to obtain reliable information about the topography and severity of the background gastritis and atrophy.

When hyperplastic polyps arise in a background of chronic atrophic gastritis (a precursor lesion for gastric adenocarcinoma) the severity and extent of the atrophic gastritis should be evaluated. Risk stratification for gastric cancer can be assessed histologically using the Operative Link for Gastritis Assessment (OLGA) or the Operative Link on Gastritis/Intestinal Metaplasia Assessment staging systems. Both require histologic grading of adequate samples from the antrum and corpus; grades then are combined to provide a risk stratification category. One can use the 5-biopsy specimen protocol recommended by the updated Sydney system. We prefer an extended
Gastric Adenomas (Raised Intraepithelial Neoplasia)

The most common gastric neoplastic polyp is an epithelial dysplastic growth still commonly referred to as an adenoma, despite the new nomenclature (raised intraepithelial neoplasia) suggested by the World Health Organization. In the Western industrialized world, *H pylori*-related sporadic gastric adenomas have become rare, accounting for less than 1% of all gastric polyps. This contrasts markedly with some East Asian regions, where the incidence of gastric cancer remains high and gastric adenomas still constitute approximately a quarter of all gastric polyps. Similar to hyperplastic polyps, gastric adenomas occur with similar frequency in men and women, most commonly in the sixth and seventh decades. Endoscopically, they have a velvety lobulated appearance and are usually solitary (Figure 4). Although they can be found anywhere in the stomach, they are located more often in the antrum. The narrow band imaging features of gastric adenomas are not yet well defined.2

Gastric adenomas consist of dysplastic epithelial cells that often arise in a background of atrophy and intestinal metaplasia typically associated with *H pylori* infection. As in the colon, gastric adenomas can be viewed as part of a sequence leading from dysplasia to carcinoma. The larger an adenomatous polyp, the greater the probability it contains foci of adenocarcinoma. Synchronous adenocarcinomas, in other areas of the stomach, have been reported in up to 30% of patients with adenomas containing foci of adenocarcinoma.48–50

**Clinical Approach**

Gastric adenomas frequently arise in a background of chronic atrophic gastritis. Because this is a precursor lesion for gastric adenocarcinoma, in addition to completely excising all adenomas, the severity and extent of the atrophic gastritis should be evaluated. The same biopsy protocols39,40 and the use of the OLGA or Operative Link on Gastritis/Intestinal Metaplasia Assessment system suggested in the section “Hyperplastic Polypos” should be followed.57,58 It must be emphasized that adenomas are neoplastic lesions (ie, past the stage of preneoplastic) and, therefore, all patients with a diagnosis of gastric adenoma need to be placed in a surveillance program irrespective of their atrophy stage. Eradication of *H pylori* followed by confirmation of the cure by biopsy examination or urea breath test is necessary in these patients.

**Histopathologic Diagnostic Tips: Special Stains, Immunohistochemistry, and Molecular Studies**

Gastric adenomas are neoplastic lesions with malignant potential. Therefore, multiple sections from each lesion must be examined to exclude invasion. Outside the research arena, neither special stains nor molecular studies are necessary.

**Gastrointestinal Stromal Tumors**

Gastrointestinal stromal tumors (GISTs) are neoplastic proliferations of the interstitial cells of Cajal (or their precursors) that can arise in any segment of the digestive tract as well as, rarely, in the abdominal and pelvic cavity. Of the estimated 4000 GISTs newly diagnosed each year in the United States, 40% to 60% originate in the stomach, where they represent approximately 2% of all tumors. GISTs are more common in men and in the gastric fundus, although they can be found in other regions of the stomach. No predisposing factors are known; thus, the gastric mucosa overlying these tumors may be...
normal or display any type of gastritis. Interestingly, microscopic GISTs have been found to be common in the upper stomach of Japanese patients who underwent gastric resections for gastric cancer, suggesting that only infrequently does a GIST enlarge and develop malignant potential.58

Endoscopically, GISTs are well-circumscribed submucosal lesions; the overlying gastric mucosa is usually normal, but it may have an eroded or ulcerated center (Figure 5A). Biopsy sampling of these tumors is often met with frustration. Because the mucosa tends to slide over benign submucosal tumors, the biopsy forceps often fail to grab an adequate fragment of GIST tissue. In these cases the pathology report often will state that the gastric mucosa is normal, sometimes inducing the clinician to believe that either there was no lesion or the quality of the pathology report was suboptimal. Therefore, the best way to obtain diagnostic tissue is to perform an endosonographic fine-needle aspiration or a tru-cut needle biopsy.

Histologically, GISTs are composed by dense aggregates of fusiform cells (spindle cells) arranged in bundles aligned in different directions (Figure 5B). Two main types of GISTs are recognized in the stomach (spindled and epithelioid), and within each type a number of histologic characteristics (presence of perinuclear vacuoles, numbers of mitoses, necrosis, and tissue invasion) help predict their behavior.57

Clinical Approach

The vast majority of GISTs that measure less than 1 cm are asymptomatic and are detected incidentally during an endoscopic examination scheduled for other indications. As GISTs grow, they may cause erosions or ulcerations in the overlaying mucosa or compress adjacent structures; consequently, the 2 more common manifestations are bleeding (occult or overt) and pain.

All GISTs must be considered as having malignant potential; up to 50% of patients with larger GISTs (>2 cm) have metastatic disease at presentation, usually to the liver.52 In practice, there is good correlation between size, mitotic activity, and clinical behavior of GISTs. Surgical resection is recommended for lesions greater than 2 cm; endoscopic enucleation followed by surveillance is an option for smaller GISTs. Endoscopic removal is controversial, however, because of reports of positive resection margins and tumor spillage.55 Tyrosine kinase inhibitors are used as targeted therapy in cases of metastasis and surgically unresectable GISTs.59 Neoadjuvant therapy with use of tyrosine kinase inhibitors after surgical resection of high-risk GISTs deters recurrence, but the optimal duration of therapy has not been determined.60

Histopathologic Diagnostic Tips: Special Stains, Immunohistochemistry, and Molecular Studies

Immunohistochemical stains are central to the diagnosis of GISTs. The c-kit proto-oncogene mutation (most often...
occurring in exon 11) is the key molecular event in gastric GISTs and can be detected by an immunohistochemical stain directed against the KIT protein. The antibody used for the staining, designated as CD117, stains approximately 95% of GISTs (Figure 5C); the remaining 5% (which typically have a more epithelioid morphology) stain with antibodies to the DOG-1 or platelet-derived growth factor α.56,57,61 If none of these 3 stains is positive on a tumor with morphologic characteristics suggestive of GIST, tumors of smooth muscle (leiomyomas) or neural (neuromas, schwannomas) origin should be considered and immunostaining for actin and S-100 should be performed.

Predictors of behavior that pathologists must evaluate in a GIST include tumor size and mitotic counts. In general, it can be stated that the larger a tumor the greater the likelihood that it has metastasized. Figures most often cited indicate that 15% of GISTs smaller than 2.5 cm metastasize, in contrast to more than 80% of GISTs larger than 6 cm.57 These data, reproduced in many subsequent studies, emphasize the malignant potential of even small GISTs. Most studies have found that higher mitotic counts are associated with decreased survival; however, the way mitotic counts traditionally are reported (per high-power field) are imprecise, not standardized, and subject to many technical and interpretational variables. Only unequivocally high mitotic counts (eg, >5 mitoses/50 high-power field) obtained under rigorously controlled conditions (details of the methods used to find and count 50 separate fields) and precise information on the exact area of a high-power field (which varies 3-fold in different types of commonly used microscopes) can be used to make a prognostic assessment.61 Therefore, when clinicians receive a report indicating a high mitotic count in a GIST, they should interpret it cautiously and question the pathologist about the methods used to reach that conclusion.

Inflammatory Fibroid Polyps

Inflammatory fibroid polyps (also known as Vanek tumors) are extremely rare lesions that represent less than 0.1% of all gastric polyps.62 Endoscopically, they are usually firm, solitary, sessile or pedunculated, and often ulcerated (Figure 6). The histologic features of these polyps are distinctive: they consist of submucosal proliferations of spindle cells, small vessels, and a conspicuous inflammatory infiltrate with a predominance of eosinophils. Hence, these polyps are occasionally

Figure 6. Inflammatory fibroid polyp. (A) Endoscopic view of an inflammatory fibroid polyp in the antrum showing a firm, well-circumscribed submucosal lesion. (B) Histologically, a flattened, often eroded, gastric epithelium lines a compact aggregate of fibrous tissue mixed with inflammatory cells. (C) Vessels usually are surrounded by a characteristic circumferential deposition of fibroblasts (onion skin), and the stroma contains myriad eosinophils.

Figure 7. Gastric neuroendocrine tumor. (A) A small gastric carcinoid with surface ulceration seen on retroflexion in the distal body. (B) Merging nests of ECL cells arranged in cords in the deeper part of carcinoids are characteristic of carcinoid tumors. (C) The neuroendocrine origin of their cells can be confirmed by a positive synaptophysin immunohistochemical stain.
(and inaccurately) referred to as eosinophilic granulomas. The adjacent mucosa usually is unremarkable. The pathogenesis of these lesions is unknown, although a familial tendency has been documented in one family.63 Immunohistochemical staining suggests these polyps have a dendritic cell origin.64 A recent study found that 70% of inflammatory fibroid polyps contain gain-of-function mutations in the platelet-derived growth factor receptor α polypeptide gene, similar to those found in CD117-negative GISTS, suggesting the possibility of a neoplastic process.65

**Clinical Approach**

Most inflammatory fibroid polyps are asymptomatic, but larger polyps have been reported to cause abdominal pain, early satiety, anemia, and gastric outlet obstruction.66 The endoscopic ultrasound appearance, characterized by an indistinct margin, a hypoechoic homogeneous lesion, and location within the second or third layer with an intact fourth layer, may be helpful in establishing the diagnosis.67-69

**Histopathologic Diagnostic Tips: Special Stains, Immunohistochemistry, and Molecular Studies**

Because fibroepithelial polyps are extremely rare, general pathologists may spend their entire career without ever seeing (or at least recognizing) one. However, once familiar with their unique morphology they can be diagnosed instantly (Figure 6). Immunohistochemical staining for CD31 (an endothelial marker) is strongly positive, but it is almost never necessary for the diagnosis and should be used only as a teaching tool.

**Gastric Neuroendocrine Tumors (Carcinoids)**

Carcinoids are neuroendocrine tumors derived from enterochromaffin-like (ECL) cells.70 The term carcinoid was discarded in the most recent (2010) World Health Organization classification of tumors in favor of neuroendocrine tumor.71 In 2 large studies (Germany in 1994 and the United States in 2008) gastric neuroendocrine tumors comprised less than 2% of gastric polyoid lesions.1-46

Gastric neuroendocrine tumors are classified in 3 distinct types. Type I tumors represent 70% to 80% of all gastric endocrine tumors. They are associated with hypergastrinemia resulting from autoimmune (corpus-restricted) atrophic gastritis and, therefore, are found more commonly in elderly patients, particularly women, with atrophic gastritis and often are associated with pernicious anemia.72-74 These tumors (Figure 7) are small (<1 cm), confined to the oxyntic mucosa, and tend to be multiple and usually co-exist with multifocal ECL cell hyperplasia. Gastric neuroendocrine tumors tend to be found incidentally, often in patients undergoing EGD as part of an evaluation for anemia. Histologically, they consist of nests or ribbons of endocrine cells (small polygonal cells with round nuclei featuring salt-and-pepper chromatin) with a very low proliferation index.

Type II gastric neuroendocrine tumors are associated with hypergastrinemia resulting from a gastrin-secreting tumor. They frequently are detected as part of the work-up for MEN-1 syndrome or for Zollinger-Ellison syndrome.75 In both instances the tumors are usually small (<1 cm) and show neither infiltrating nor pleomorphic features. In patients with MEN-1 syndrome the gastric mucosa is normal or mildly inflamed, but not atrophic. The fundic mucosa of patients with Zollinger-Ellison syndrome often is hypertrophic, with long densely packed oxyntic glands and no significant inflammation. This type of neuroendocrine tumor is the most uncommon, representing only 5% to 8% of gastric neuroendocrine tumors.76,77 Type III (sporadic) neuroendocrine tumors are not associated with hypergastrinemia, are generally solitary, arise in otherwise healthy gastric mucosa, and are not accompanied by ECL cell hyperplasia. These tumors, which represent approximately 20% of all gastric neuroendocrine tumors, usually are detected when they become symptomatic, either secondary to mucosal erosion and blood loss or metastasis. Because these events tend to occur only after the tumors reach a certain size, these tumors are usually larger than 1.5 cm, display infiltrating growth patterns with areas of necrosis, and show various degrees of pleomorphism. Their proliferation index is high (mitotic count >20 per high-power field or a Ki-67 index > 20%). Type III neuroendocrine tumors have a generally poor prognosis with a mean survival of 28 months.73,78

**Clinical Approach**

Type I and II tumors often can be removed endoscopically. In select patient with numerous and recurrent type I neuroendocrine tumors, antral resection could be a reasonable option. Antrectomy works by reducing the gastrin-producing cell mass in the stomach, thus removing the stimulus (i.e., hypergastrinemia) for ECL cell proliferation.79 Newer treatments such as the gastrin receptor antagonist netazepide are being investigated and could represent an alternative new medical treatment for type I gastric carcinoids.80 Patients with sporadic carcinoids (type III) may present with anemia, epigastric pain, or signs and symptoms caused by metastases, including the rare carcinoid syndrome (characterized by cutaneous flushing, diarrhea, bronchospasm, and cardiac valvular lesions). Surgery followed with chemotherapy is the treatment of choice.

**Histopathologic Diagnostic Tips: Special Stains, Immunohistochemistry, and Molecular Studies**

Neuroendocrine tumors are best diagnosed with the help of an immunohistochemical stain (synaptophysin, chromogranin A, or CD56). These 3 stains are essentially equivalent in their ability to highlight neuroendocrine markers: their specific use is mostly a matter of preference for each pathologist. In addition, a Ki-67 stain should be performed to count the percentage of proliferating cells and to determine the grade of the tumor (Figure 8).

**Approach to Gastric Polyps Found at Endoscopy**

Because most polyps are found incidentally during upper endoscopies, it is crucial that the endoscopist be prepared to acquire as much information as possible during the procedure to help with the future management of the polyp.

If the appearance strongly suggests fundic gland polyps, biopsy specimens from 1 or more polyps should be taken; polyps larger than 1 cm should be resected. In the setting of fundic gland polyps special attention should be given to atyp-
ical-looking lesions, all of which should undergo a biopsy examination because they may represent other, more clinically relevant, lesions. If the appearance is not suggestive of fundic gland polyps, the endoscopist should consider complete removal of all polyps that measure 1 cm or more; if not removed such polyps should be adequately sampled. In the case of larger polyps, after the histopathologic diagnosis is received, a decision needs to be made regarding whether polypectomy is needed and, if it is, should it be endoscopic or surgical. Several factors should be considered when making that decision: (1) risk of missing more serious pathology in the large polyps, (2) the presence of symptoms, (3) the patient’s overall health status and preferences, and (4) local expertise. Considering that many endoscopists are not experienced with the resection of large polyps and the risk of complications is not insignificant, the biopsy-first approach is reasonable because it allows definitive treatment to be planned according to pathology results and after consultation with the patient. If resection is planned, the endoscopist should be prepared to deal with potential complications. Many of these lesions are highly vascular and tend to bleed; some (inflammatory fibroid polyps, carcinoids, and GISTs) have submucosal components that increase the risk of perforation.

The conscientious endoscopist should be guided by the principle that no polyp is an island unto itself. Thus, after polyps are removed or sampled, the nonaffected gastric mucosa should be inspected and a minimum of 3 biopsy specimens from the antrum (including one from the incisura angularis) and 2 to 4 from the corpus, sampling both the greater and lesser curvature, should be submitted for pathologic examination, ideally in separate containers. Putting them into separate containers makes possible a more precise topographic definition of any abnormalities. The information so acquired will allow determining, for example, whether the patient has *H pylori* infection, atrophic gastritis, possibly with diffuse neuroendocrine hyperplasia, or a normal mucosa. Each of these findings would point to different management directions.

**Follow-up Evaluation**

There is a dearth of data on both the short- and the long-term follow-up evaluation of gastric polyps; therefore, no evidence-based guidelines exist. A surveillance endoscopy on nonfundic gland polyps within 1 year is a reasonable approach to evaluate the site for recurrence and to assess for new polyps. Follow-up evaluation after resection of polyps with high-grade dysplasia or early cancer should be individualized, but (at least for the first 2–3 years) short intervals (eg, 6 mo) would seem desirable. Gastric carcinoids managed endoscopically (usually type 1) should be followed up with endoscopy every 1 to 2 years.

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1. PPI's should be discontinued if:
   a. Fundic gland polyps are present in any number or size
   b. Fundic gland polyps >1cm or more than 20 polyps are present
   c. H. pylori is present
   d. Serum gastrin is >400

2. Histologic features of gastric hyperplastic polyps include
   a. Dilated oxyntic glands
   b. Dysplastic epithelial cells in a background of intestinal metaplasia
   c. Dilated and branching foveolae, chronic inflammation and smooth muscle
   d. Main be ulcerated, eroded or inflamed

True or False

3. Hyperplastic polyps >1cm should be removed, adjacent mucosa should be biopsied

4. Polyps presumed to be fundic gland polyps on endoscopy should be removed if >1cm or biopsied if smaller but located in the antrum

5. Hyperplastic polyps are more common when H. pylori is present

6. GISTs are more common in females, and are often located in the antrum

7. The eradication of H. pylori in industrialized nations has increased the prevalence of hyperplastic polyps, while decreasing fundic gland polyps.

8. Type III gastric carcinoids are associated with normal gastric mucosa and no ECL hyperplasia

9. Gastric polyps showing one or more dilated glands and flattened parietal and mucous cells are likely related to the use of PPI's

10. Fundic gland polyps are more common in people with H. pylori

11. Hyperplastic polyps are more common in the antrum than the fundus

12. Gastric adenomas are more common in people with H. pylori infection

13. Small GIST's (<3cm) rarely metastasize

14. A predominance of eosinophils mixed with spindle cells is typically seen in inflammatory fibroid polyps

15. Type I carcinoids are associated with autoimmune gastritis but not elevated gastrin