Gastric Polyps

Classification and Management

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• Gastric polyps can be broadly defined as luminal lesions projecting above the plane of the mucosal surface. They are relatively frequent in routine pathology practice, where the main goal is to rule out the possibility of malignancy. Various subtypes of gastric polyps are recognized and generally divided into nonneoplastic and neoplastic. We will review herein only a limited subset of gastric polyps representing the most common or, sometimes, challenging.

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Most gastric polyps are incidentally discovered in about 2% of upper endoscopies, most performed for unrelated reasons.[1] Occasionally, they become inflamed and eroded, and bleeding is unusual. Gastric obstruction is also an uncommon event associated with large distal lesions.

The endoscopic appearance of gastric polyps is variable, ranging from slightly raised plaques to soft multilobed nodules to, more rarely, broad-based or sessile lesions. Although the various types of polyps cannot be distinguished with certainty on the basis of the endoscopic appearance, several characteristics can help endoscopists predict the diagnosis with some confidence. Topography is important, since some types of polyps are found primarily in one part of the stomach. For example, fundic gland polyps are never antral, whereas adenomas have a distinct tendency to be antral. Some polyps have a tendency to be multiple. This particularly applies to hyperplastic polyps, fundic gland polyps, carcinoids, and metastases. Color is of little value, since most common polyps are salmon/pink in appearance.

The description of all polypoid lesions of the stomach goes beyond the scope of this review (Table). However, over the last few years numerous morphologic studies have refined the diagnostic features of the commonly encountered lesions. Those will be discussed herein.

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NONNEOPLASTIC POLYPS

Hyperplastic Polyps

These benign lesions are the second most common type of gastric polyp after fundic gland polyps.[2–5] They are sessile or pedunculated and composed of elongated and distorted pits lined by foveolar epithelium, very few if any glands, and an inflamed, edematous lamina propria. Pyloric (antral glands), chief cells, and parietal cells are rarely seen.[6]

Clinical and Endoscopic Findings.—Gastric hyperplastic polyps are randomly distributed throughout the stomach. They have a wide age range distribution but are more common with increasing age (mean age, 65.5–75 years). A slight predisposition is noted in women, who represent between 58% and 70.5% of patients. Hyperplastic polyps can be seen throughout the stomach. A total of 24% to 60% of hyperplastic polyps are located in the antrum, 29% to 56.3% are in the body fundus, and only about 2.5% are in the cardia.[4,7,8]

Hyperplastic polyps are single in about two thirds of cases. According to one series, most measure less than 1 cm, and polyps larger than 2 cm represent only 10% of cases.[7] However, small polyps should be distinguished from foveolar hyperplasia.[8,9] Small lesions have a smooth, dome-shaped surface. Larger polyps, some measuring up to 13 cm, are usually lobulated and sometimes pedunculated. Superficial erosion of larger cases commonly occurs. When distal, the larger polyps can also manifest with gastric outlet obstruction. There are also rare reports of hyperplastic polyps prolapsed into the duodenum with obstruction of the ampulla of Vater and secondary pancreatitis.[10,11]

Etiology and Pathogenesis.—The stimuli responsible for the development of hyperplastic polyps are not known. They are generally thought to result from excessive regeneration following mucosal damage and, consequently, commonly occur in chronic *Helicobacter pylori*–associated gastritis (25% of the cases), in pernicious anemia, adjacent to ulcers and erosions, or at gastroenterostomy sites.[8,12,13] The majority develop in gastric mucosa, showing some degree of chronic atrophic gastritis and intestinal metaplasia. They also occur at the gastric cardia/gastroesophageal junction of patients with chronic esophageal reflux.[14,15]

Histopathology.—Histologically, hyperplastic polyps are characterized by marked elongation of the pits with branching, resulting in a corkscrew appearance or in cystic dilatation of foveolae (Figure 1). Another feature is the

Classification of Gastric Polyps
1. Nonneoplastic Polyps
Hyperplastic
Usual (sporadic) type
Gastroenterostomy stoma
GE junction (reflux) polyps
Inflammatory fibroid polyp
Hamartomatous and developmental
Peutz-Jegher
Juvenile
Cowden disease
Miscellaneous lesions
Myoepithelial hamartomas and ectopic pancreas
Heterotopic gastric gland polyp
Cronkhite-Canada syndrome
2. Neoplastic Polyps
Adenoma
Carcinoma (primary or secondary)
Carcinoids
Fundic gland polyp
3. Miscellaneous Lesions With Polypoid Growth Pattern
Xanthelasma
Lymphoid hyperplasia/lymphoma
Mesenchymal stromal tumors
Gastrointestinal tumors (benign/malignant)
Smooth muscle tumors (benign/malignant)
Glomus tumor
Neural tumors
Schwannoma/neuroma
Ganglioneuromas
Granular cell tumor
Other rare tumors
Lipoma/liposarcoma
Rhabdomyosarcoma and fibrous histiocytoma
Vascular
Hemangioma/lymphangioma
Hemangiosarcoma—Kaposi sarcoma

excess of edematous lamina propria infiltrated by plasma cells, lymphocytes, eosinophils, mast cells, macrophages, and variable numbers of neutrophils. Interspersed wisps of smooth muscle fibers are quite commonly seen between the gastric pits and arise from thickened and split muscularis mucosae. The gastric glands do not normally participate in the formation of the polyps.[16] The foveolae are lined by a single layer of hyperplastic foveolar-type epithelium, although pyloric-type glands, chief cells, parietal cells, and foci of intestinal metaplasia may be found.

The surface of the polyps may be ulcerated and acutely inflamed, showing regenerative atypia of epithelial and stromal cells with sometimes prominent reparative granulation tissue. There also may be invagination of the surface mucosa with budding, which may produce a back-to-back appearance, as well as the appearance of pseudoinvasion.[17] These changes can cause major diagnostic problems, since true carcinoma may be found in hyperplastic polyps.[18]

Polypoid hyperplasia or hyperplastic polyps of the gastroesophageal junction have been observed variably in the setting of gastroesophageal reflux disease. They are believed to represent a regenerative response to surrounding mucosal injury, such as ulcers, erosive esophagitis, or ''junctitis'' of the gastroesophageal junction.[14,15] Histologically, they are mostly composed of cardiac-type mucosa. Admixed squamous mucosa and, rarely, parietal cells can also be seen. Intestinal metaplasia is variably present, and dysplasia is rare (<3%).[15]

Among the few challenges when evaluating hyperplastic polyps, distinguishing between regenerative changes and dysplasia may be the most difficult. When attenuated epithelium is seen actively growing over an ulcerated surface, then it can reasonably be presumed that the pits in the immediate vicinity of the ulceration, as well as the attenuated epithelium, are all showing regenerative changes. In some polyps, however, the typical appearance of dysplasia may be seen, and very rarely, one is surprised to find a focus of carcinoma.[18]

Although classically discussed in the differential diagnosis, hyperplastic polyps are easily distinguished from Ménétrier disease by their smaller size and the presence of intervening normal mucosa (unless they are numerous). However, the distinction from juvenile polyposis rests entirely on the clinical diagnosis and the demonstration of juvenile polyposis in the large bowel. The differentiation from Cronkhite-Canada syndrome may be difficult and, unless diffuse, may depend on the recognition of ectodermal features clinically.

Clinical Significance and Treatment.—Over time, hyperplastic polyps can increase in number or regress, either spontaneously or following *Helicobacter pylori* eradication.[19] Malignant transformation, although rare, is well documented. A small proportion (1.5%–3% of the cases), usually those measuring greater than 2 cm, show dysplasia or even intramucosal carcinoma.[18,20] Thus, the larger polyps should be completely excised for histologic evaluation. Also, given the frequent surrounding background of intestinal dysplasia, an association with a synchronous carcinoma elsewhere in the stomach is recognized, and therefore careful endoscopic assessment surrounding mucosa is important.[5,18]

Inflammatory Fibroid Polyp (Eosinophilic Granuloma-Vanek Tumor)

In 1949, Vanek described inflammatory fibroid polyp as ''gastric submucosal granuloma with eosinophilic infiltration.''[21] These polyps are characterized by the proliferation of spindle cells, small blood vessels, and inflammatory cells, often dominated by eosinophils.[22]

Clinical and Endoscopic Findings.—These uncommon polyps of unknown etiology may be found throughout the gastrointestinal tract, but they are most common in the antropyloric region (80%). They are diagnosed in male and female adults of all ages and are associated in some cases with hypochlorhydria or achlorhydria.[23,24] They may be found incidentally or during evaluation of gastric hemorrhage, anemia, or symptoms of gastric outlet obstruction. Inflammatory fibroid polyps are well-circumscribed, solitary, small sessile, or pedunculated lesions. Inflammatory fibroid polyps can be ulcerated, sometimes to a degree that makes a confident diagnosis difficult.

Etiology and Pathogenesis.—Although an allergic cause has been suggested to play a role in the development of these polyps,[21] no specific cause has been identified.

Histopathology.—Inflammatory fibroid polyps are usually centered on the submucosa, although purely mucosal lesions have been described. They are composed of small, thin-walled blood vessels surrounded by short spindle cells that may be arranged in an ''onion-skin'' pattern around larger vessels (Figure 2). Immunohistochemical

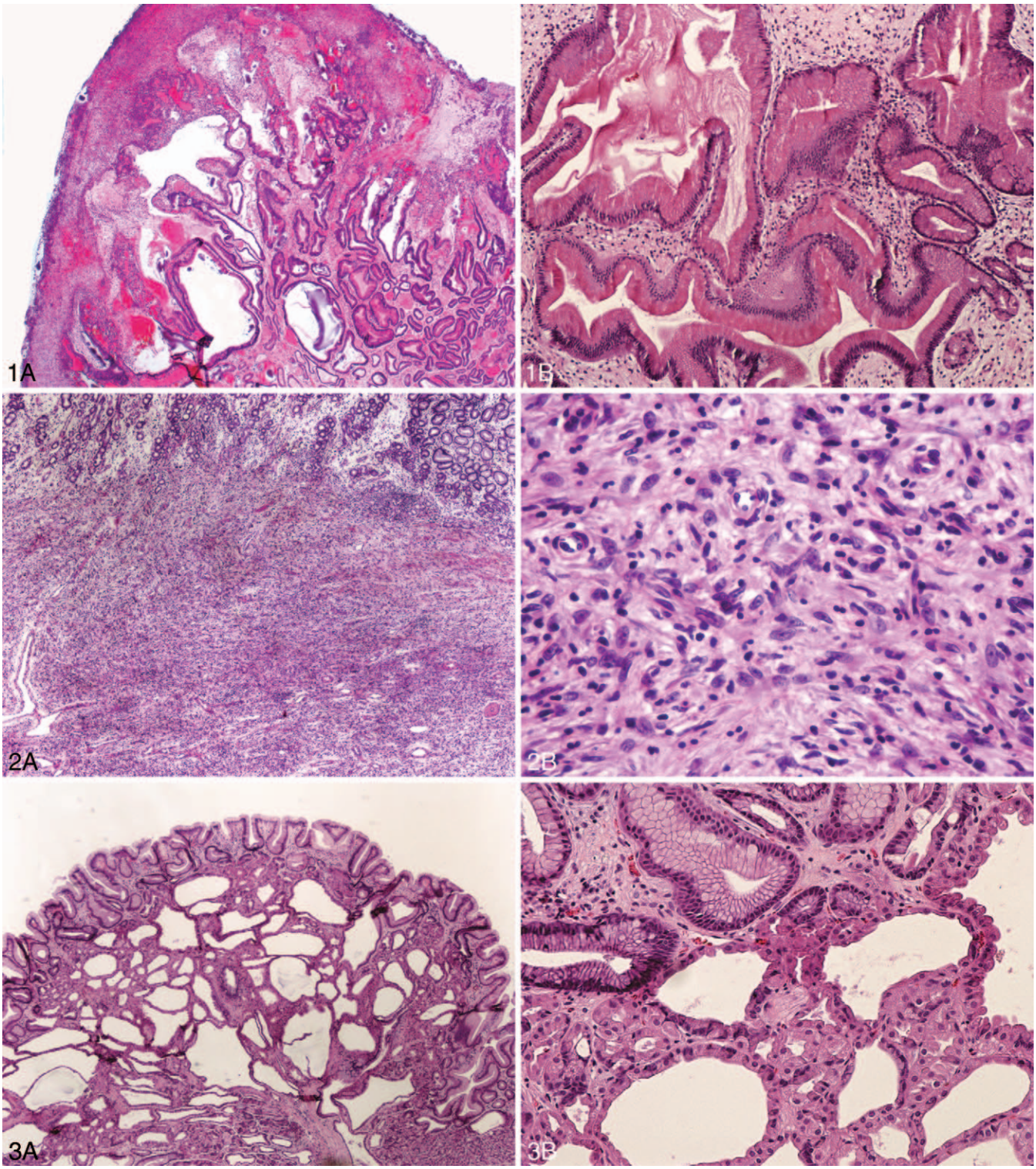

Figure 1. *Hyperplastic gastric polyp. A, The smooth-surfaced polyp is characterized by foveolar elongation and cystic dilatation. This example is characterized by marked erosion of the surface (hematoxylin-eosin, original magnification ×20). B, Higher magnification demonstrates the cytologically normal but architecturally deformed foveolae. Note the conspicuous edematous lamina propria with scattered chronic inflammation (hematoxylin-eosin, original magnification ×100).*

Figure 2. *Inflammatory fibroid polyp. A, The spindle cell proliferation expands the deepest aspect of the mucosa (hematoxylin-eosin, original magnification ×40). B, Higher magnification shows the characteristic short, bland spindle cells intermixed with chronic inflammatory cells (hematoxylin-eosin, original magnification ×400).*

Figure 3. *Fundic gland polyp. A, The lesion is composed of cystically distended glands (hematoxylin-eosin, original magnification ×20). B, Higher magnification shows normal glandular component with chief cells and parietal cells (hematoxylin-eosin, original magnification ×200).*

evaluations have shown these cells to be consistently CD34 positive and c-kit negative, while frequent fascin positivity suggests a dendritic origin.[24,25] Sometimes ''floret''-like multinucleated giant cells with hyperchromatic nuclei are seen. A chronic inflammatory cell infiltrate is common, often dominated by eosinophils.

Clinical Significance and Treatment.—Most patients are asymptomatic and are incidentally diagnosed; furthermore, these polyps usually do not recur after resection.[22] Therefore, local excision is an adequate treatment.

Xanthoma/Xanthelasma

These clinically insignificant lesions are found with increasing age, in males more commonly than in females, and are often associated with chronic gastritis and intestinal metaplasia, as well as bile reflux gastropathy.[26,27] They are not related to hypercholesterolemia and may be found in association with hyperplastic polyps. Grossly, they are single or multiple, 1 to 2 mm in diameter, round or oval, well circumscribed, yellow, macular, or nodular lesions. They are found most frequently along the lesser curvature. Histologically, they consist of accumulations of mature lipid-laden macrophages occupying the lamina propria and containing cholesterol and neutral fat. Important differential diagnoses include mycobacterium avium intracellulare, muciphages, granular cell tumors, and signet ring cell carcinomas.[28] Clinical setting and appropriate use of immunohistochemical studies help in rendering an appropriate diagnosis.

Hamartomatous Polyp of the Peutz-Jeghers Type

The gastric mucosa may be involved in Peutz-Jeghers polyposis, although less frequently than the small intestine or colon.[29,30] Gastric hamartomatous polyps are composed of hyperplastic glands lined by foveolar-type epithelium and separated by branching cores of smooth muscle, with atrophy of the deep glandular components. Rare reports of gastric carcinoma in Peutz-Jeghers polyposis are described, but it is far from clear how often this has arisen within a preexisting polyp.[31–33] There is only one report on record that clearly illustrated the presence of dysplasia in a gastric Peutz-Jeghers polyp.[34]

Juvenile Polyp

Gastric juvenile polyps are rarely observed and often occur within the context of juvenile polyposis, either of the stomach alone or of the entire gastrointestinal tract (with or without a family history).[30,35] They may present at any age, usually with anemia or hypoproteinemia, and are most common in the antrum. They are composed of edematous and inflamed mucosa with marked elongation, tortuosity, and cystic dilatation of the foveolar zones, and thus can easily be confused with hyperplastic polyps if appropriate clinical information is not provided. Juvenile polyposis is associated with an increased risk of cancer, particularly in the colon, but the stomach also may be at risk.[36]

Gastric Polyps in Cowden Disease

Gastric polyps may also occur in Cowden disease and may consist of enlarged, elongated foveolar glands along with more basal, cystically dilated glands that contain papillary infoldings. Smooth muscle fibers are intermingled within the mucosal components, and the cystic structures sometimes extend into the submucosa.[37]

Gastric Polyps in Cronkhite-Canada Syndrome

These polyps occur usually in conjunction with lesions in other parts of the gastrointestinal tract. They are indistinguishable from juvenile and hyperplastic polyps and can be diagnosed only in the presence of clinical evidence of alopecia, nail atrophy, or hyperpigmentation.[38,39]

NEOPLASTIC POLYPS

Fundic Gland Polyps

Fundic gland polyps (FGPs) are small sessile lesions that occur uniquely in the fundus and upper body of the stomach. Their morphology is characteristic with cystic transformation of the gland lined by parietal cell and chief cells.[6]

Clinical and Endoscopic Findings.—FGPs may occur sporadically, in patients with familial adenomatous polyposis, or as a familial condition confined to the stomach without polyposis coli.[30,40–43] Endoscopically, they appear as glassy, transparent, sessile polyps, less than 1 cm in diameter. These are usually multiple and may be found in men and women of any age. Their association with prolonged proton pump inhibitor therapy is debated, in part because of the inhibiting role of *H pylori*, which may inhibit their formation and has not been controlled in various studies.[41,44]

Etiology and Pathogenesis.—Although traditionally thought to be hamartomatous in origin, the frequent finding of genetic alteration in familial adenomatous polyposis and also in sporadic cases strongly suggests that these lesions are actually neoplastic. Indeed, alterations of the APC–β-catenin pathway have been reported in both sporadic and syndromic FGPs. Activating somatic mutations (at GSK-3β phosphorylation sites) of exon 3 of the β-catenin gene have been detected in the foveolar and glandular epithelium of most cases of sporadic FGPs, but also in proton pump inhibitor–associated FGPs, thus underlining the nosologic similarity of these polyps. Instead of β-catenin gene mutations, syndromic polyps harbor germline APC mutations and subsequent somatic mutation.[45,46]

Histopathology.—FGPs are composed of cystically dilated glands lined by fundic epithelium, including parietal cells and chief cells, admixed with normal glands[41] (Figure 3). The overlying foveolae are shortened, and there is usually no inflammation or evidence of atypia.[47] There may be an irregular, disordered distribution of smooth muscle fibers around the cystic glands. In patients on proton pump inhibitors, there is associated hypertrophy and hyperplasia of parietal cells that protrude into the lumen of the pits, producing a serrated profile.[48]

Clinical Significance and Treatment.—Spontaneous regression has been well documented,[40,49] and despite evidence for a neoplastic origin, most FGPs are not premalignant. Thus, notwithstanding the rare reports of dysplasia, endoscopic surveillance for patients with sporadic FGPs is not necessitated. However, the finding of FGPs in a young patient merits considering the possibility of underlying familial adenomatous polyposis. In patients with familial adenomatous polyposis, FGPs with dysplasia can be seen in up to 40% of the patients.[50,51]

Adenoma

Gastric adenomas are defined by the World Health Organization as circumscribed, polypoid lesions composed

of either tubular and/or villous structures lined by dysplastic epithelium.[52]

As in any segment of the gastrointestinal tract, gastric epithelial dysplasia is defined as a neoplastic epithelial alteration representing both a precursor lesion of adenocarcinoma and also a marker of high risk.

Clinical and Endoscopic Findings.—The prevalence of gastric adenoma ranges from 0.5% to 3.75% in countries in the Western Hemisphere, whereas it is reported to occur between 9% and 20% in nations where high risk of gastric cancer is reported.[53–56] They usually arise in the context of atrophic gastritis with intestinal metaplasia,[57,58] and the majority are found in the antrum, with the angulus and fundus a close second.[59] Most are solitary, exophytic sessile or pedunculated lesions and usually measure up to 3 to 4 cm in size.[5,60] More rarely, lesions that are ''flat'' or even depressed below the contour of the surrounding mucosa are observed, suggesting that adenoma and dysplasia should be considered a single group.[61]

Gastric adenomas typically present with a velvety lobulated surface contrasting with smooth and atrophic adjacent mucosa. They are usually asymptomatic, unless they ulcerate and bleed. Rarely, they give rise to gastric outflow obstruction.

Etiology and Pathogenesis.—Most gastric adenomas arise in the context of atrophic gastritis with intestinal metaplasia.[57,58] Their incidence increases with age and may occur in individuals with familial adenomatous polyposis.[30,42,62] On some occasions, other types of gastric polyps, such as hyperplastic polyps, FGPs associated with familial adenomatous polyposis, as well as those of familial juvenile polyposis, may show dysplastic transformation.

Histopathology.—Most gastric adenomas are composed of tubules or villi of dysplastic epithelium, which usually show some degree of intestinal-type differentiation toward absorptive cells, goblet cells, endocrine cells, or even Paneth cells (Figure 4). Gastric adenomas can be subdivided according to the degree of dysplasia (low or high grade) based on the degree of nuclear crowding, hyperchromasia, stratification, mitotic activity, cytoplasmic differentiation, and architectural distortion.[63,64]

A minority of gastric adenomas show morphologic and mucin histochemical characteristics of gastric foveolar or pyloric gland–type epithelium (Figure 5), and others have combined gastric and intestinal-type features.[52,65] Pyloric adenomas are characteristically composed of a short columnar epithelium showing basal nuclei and pale eosinophilic cytoplasm. They are more common in older patients and are more common in women than in men. Interestingly, they also seem to be more frequently diagnosed in the body fundic mucosa. In a large series of cases, 26% of pyloric gland adenomas showed evidence of malignant transformation.[66] Another rare variant, ''Paneth cell adenoma,'' is predominantly composed of Paneth cells.[67]

As with their colonic counterparts, the risk of malignancy in gastric adenomas is related to size, degree of dysplasia, and villosity of growth pattern. Small, pedunculated adenomas measuring less than 1 cm are usually composed of low-grade tubular dysplastic epithelium. Larger adenomas are more frequently villous with high-grade dysplasia, and a significant proportion contain carcinomatous transformation; the incidence reaches 40% to 50% of lesions larger than 2 cm.[52,68] However, caution is necessary, since a focus of adenocarcinoma can be observed in small adenomas.[68] A diagnosis of adenocarcinoma implies the presence of invasion of the neoplastic epithelium into the lamina propria. In some respects, the distinction between a pure gastric adenoma and adenocarcinoma in a polyp is purely academic, since the risk of metastatic spread from an intramucosal polypoid adenocarcinoma that has been completely excised is negligible, and they both should be managed endoscopically.

Clinical Significance and Treatment.—Since they are preinvasive neoplasms with potential for progression to adenocarcinoma,[5,58,63] gastric adenomas must be treated by local excision, usually endoscopic polypectomy or endoscopic mucosal resection. In addition, since they may be accompanied by coexistent carcinoma elsewhere in the stomach, an association that appears to be particularly common in males, thorough evaluation of the complete stomach is warranted.[58,60]

Gastric Carcinoid

Gastric carcinoids are defined by the World Health Organization as well-differentiated endocrine neoplasms composed of nonfunctioning enterochromaffin-like cells arising in the oxyntic mucosa of the corpus or fundus.[69]

Clinical and Endoscopic Findings.—Gastric carcinoids are rare, representing less than 0.5% of gastric neoplasm, and can be seen in three distinct clinical settings: Autoimmune atrophic gastritis patients with concomitant Zollinger-Ellison syndrome and MEN-1 syndrome, or sporadically.[70,71] In the first two settings, they commonly present as multiple broad-based, yellowish, polypoid lesions, usually less than 2 cm in size and overlined by an unremarkable mucosa.[71–73] In the sporadic setting, the tumors are larger and single and can present with features similar to those of a carcinoma (ie, gastrointestinal hemorrhage, obstruction, or metastases).[74] Only rarely do patients present with an atypical carcinoid syndrome with flushing, or hypersecretory syndromes such as Zollinger-Ellison syndrome or ACTH production.[75]

Etiology and Pathogenesis.—In the two most common forms, gastric carcinoids are associated with precursor lesions composed of various degrees of enterochromaffin-like cell proliferation, classified in four groups as hyperplasia, adenomatoid hyperplasia, dysplasia, and neoplasia. Hyperplasia is defined as clusters of a few cells present either within the glands or lying within the lamina propria. The close proximity of five or more hyperplastic nodules constitutes an adenomatoid hyperplasia. The fusion of adenomatoid hyperplastic nodules leads to enterochromaffin-like cell dysplasia (greater than 150 μm). Eventually, intramucosal lesions greater than 0.5 mm in diameter will constitute an intramucosal carcinoid tumor, whereas extension beyond the muscularis mucosa will qualify for invasive carcinoid.[72,76]

Histopathology.—Gastric carcinoids exhibit characteristic ribbons or trabecular patterns with occasional rosetting. Insular organization can also be seen. The nuclei are usually centrally located and demonstrate a finely stippled chromatin (Figure 6). Small nucleoli and infrequent mitosis can be observed. Various histologic appearances ranging from plasmacytoid-like appearance to spindle cell configuration, rhabdoid features, or anaplastic variant are occasionally reported. In such cases, poorly differentiated adenocarcinoma, lymphoma and, less commonly, gastrointestinal stromal tumor may enter the differential diagnosis.

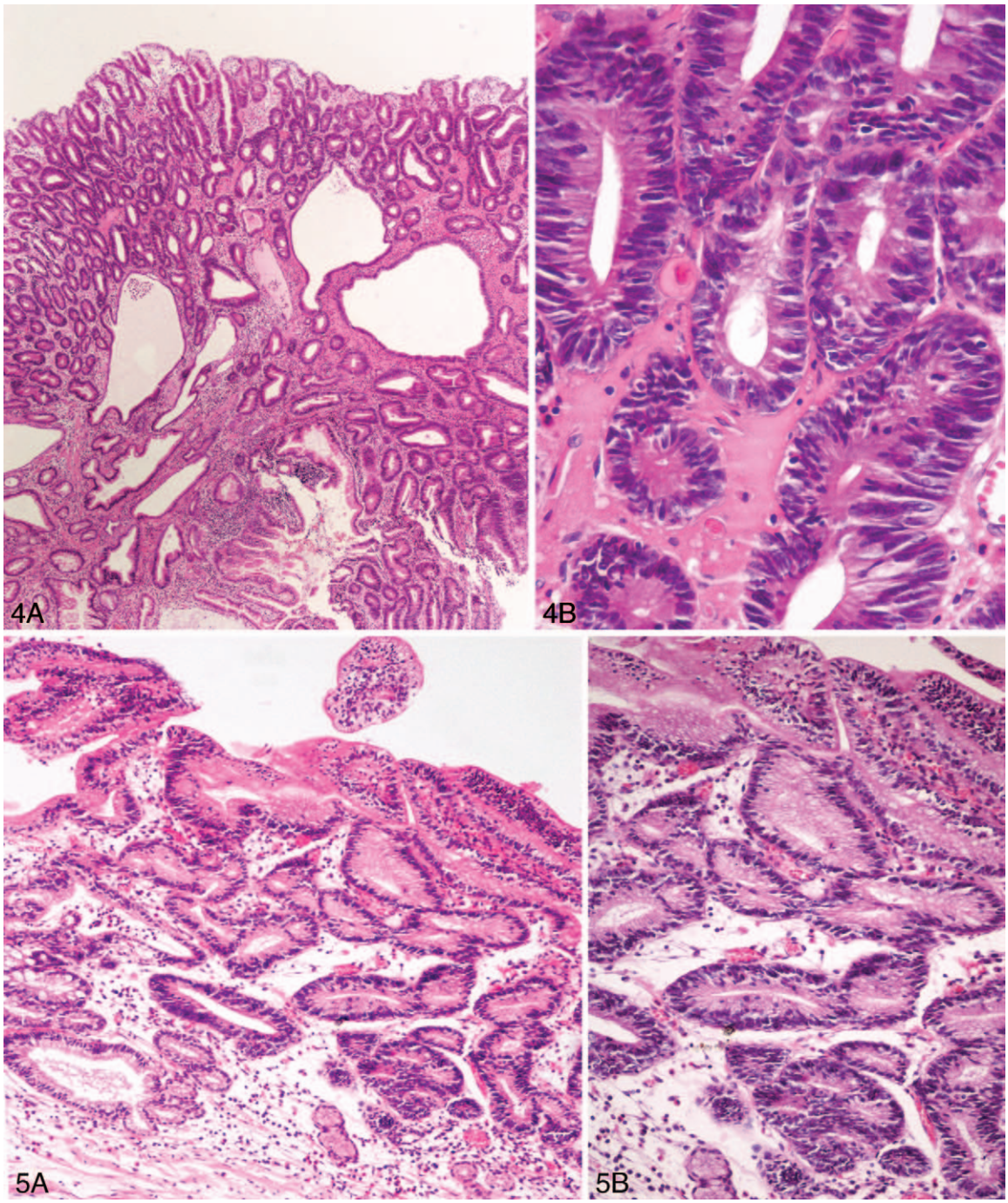

Figure 4. *Gastric adenoma, intestinal type. The scanning view (A) highlights the architectural glandular disarray (hematoxylin-eosin, original magnification ×20), whereas the close-up (B) illustrates the characteristic low-grade dysplastic changes (i.e., mucin depletion) and nuclear changes, such as hyperchromasia, stratification, and overlapping (hematoxylin-eosin, original magnification ×200).*

Figure 5. *Type 2 gastric dysplasia, low grade. In addition to glandular crowding and disarray (A; hematoxylin-eosin, original magnification ×40), the higher magnification (B) shows distinctly mucin-rich foveolar cells with nuclear crowding, hyperchromasia and limited stratification (hematoxylin-eosin, original magnification ×100). The absence of serrated architectural changes and the presence of nuclear atypia exclude a diagnosis of reactive foveolar hyperplasia.*

The cells are immunoreactive with chromogranin A, but usually not for chromogranin B.[77] Synaptophysin is positive in about 50% of the cases. Serotonin, pancreatic polypeptide, histamine, gastrin and, rarely, ACTH also can be detected.

Clinical Significance and Treatment.—Large carcinoid tumors can metastasize to lymph nodes and the liver as well as more distantly.[69,74] However, their growth is usually slow, and extended survival is compatible with distant metastases. Size and invasiveness correlate best with the probability of metastases. Carcinoids measuring less than 2 cm, and multiples, have a very low risk of metas-

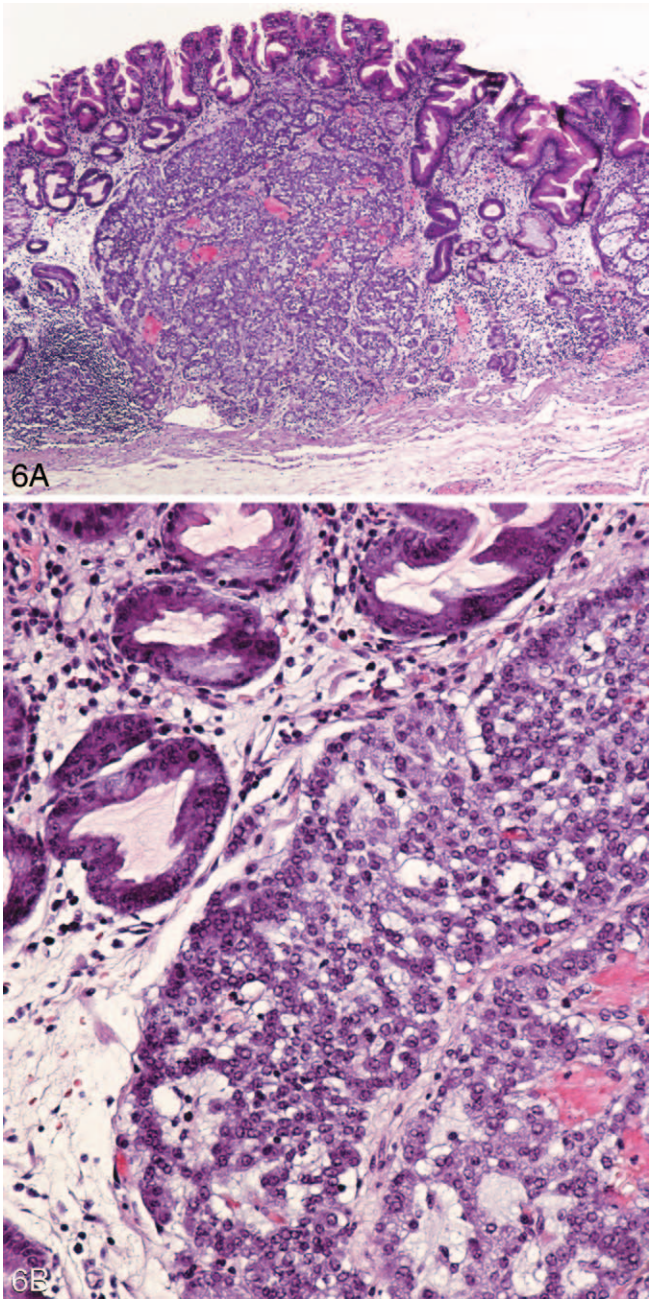

Figure 6. *Carcinoid polyp. A, Note the distinct organoid growth pattern (A) (hematoxylin-eosin, original magnification ×20). B, Higher magnification highlights the bland nuclear features with small, round nuclei with stippled chromatin (hematoxylin-eosin, original magnification ×100).*

tases, whereas tumors measuring less than 1 cm in diameter may remain stable for many years, often with no growth.[71,74] It is recommended that tumors larger than 2 cm in diameter be resected, since they have a significant risk for lymphatic invasion and metastases. The prognosis is highly variable and depends on multiple factors (ie, size, invasiveness, and histologic features).[69,74,78]

Therapeutic strategies differ depending on the clinical presentations. Large, single gastric carcinoids should be resected like other epithelial gastric tumors. The management of multiple, small, superficial carcinoids is more problematic. Successful endoscopic removal of small carcinoids has been reported by some, whereas others prefer an antrectomy that by abolishing hypergastremia causes regression of the hyperplastic lesions as well as, in one report, the carcinoid tumors.

In conclusion, the existence of different subtypes of gastric polyps, all with different risks of malignant transformation, makes their histologic analysis mandatory. Consequently, the surgical pathologist ought to not only recognize the diagnostic criteria but also be aware of the clinical implications and be able to help his or her clinical colleagues in making the most appropriate therapeutic decisions.

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