CHAPTER 17

# Polyps of the Stomach

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| Nonepithelial Polyps | Miscellaneous Rare Polyps and Polyp-Like Lesions |
|---|---|
| *Inflammatory Fibroid Polyp* | *Oxyntic Gland Hyperplasia/Adenoma* |
| *Inflammatory Myofibroblastic Tumor* | *Xanthoma* |
| *Gastrointestinal Stromal Tumors* | *Histiocytosis X* |
| *Vascular Tumors* | *Granuloma* |
| **Lymphoid Polyps** | *Amyloidosis* |
| *Lymphoid Hyperplasia* | *Calcium Deposits* |
| *Lymphoma* | *Hemosiderosis* |

Gastric polyps are identified in 3% to 5% of upper GI endoscopic procedures.[1-3] Polyps may develop as a result of epithelial or stromal cell hyperplasia, inflammation, ectopia, or neoplastic alteration. This chapter classifies gastric polyps according to the predominant cell type (e.g., epithelial, lymphoid, mesenchymal) responsible for polyp growth (Table 17-1).

The importance of clinicopathologic correlation cannot be overstated in the evaluation of gastric polyps. Anatomic location, endoscopic appearance, number of lesions, and presence or absence of pathology in the surrounding gastric mucosa are critical pieces of information usually helpful for proper classification of gastric polyps. For example, biopsies obtained from tissue adjacent to an ulcer may show an expanded lamina propria, foveolar hyperplasia, and marked regenerative changes that can mimic a hyperplastic polyp or an adenoma and can lead to an incorrect diagnosis if the endoscopic findings are not known.[4]

## Hyperplastic Polyps

### CLINICAL FEATURES AND PATHOGENESIS

Numerous synonyms, including *inflammatory* polyp, *regenerative* polyp, and *hyperplasiogenous* polyp, have been used to describe this lesion. The diversity of names is not surprising given the prevalence and pathologic diversity of these lesions. Hyperplastic polyps represent approximately 75% of all gastric polyps.

More than 85% of hyperplastic polyps occur on a background of chronic gastritis,[5,6] and this observation has led observers to conclude that these lesions develop as a consequence of an exaggerated mucosal response to tissue injury and inflammation.[7] It is generally believed that gastritis initiates the process of injury and that the mucosal healing response results in a stepwise progression through the phases of foveolar hyperplasia and polypoid foveolar hyperplasia and, ultimately, to the formation of a hyperplastic polyp. Conditions associated with the development of hyperplastic polyps include *Helicobacter pylori* gastritis, chronic non–*H. pylori* gastritis, chemical or reactive gastritis, including gastritis secondary to bile reflux, and gastritis related to Billroth II gastrectomy.[6,8-10] Hyperplastic polyps are most commonly identified in the antrum. The tendency of hyperplastic polyps to occur more proximally in autoimmune gastritis (which involves the corpus of the stomach) than in other types of gastritis[6] also supports the contention that hyperplastic polyps probably occur as a consequence of chronic injury.

Hyperplastic polyps are detected most often in older patients, with a peak incidence in the sixth and seventh decades of life. They occur equally in both sexes or perhaps with a slight male predominance.[6,8,9,11,12] Regression of hyperplastic polyps has been documented in up to 71% of patients with *H. pylori* infection after eradication of the bacterial infection.[13]

### PATHOLOGIC FEATURES

Nearly 50% of hyperplastic polyps measure less than 0.5 cm at diagnosis, and the majority are smaller than 1 cm. However, in rare cases, sizes of up to 12 cm may be reached. As noted, hyperplastic polyps occur most commonly in the antrum but can be found anywhere in the stomach. They may develop as a solitary lesion but frequently occur as multiple polyps, particularly in patients with atrophic gastritis. Grossly, they are typically ovoid in shape and contain a smooth surface contour, although villiform or pedunculated elements may be noted as well (Fig. 17-1). Surface erosion is often present. Rarely, patients may have more than 50 polyps, in which case a diagnosis of gastric hyperplastic polyposis should be considered, although discrete criteria for this syndrome have not been well established.[14]

Microscopically, hyperplastic polyps are characterized by the presence of architecturally distorted, irregular, cystically dilated, and elongated foveolar epithelium (see Fig. 17-1). Crowding of cells and infolding of the epithelium often impart a corkscrew appearance. Foveolar cells

**TABLE 17-1** Classification of Gastric Polyps

| |
|---|
| ***Hyperplastic Polyps*** |
| Hyperplastic polyp |
| Polypoid foveolar hyperplasia |
| Foveolar polyp |
| Gastritis cystica polyposa/profunda |
| Ménétrier's disease |
| ***Inflammatory Polyps*** |
| Inflammatory retention polyp |
| Polypoid gastritis |
| ***Hamartomatous Polyps*** |
| Fundic gland polyp |
| Peutz-Jeghers polyp |
| Juvenile polyp |
| Cronkhite-Canada syndrome–associated polyp |
| ***Heterotopic Polyps*** |
| Heterotopic pancreatic polyp |
| Pancreatic acinar metaplasia |
| Brunner's gland hyperplasia |
| ***Epithelial Polyps*** |
| Adenoma |
| Polypoid carcinoma |
| Carcinoid tumor |
| Metastatic carcinoma |
| ***Nonepithelial Polyps*** |
| Inflammatory fibroid polyp |
| Inflammatory myofibroblastic tumor |
| Gastrointestinal stromal tumor |
| Vascular tumor |
| Lymphoid hyperplasia |
| Lymphoma |
| ***Miscellaneous Polyps and Polyp-Like Lesions*** |
| Oxyntic gland hyperplasia/adenoma |
| Xanthoma |
| Histiocytosis X |
| Granuloma |
| Amyloidosis |
| Calcium deposits |
| Hemosiderosis |

typically have abundant mucinous cytoplasm but may be mucin-depleted focally and contain slightly enlarged and hyperchromatic nuclei with prominent nucleoli, features that are considered regenerative. Mitotic activity may be brisk in areas of active inflammation and surface ulceration. Pseudogoblet or globoid mucinous cells, which are also frequently present, appear as cells containing apically located nuclei and basally oriented mucous vacuoles. These cells were once considered dysplastic but are now commonly recognized as reactive. Thus, the previously used term *globoid dysplasia* has been discarded in favor of the more descriptive term *dystrophic goblet cell*. Intestinal metaplasia is noted in less than 25% of hyperplastic polyps and is more often present in the surrounding nonpolypoid mucosa. The lamina propria of hyperplastic polyps is typically edematous and congested with variable acute and chronic inflammation. The inflammatory infiltrate is usually most prominent in the superficial aspects of the polyp and is often associated with surface erosions. In rare cases, granulation tissue associated with ulcerations may show marked atypical pseudosarcomatous changes in the stromal fibroblasts and endothelial cells that are, in fact, reactive (see Fig. 17-1G). Nodular lymphoid aggregates, with or without germinal centers, may be present as well. Most well-developed hyperplastic polyps also contain thin bundles of smooth muscle that extend upward from the muscularis mucosae toward the polyp surface. *H. pylori* have been documented in up to 76% of hyperplastic polyps.[6,13]

The natural history of hyperplastic polyps is poorly understood, but one report suggests that up to 67% remain stable, 27% may enlarge, and 5% shrink in size.[15,16] Up to 50% of patients develop recurrent polyps after endoscopic resection.[17,18] Because of the risk of dysplasia in larger polyps, resection is often recommended for all polyps greater than 1.5 cm in size.

## DYSPLASIA IN HYPERPLASTIC POLYPS

The incidence of dysplasia in hyperplastic polyps ranges from 1% to 20%.[6,19-25] Although universal agreement has not been reached, it appears that the risk of dysplasia is related to polyp size; it occurs rarely in polyps smaller than 1.5 cm in diameter. The risk of dysplasia increases progressively in polyps that exceed 2 cm. Age is also a risk factor in that both dysplasia- and carcinoma-containing hyperplastic polyps tend to occur in patients older than 50 years. Carcinoma is uncommon within hyperplastic polyps but, when present, is thought to develop from underlying dysplastic epithelium. Some data suggest that *p53* mutations, chromosomal loss, and chromosomal gain may all be important in the development of dysplasia and carcinoma in gastric hyperplastic polyps, but further work is needed to better define the molecular biology of neoplastic transformation in these lesions.[26,27]

The microscopic appearance of dysplasia in hyperplastic polyps is similar to that in other areas of the GI tract and

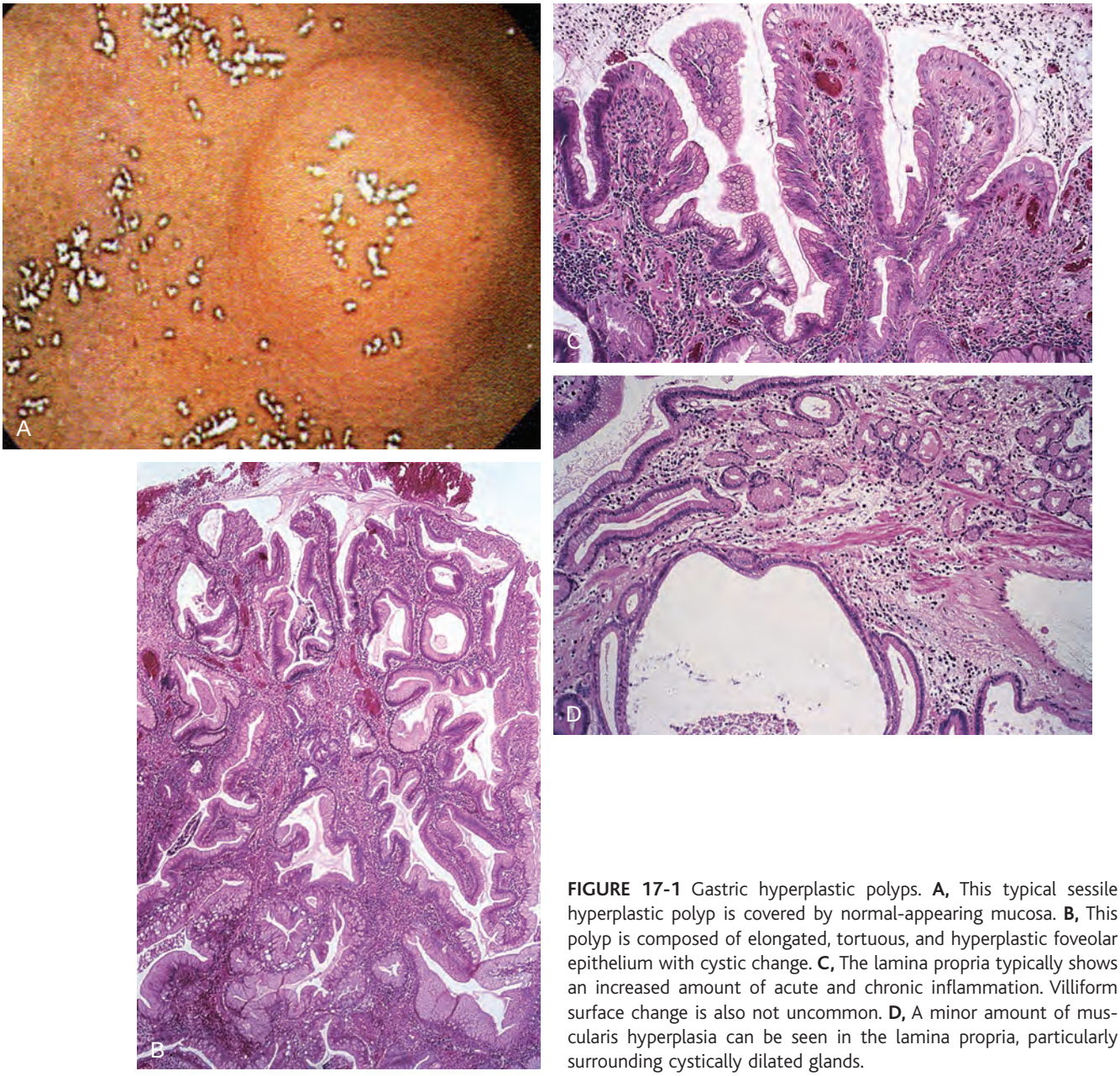



**FIGURE 17-1** Gastric hyperplastic polyps. **A,** This typical sessile hyperplastic polyp is covered by normal-appearing mucosa. **B,** This polyp is composed of elongated, tortuous, and hyperplastic foveolar epithelium with cystic change. **C,** The lamina propria typically shows an increased amount of acute and chronic inflammation. Villiform surface change is also not uncommon. **D,** A minor amount of muscularis hyperplasia can be seen in the lamina propria, particularly surrounding cystically dilated glands.

is categorized as either low- or high-grade dysplasia (Fig. 17-2). In low-grade dysplasia, the epithelium is composed of cells with hyperchromatic elongated nuclei, clumped chromatin, and pseudostratification. These changes always involve the surface epithelium but may also occur in the deep glands. Multiple nucleoli are not uncommon. Mitotic activity is brisk and may show atypia, particularly at the surface of the polyp. High-grade dysplasia is characterized by a greater degree of nuclear pleomorphism, loss of cell polarity, and more abundant abnormal mitoses. Architectural distortion of the epithelium may also occur in the form of back-to-back gland formation and full-thickness nuclear stratification. Overall, the architecture is more complex in high-grade dysplasia, with the formation of cribriform profiles and tubular budding. Moreover, features of cellular differentiation, such as cytoplasmic mucin, are progressively lost in high-grade dysplasia.

The primary differential diagnosis of a hyperplastic polyp with dysplasia is a polyp with marked regeneration (Table 17-2). The single most useful feature to distinguish between these lesions is the presence of nuclear atypia at the surface of the hyperplastic polyp with dysplasia. Cytologic atypia limited to the deeper proliferative zones in the polyp and combined with some degree of surface maturation is more often regenerative than dysplastic (Fig. 17-3). The diagnosis of dysplasia limited to proliferative zones

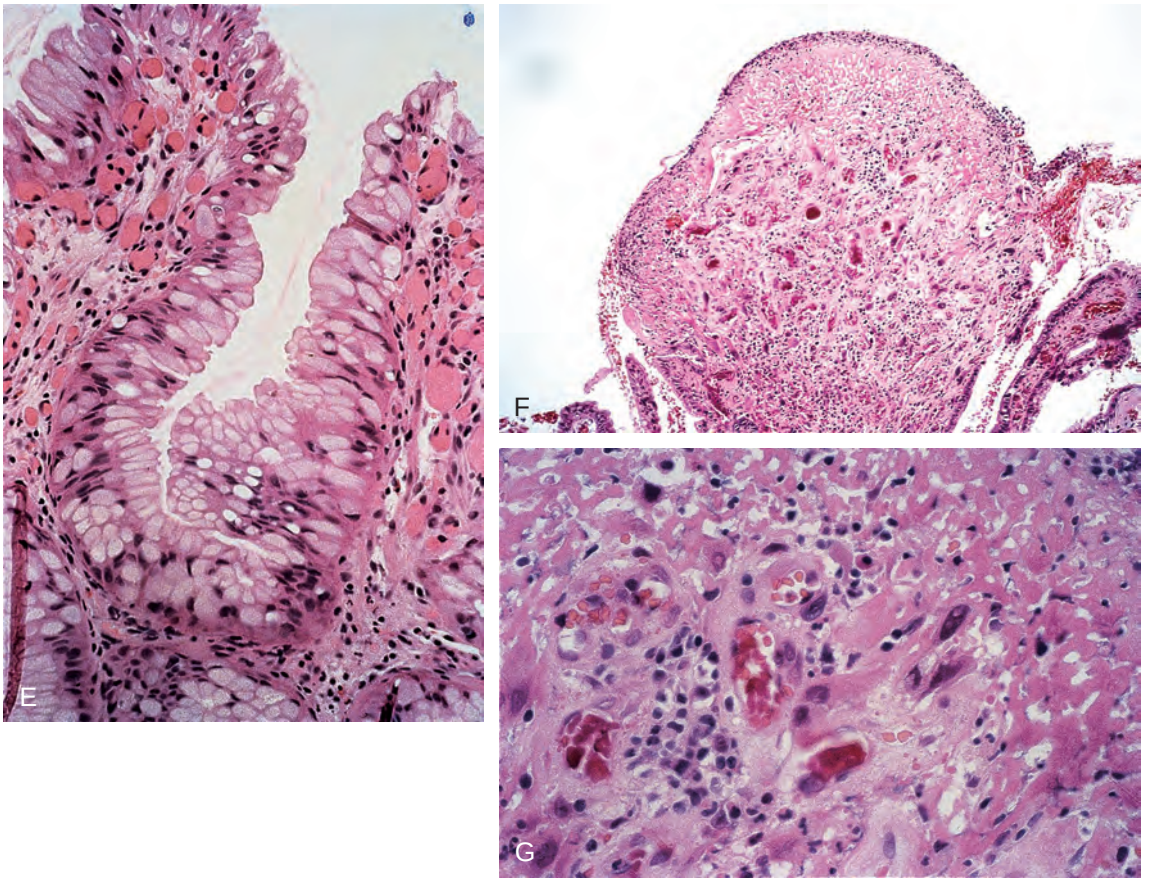



**FIGURE 17-1, cont'd** **E**, The surface or foveolar epithelium, or both, often show a proliferation of dystrophic goblet cells, which may give a false appearance of signet ring cell carcinoma in situ. **F**, Focal ulceration is not uncommon in hyperplastic polyps. **G**, In this example, a marked pseudosarcomatous proliferation of reactive fibroblasts and endothelial cells is present in the granulation tissue.

should not be considered unless there is significant cell pleomorphism or loss of cell polarity (or both). In the presence of active inflammation, the degree of atypia may be marked, and a diagnosis of dysplasia should be made with great caution. In contrast, nuclear pleomorphism and loss of cell polarity, particularly in the absence of prominent nucleoli, favor a diagnosis of dysplasia. In addition, architectural aberration, such as a cribriform growth pattern, suggests dysplasia. An abrupt change in the degree of epithelial atypia in areas away from active inflammation strongly favors a diagnosis of dysplasia.

Hyperplastic polyps with dysplasia should also be differentiated from gastric adenomas. Adenomas are typically characterized by the absence of adjacent, or underlying, hyperplastic foveolar epithelium, cystic change, and inflammatory stroma, all of which are characteristic of hyperplastic polyps.

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of gastric hyperplastic polyps includes polypoid gastritis, polypoid foveolar hyperplasia, gastritis cystica polyposa/profunda, fundic gland polyps, polyps associated with Ménétrier's disease, Cronkhite-Canada syndrome, juvenile polyposis, and Peutz-Jeghers polyposis. Features helpful in determining the correct diagnosis are summarized in Table 17-3. The polyps in polypoid gastritis and polypoid foveolar hyperplasia are typically smaller than hyperplastic polyps and lack cystically dilated, irregular, and tortuous foveolar epithelium. Additionally, the lamina propria of polypoid foveolar hyperplasia is marked by less inflammation and lacks smooth muscle hyperplasia.

Gastritis cystica polyposa/profunda is closely related to hyperplastic polyps in both pathogenesis and morphologic appearance (see Gastritis Cystica Polyposa/Profunda, later). The surface and intraluminal portions of these two types of lesions may be identical. However, unlike hyperplastic polyps, gastritis cystica polyposa is characterized by the presence of cystically dilated, distorted, and irregularly shaped epithelium or glands (or both), located in either the muscularis mucosae or the submucosa. Additionally, polyps related to gastritis cystica polyposa often develop adjacent to stoma sites in patients who have had a partial gastrectomy.

In contrast to hyperplastic polyps, fundic gland polyps show surface and foveolar hypoplasia and contain cystically

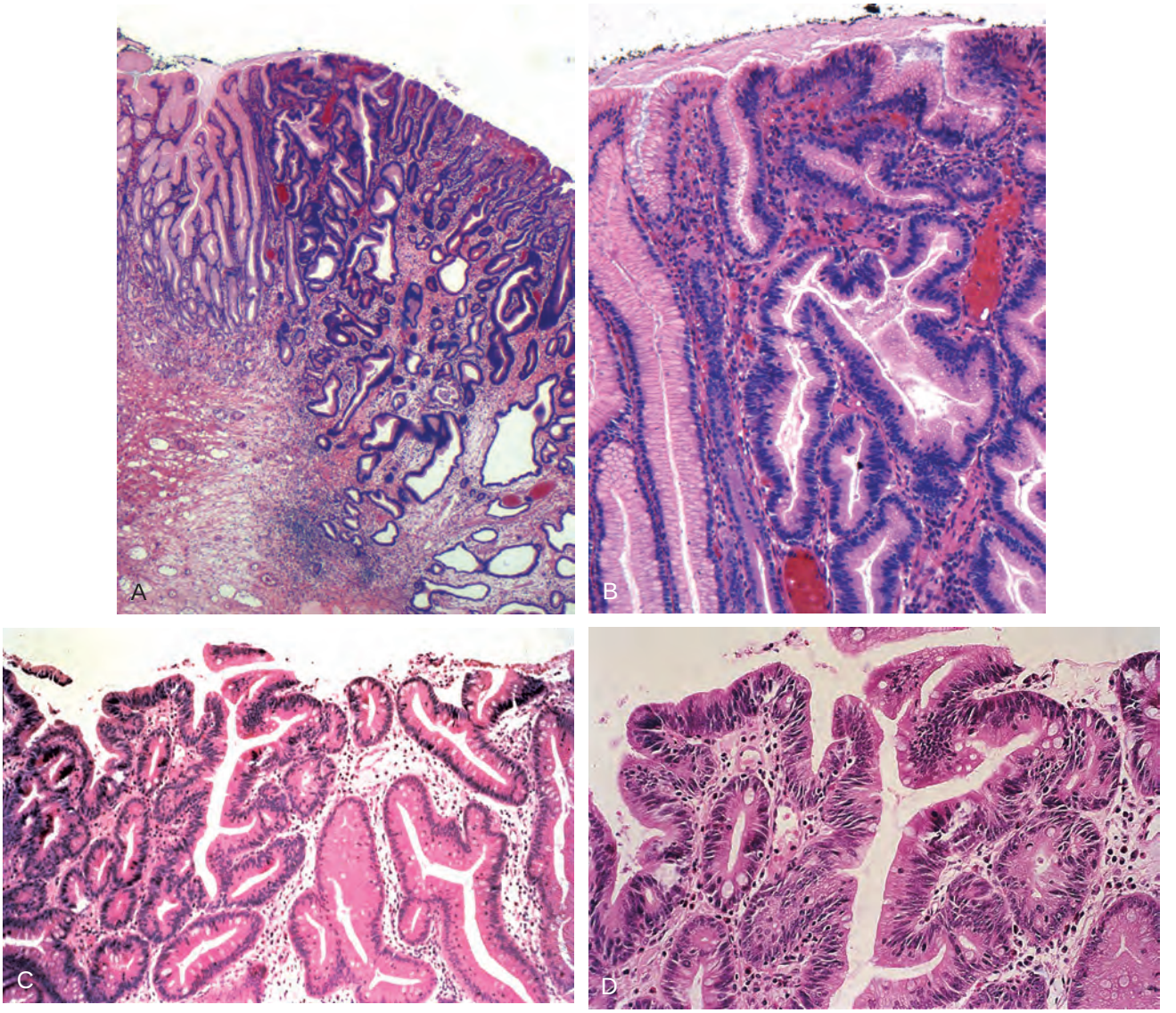



**FIGURE 17-2** Dysplasia arising in gastric hyperplastic polyps. **A,** Low-power view shows an area of low-grade dysplasia *(right)* adjacent to an area of hyperplastic foveolar epithelium *(left)*. **B,** Higher-power view of the area seen in **A** shows focal intestinal metaplasia in the non-dysplastic epithelium *(left)* and cytologic atypia, typical of dysplasia, extending to involve the surface epithelium *(right)*. This is consistent with low-grade dysplasia. **C,** Medium-power view shows an area of low-grade dysplasia *(left)* adjacent to an area of hyperplastic foveolar epithelium with intestinal metaplasia *(right)*. **D,** Dysplastic epithelium consists of cells with hyperchromatic, elongated, atypical nuclei, increased mitoses, and mucin depletion. Surface maturation is absent.

dilated glands lined predominantly by parietal and chief cells. Occasional cysts may also contain mucous cells. Fundic gland polyps do not normally contain prominent inflammation, ulceration, or marked regenerative changes typical of hyperplastic polyps.

Polyps associated with Ménétrier's disease, Cronkhite-Canada syndrome, and juvenile polyps are histologically similar to hyperplastic polyps. In these instances, appropriate clinical and endoscopic information is essential to establish a correct diagnosis.

Peutz-Jeghers polyps of the stomach reveal a characteristic arborizing pattern of smooth muscle that is more extensive than that of hyperplastic polyps. Peutz-Jeghers polyps lack significant stromal inflammation and are usually not associated with an underlying chronic gastritis. However, other features of Peutz-Jeghers polyps are similar to those of hyperplastic polyps.

## MORPHOLOGIC VARIANTS

### Polypoid Foveolar Hyperplasia

Polypoid foveolar hyperplasia is generally regarded as a precursor to hyperplastic polyps. Like hyperplastic polyps, polypoid foveolar hyperplasia is a regenerative lesion associated with chronic gastritis, as well as other types of acute and chronic mucosal injury.[5] For example, polypoid

**TABLE 17-2** Differentiation of Dysplasia from Regeneration in Gastric Polyps

| Feature | Negative for Dysplasia (Regeneration) | Indefinite for Dysplasia | Low-Grade Dysplasia | High-Grade Dysplasia |
|---|---|---|---|---|
| Surface maturation | Present | Present | Absent | Absent |
| Increased mitoses | Variable | Variable | Yes | Yes |
| Atypical mitoses | No | No | Few | Increased |
| Nuclear shape | Ovoid | Ovoid to elongated | Elongated | Elongated and/or irregular |
| Chromatin pattern | Hyperchromatic | Hyperchromatic | Irregular, hyperchromatic | Irregular, vesicular |
| Prominent nucleoli | Present | Variable | Absent | Present, often multiple |
| Nuclear stratification | Absent | Absent | Mild | Marked |
| Mucin depletion | Variable | Frequent | Frequent | Frequent |
| Gland size | Small | Small | Small | Irregular |
| Budding/branching | Absent | Absent | Focal | Prominent |
| Cribriform profiles | Absent | Absent | Absent | Frequent |
| Inflammation | Often present | Variable | Usually absent | Usually absent |

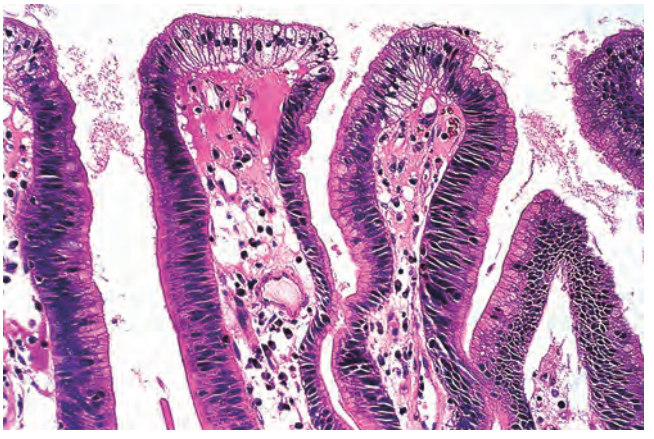


**FIGURE 17-3** Marked regenerative atypia in a gastric hyperplastic polyp. In contrast to true dysplasia, regenerating epithelium shows some surface maturation. Contrast to Figure 17-2.

foveolar hyperplasia often develops at the mucosal edges of surface erosions, ulcers, and carcinomas, or adjacent to gastrojejunostomy stomas; it may also be associated with the use of nonsteroidal anti-inflammatory drugs, bile reflux, alcohol use, or cytomegalovirus infection.[17,18,28,29] Polypoid foveolar hyperplasia may remain stable in size, regress, or grow. The proportion of these lesions that ultimately progress to hyperplastic polyps is unknown.

Grossly, polypoid foveolar hyperplasia usually appears as a sessile lesion that measures 1 to 2 mm in diameter. Lesions may be single or multiple and are most often found in the antrum. Microscopically, polypoid foveolar hyperplasia is characterized by simple hyperplasia of the gastric foveolar epithelium without cystic change or significant distortion. The foveolar regions are increased in length with luminal serration that imparts a corkscrew-like pattern (Fig. 17-4). The foveolae are typically crowded and tightly packed, with little intervening stroma. The epithelium is often mucin depleted and reactive in appearance, with mitotic figures, enlarged nuclei, and prominent nucleoli. Various degrees of intestinal metaplasia may be seen. The lamina propria may have a mild lymphoplasmacytic infiltrate, but smooth muscle proliferation is typically absent unless there is associated bile reflux.

## Gastric Foveolar Polyps

Gastric foveolar polyps were originally described by Goldman and Appelman in 1972.[30] It is unclear whether these represent regenerative lesions, a subtype of hyperplastic polyp, or hamartomatous proliferations. In fact, foveolar polyp is not universally accepted as a separate polyp type, perhaps because foveolar hyperplasia occurs so frequently in other reactive lesions. Foveolar polyps are found primarily in the antrum and are generally smaller than 2 cm in diameter.[30] However, some can reach sizes of up to 8 cm.[12] They are composed of densely packed foveolar mucinous epithelium that forms an arborizing network. Intestinal metaplasia is noted in approximately 33% of cases. Inflammation is conspicuously absent. Notably, of the eight patients originally described,[30] one had coexisting gastric carcinoma, and a second had colonic carcinoma. However, foveolar polyps are not normally believed to be associated with an increased risk of malignancy. Foveolar polyps can be differentiated from hyperplastic polyps and

**TABLE 17-3** Features of Gastric Polyps

| Polyp Type | Prevalence | Site | Architecture | Stroma | Adjacent Mucosa | Malignant Potential | Comments |
|---|---|---|---|---|---|---|---|
| Hyperplastic polyp | 75% of gastric polyps | Antrum > body | Elongated, cystic, and distorted foveolar epithelium; often marked regeneration | Inflammation, edema, smooth muscle hyperplasia | Chronic gastritis | <2% | *Helicobacter pylori* often present; dysplasia in 1%-20%; greatest in polyps >2 cm and in patients >50 years |
| Polypoid gastritis | 2nd most common polyp | Antrum > body | Normal architecture ± foveolar hyperplasia | Inflammation | Chronic gastritis | None | *H. pylori* often present, often multiple |
| Polypoid foveolar hyperplasia | Very common | Antrum > body | Elongated foveolar epithelium; no cysts | Normal lamina propria ± edema | Erosion, chronic gastritis, or normal | None | Increased with NSAIDs, alcohol, bile reflux, and after Billroth II gastrectomy |
| Fundic gland polyp | Common | Body only | Normal or distorted glands and microcysts lined by parietal and chief cells | Normal ± minimal inflammation | Normal | Rare | May be multiple in FAP; dysplasia in up to 40% of FAP-associated lesions and <1% of sporadic lesions |
| Adenoma | Common | Antrum > body | Dysplastic intestinal- or gastric-type epithelium; architecture varies with grade | ±Inflammation | Chronic gastritis or normal | 30% or more | Usually solitary |
| Gastritis cystica polyposa | Rare | Body > antrum | Entrapped, distorted, cystically dilated glands in muscularis; no atypia | Inflammation, edema, smooth muscle hyperplasia | Chronic atrophic gastritis | None | Most common after Billroth II gastrectomy and severe atrophic gastritis |
| Juvenile polyp | Rare | Body > antrum | Similar to hyperplastic polyp | Inflammation, edema, smooth muscle hyperplasia | Normal | Slight in stomach, greater elsewhere | Clinical history of polyps at other GI sites |
| Peutz-Jeghers polyp | Very rare | Any site | Normal gastric cell types in arborizing muscle network | Normal lamina propria | Normal | 2%-3% | Clinical history of other GI polyps, associated skin changes |
| Ménétrier's disease | Very rare | Body only | Foveolar hyperplasia, cysts, atrophy of glands | Normal or increased lymphocytes | Normal antrum | Very rare | Diffuse rugal hypertrophy, hypoproteinemia |

*FAP, familial adenomatous polyposis; NSAIDs, nonsteroidal anti-inflammatory drugs.*

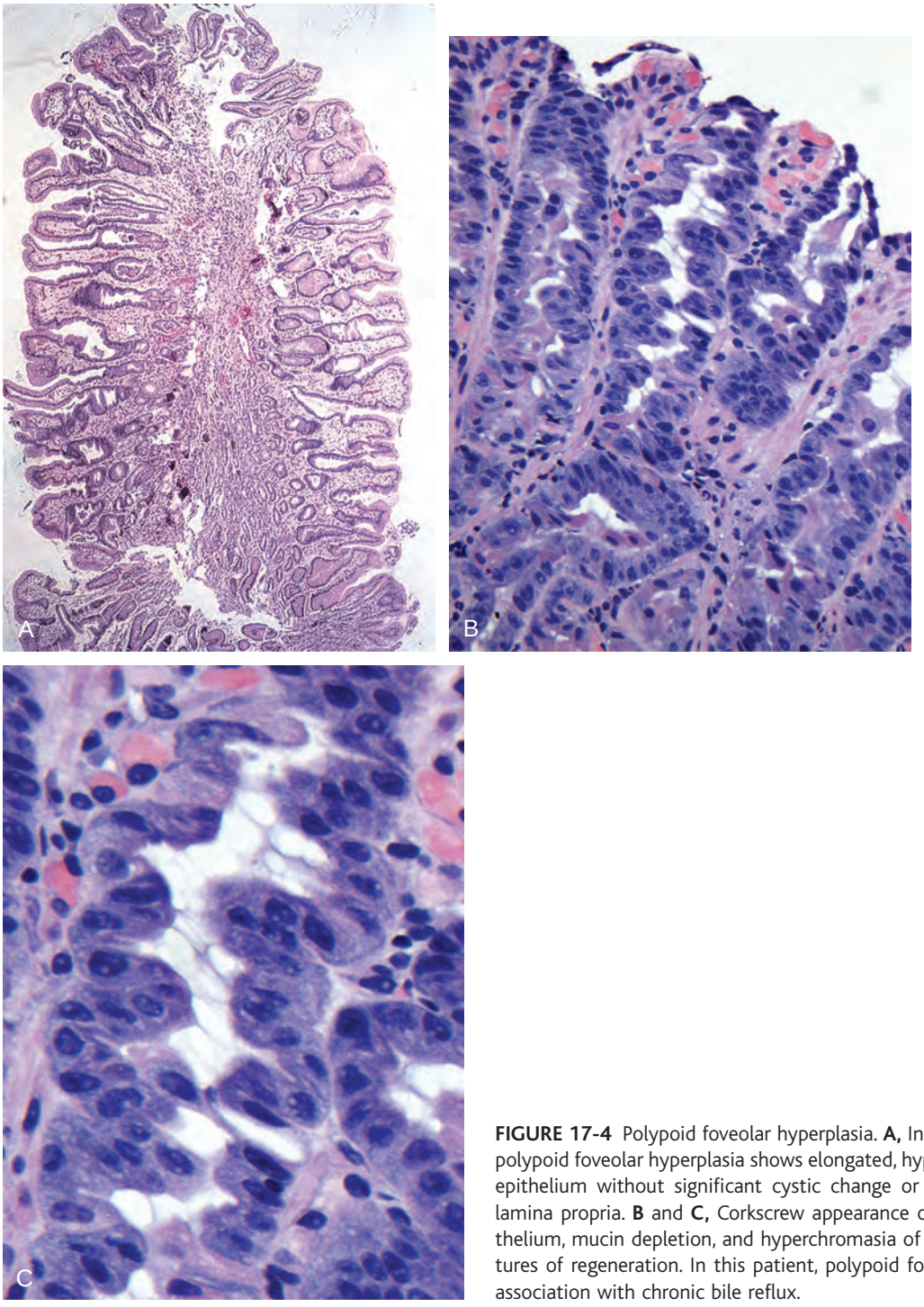



**FIGURE 17-4** Polypoid foveolar hyperplasia. **A,** In contrast to hyperplastic polyps, polypoid foveolar hyperplasia shows elongated, hyperplastic, and tortuous foveolar epithelium without significant cystic change or increased inflammation in the lamina propria. **B** and **C,** Corkscrew appearance of the hyperplastic foveolar epithelium, mucin depletion, and hyperchromasia of the epithelial nuclei are all features of regeneration. In this patient, polypoid foveolar hyperplasia developed in association with chronic bile reflux.

polypoid foveolar hyperplasia by the absence of both an inflammatory infiltrate and cystic change.

## Gastritis Cystica Polyposa/Profunda

Gastritis cystica polyposa/profunda is defined as a hyperplastic polyp that contains foci of misplaced foveolar or glandular epithelium (or both) in the muscularis mucosae or in deeper portions of the submucosa or muscularis propria. The lesion is termed *polyposa* when an intraluminal polyp is present and *profunda* when the bulk of the lesion is located in the wall of the stomach, both of which may result in gastric bleeding.[31] Although these lesions may develop in previously nonsurgically altered stomachs, more often they occur in patients with partial gastrectomy-induced chronic bile reflux.[32-37] Gastritis cystica polyposa is also referred to as stromal polypoid hypertrophic gastritis when it occurs in a postoperative gastric remnant. Because of the association with chronic gastritis

and partial gastrectomy, it is presumed that gastritis cystica polyposa/profunda is caused by an exuberant reactive proliferation with trauma-induced entrapment of epithelium in deep portions of the gastric wall. However, the reasons for the development of epithelial cysts in deeper portions of the gastric wall are not clear. Some have suggested that local ischemia or mucosal prolapse is critical to the development of submucosal or mural cysts.

Pathologically, polyps of gastritis cystica polyposa/profunda are usually located on the gastric side of gastroenteric anastomoses. Rarely, they develop on a background of chronic gastritis and are grossly indistinguishable from hyperplastic polyps. Lesions may reach up to 3 cm in diameter and are often associated with enlarged rugal folds. The characteristic histologic feature is the presence of entrapped epithelium or glands in, or beneath, the muscularis mucosae of the polyp (Fig. 17-5). The epithelium may be mucinous or glandular, is often cystic, and is usually surrounded by a rim of lamina propria–like stroma. The cysts are usually entrapped in dense, disorganized bundles of smooth muscle that extend downward from the muscularis mucosae. Hyperplasia, reactive changes, and mucin depletion in the epithelium are usually marked, imparting an atrophic appearance to the epithelium. Often an associated inflammatory infiltrate composed of neutrophils and mononuclear cells is found in the lamina propria. Superficial erosion and intestinal metaplasia may also occur. Rarely, dysplasia may develop in association with gastritis cystica polyposa/profunda, but it is unclear if the frequency of occurrence is equal to, or greater than, that of ordinary hyperplastic polyps.

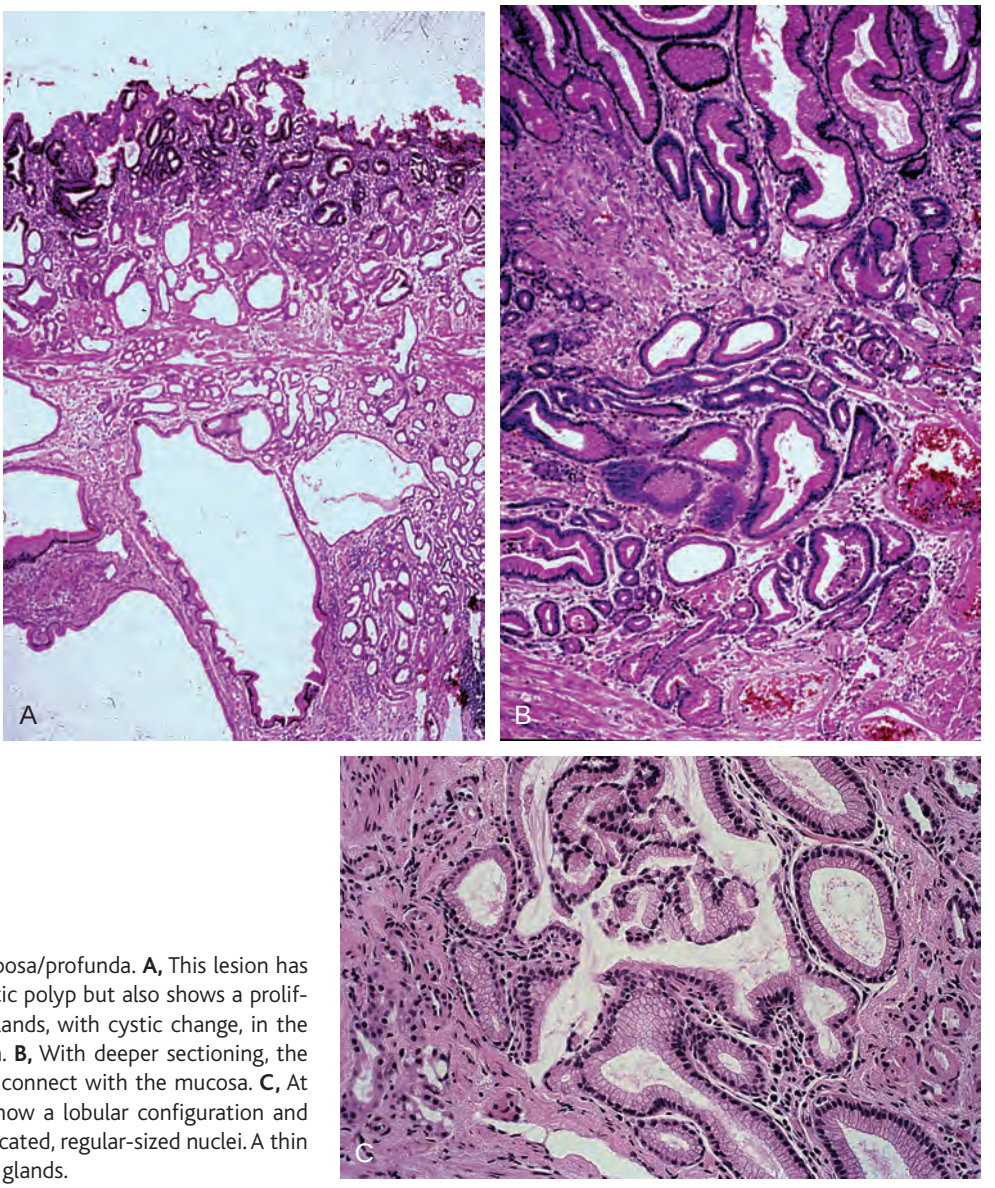



**FIGURE 17-5** Gastritis cystica polyposa/profunda. **A,** This lesion has the mucosal features of a hyperplastic polyp but also shows a proliferation of small to medium-sized glands, with cystic change, in the muscularis mucosae and submucosa. **B,** With deeper sectioning, the misplaced glands in the submucosa connect with the mucosa. **C,** At high power, the misplaced glands show a lobular configuration and are composed of cells with basally located, regular-sized nuclei. A thin rim of lamina propria surrounds the glands.

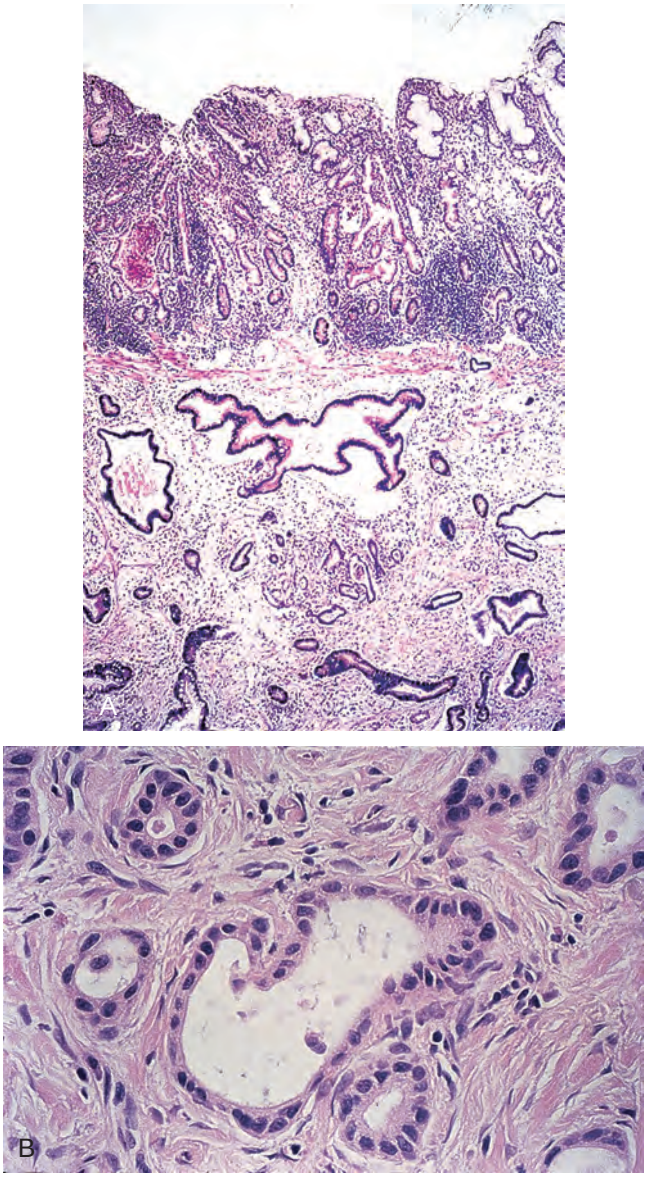



**FIGURE 17-6** Well-differentiated adenocarcinoma arising in association with chronic gastritis. **A,** In contrast to misplaced glands in gastritis cystica polyposa/profunda, carcinomatous glands are highly irregular in size and shape, show jagged edges, and are arranged in a haphazard nonlobular fashion. **B,** At high power, malignant glands show a greater degree of cytologic atypia, loss of polarity, hyperchromasia and, most importantly, they do not contain a rim of lamina propria surrounding the glands. The size and shape of the glands vary significantly.

On occasion, it may be difficult to distinguish between misplaced epithelium in gastritis cystica polyposa/profunda and a well-differentiated invasive adenocarcinoma (Fig. 17-6). Features such as desmoplasia, cellular pleomorphism, irregularity in the size and shape of the glands, atypical mitoses, and lack of a lamina propria rim surrounding the epithelium in question strongly favor a diagnosis of adenocarcinoma (Table 17-4).

**TABLE 17-4** Differentiation between Gastritis Cystica Polyposa/Profunda and Invasive Adenocarcinoma

| Feature | Gastritis Cystica Polyposa/Profunda | Invasive Adenocarcinoma |
|---|---|---|
| Overlying hyperplastic polyp | Yes | No |
| Overlying dysplasia | No | Frequent |
| Inflammation | Prominent | Absent |
| Smooth/lobular gland profiles | Yes | No |
| Irregular, distorted glands | No | Yes |
| Wide variation in size and shape of glands | No | Yes |
| Rim of lamina propria surrounding glands | Usually | Never |
| Mitoses | Rare | Common |
| Stromal desmoplasia | No | Often |
| Intraluminal necrosis | No | Occasional |
| Deep (muscularis propria or serosal) penetration | Rare | Not uncommon |

## Ménétrier's Disease

### CLINICAL FEATURES

Ménétrier's disease is a rare disorder characterized by diffuse hyperplasia of the foveolar epithelium of the body and fundus combined with hypoproteinemia resulting from protein-losing enteropathy. Other symptoms, such as weight loss, diarrhea, and peripheral edema, are also often present. In rare (mostly pediatric) cases, the antrum may be involved. In adults, onset is typically between 30 and 60 years of age, with a male-to-female ratio of 3:1. The syndrome is characterized by pronounced GI protein loss and hypoalbuminemia.[38,39] Although the clinical and pathologic features of Ménétrier's disease in children are essentially similar to those in adults, many children have a history of recent respiratory infection, peripheral blood eosinophilia, and cytomegalovirus infection.[40] Interestingly, the disease

is usually self-limited in children, generally lasting only several weeks.[41,42]

## PATHOGENESIS

Ménétrier's disease is a hyperplastic gastropathy that, in many cases, is driven by excessive secretion of transforming growth factor α (TGF-α).[43] In children, some cases appear to be associated with cytomegalovirus or other infections.[29,40,44] In these cases, spontaneous and treatment-associated remissions may occur. In contrast, although *H. pylori* infection and various other conditions have been associated with Ménétrier's disease in adults, antibiotics, acid suppression, octreotide, and anticholinergic agents have had therapeutic benefit only rarely in adult patients.[45,46] Transgenic mice that overexpress TGF-α in the stomach show many of the clinical and histologic features of Ménétrier's disease, such as marked foveolar hyperplasia, reduced numbers of parietal cells, and decreased acid production.[47,48] In one patient, cessation of nausea and vomiting, increased serum albumin, and partial restoration of parietal cell mass occurred after experimental treatment with a monoclonal antibody against the TGF-α receptor (epidermal growth factor receptor).[49] These findings have been repeated in additional patients, which validates the pivotal role of TGF-α in the pathogenesis of Ménétrier's disease and a potential mechanism of targeted biologic therapy.[50,51]

## PATHOLOGIC FEATURES

On endoscopic examination, Ménétrier's disease is characterized by diffuse irregular enlargement of the gastric rugae. However, some areas may appear polypoid. Enlarged rugae typically involve the body and fundus but may also involve the antrum in rare instances.[52] Histologically, the most characteristic feature of Ménétrier's disease is foveolar (mucous cell) hyperplasia (Fig. 17-7). The foveolae are elongated and have a corkscrew appearance. Cystic dilation is also common. Hyperplastic mucous cells are typically fully differentiated without regenerative features or mucin depletion. Inflammation is usually only modest, and ulceration is not normally present. Intestinal metaplasia is usually absent. Some

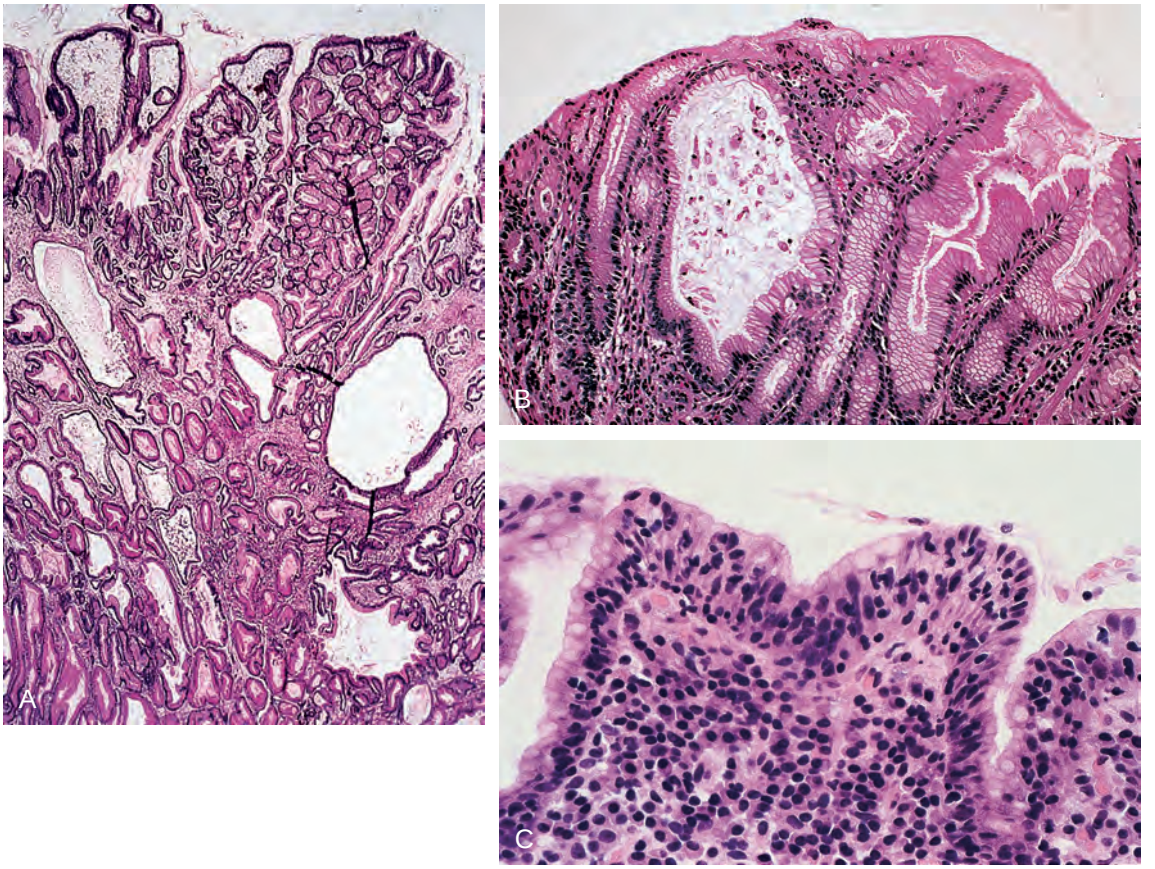



**FIGURE 17-7** Ménétrier's disease. **A,** At low power, a biopsy from Ménétrier's disease may look histologically similar to a hyperplastic polyp, being composed of irregular, tortuous, cystically dilated, and elongated foveolar epithelium. The glandular compartment *(bottom)* shows inflammation and atrophy. **B,** A biopsy from a patient with Ménétrier's disease may look histologically similar to the surface of a hyperplastic polyp. **C,** In some cases of Ménétrier's disease, a marked degree of intraepithelial lymphocytosis simulating lymphocytic gastritis is present.

cases show marked intraepithelial lymphocytosis. Diffuse or patchy glandular atrophy and hypoplasia of parietal and chief cells are also characteristic features of Ménétrier's disease.

A diagnosis of Ménétrier's disease may be difficult to establish on analysis of mucosal biopsies alone because some of the histologic features may mimic hyperplastic polyps. Thus, clinical information is essential to establish a correct diagnosis. In addition, Ménétrier's disease must be distinguished from other causes of enlarged gastric rugae, such as chronic gastritis, Zollinger-Ellison syndrome, and infiltration by tumor cells, such as lymphoma. Most of these are easily distinguished by biopsy analysis. For example, chronic gastritis shows abundant inflammation in the lamina propria without marked foveolar hyperplasia. The absence of foveolar hyperplasia and the presence of parietal cell hyperplasia distinguish the mucosal changes associated with Zollinger-Ellison syndrome from Ménétrier's disease. Lymphoma and other infiltrating tumors may also mimic Ménétrier's disease grossly, but biopsies are typically diagnostic.

### TREATMENT

In the past, the treatment of Ménétrier's disease was mainly supportive and provided in the form of serum albumin and nutritional supplementation. In severe cases, gastrectomy is necessary.[53] Most recently, long-term therapy with a monoclonal antibody that blocks TGF-α ligand binding to the epidermal growth factor receptor has been reported to have efficacy. Larger-scale clinical trials are now in progress.[50] Understanding the pathogenesis of Ménétrier's disease may also shed new light on the poorly defined association between Ménétrier's disease and adenocarcinoma, as the role of epidermal growth factor receptor signaling in GI neoplasia is well established.[54-56]

## Inflammatory Polyps

### INFLAMMATORY RETENTION POLYP

Inflammatory retention polyps are uncommon lesions that usually occur in association with *H. pylori* gastritis. Some cases are associated with hypergastrinemia.[8,9,54] Endoscopically, these are sessile lesions with a smooth surface contour. Microscopically, prominent foveolar cysts filled with retained mucus and variable numbers of neutrophils are characteristic features. The stroma is often edematous and may contain prominent polymorphonuclear and mononuclear inflammatory infiltrates. Deeper areas of the polyp are typically devoid of epithelium, characterized instead by an edematous inflammatory stroma; in some cases, a loose proliferation of small blood vessels is also seen. Similar to other inflammatory polyps, retention polyps may regress after eradication of the underlying gastritis.

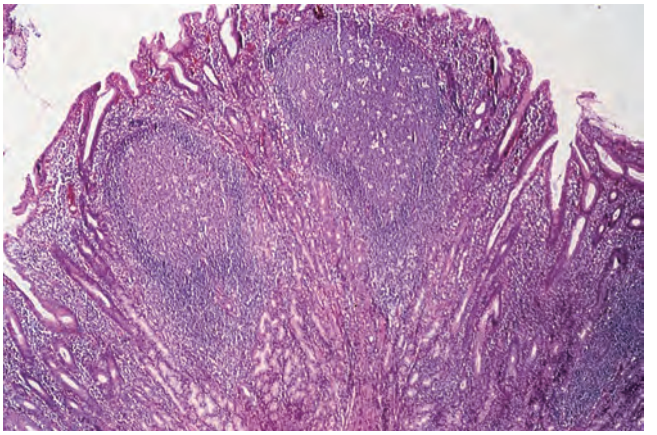


**FIGURE 17-8** Polypoid area of gastritis in a patient with chronic active *Helicobacter pylori* gastritis. In this case, prominent reactive lymphoid follicles in the mucosa, combined with inflammation in the lamina propria, impart a polypoid appearance to the mucosa.

### POLYPOID GASTRITIS

Polypoid gastritis develops as a result of chronic gastritis; it is characterized by localized expansion of lamina propria by inflammatory cells and lymphoid aggregates. Polypoid gastritis typically occurs in patients 10 years younger than those with hyperplastic polyps. The major risk factor is *H. pylori* gastritis.[55] Less commonly, polypoid gastritis may develop as a result of chronic atrophic gastritis. Polypoid gastritis is present in approximately 1% of all patients who undergo upper GI endoscopy.

Pathologically, these polyps are well-circumscribed nodules that usually measure less than 0.5 cm in diameter. They are most common in the antrum but can be located anywhere in the stomach. Histologically, they are characterized by epithelial regeneration with increased mitotic activity, marked acute and chronic lamina propria inflammation (Fig. 17-8), and nodular lymphoid aggregates. The polymorphic mixed inflammatory infiltrate, which includes neutrophils, plasma cells, and lymphocytes, and the absence of a homogeneous population of atypical lymphocytes and lymphoepithelial lesions are useful features for distinguishing these lesions from lymphoma.

## Hamartomatous Polyps

The most common hamartomatous lesions of the stomach are fundic gland polyps, although classification of these lesions as hamartomas is controversial (see later). Other less common hamartomatous polyps are usually associated with distinct polyposis syndromes, such as Peutz-Jeghers syndrome, juvenile polyposis, or, rarely, Cronkhite-Canada syndrome. Thus, in most instances, an accurate diagnosis is highly dependent on correlation of the pathologic findings with relevant clinical and endoscopic information.

## FUNDIC GLAND POLYP

### Clinical Features

Fundic gland polyps may be sporadic but they are also common among patients with familial adenomatous polyposis (FAP).[56] These polyps are identified in approximately 0.8% to 5% of patients who undergo upper GI endoscopy. Most patients are asymptomatic. However, symptoms such as nausea, vomiting, and epigastric pain may occur in patients with large or multiple polyps. They occur more often in women (female-to-male ratio, 5:1) at an average age of 53 years.[57] Recently, the prevalence of fundic gland polyps has increased dramatically because of their association with proton pump inhibitor therapy.[58-60] These lesions may also develop in Zollinger-Ellison syndrome. Up to 90% of patients with FAP have fundic gland polyps in oxyntic mucosa.[56,61-65] In FAP, polyps are highly associated with adenomatous polyposis coli (APC) gene mutations[66] and less frequently demonstrate mutations in β-catenin, another component of the APC signaling pathway (Table 17-5).[66-68] This contrasts with the molecular profile of sporadic lesions, which are associated with activating β-catenin mutations in more than 90% of cases, but with APC gene mutations in less than 10% of cases.[63,66] Although tumor suppressor gene methylation occurs more commonly in sporadic than in FAP-associated fundic gland polyps, the presence or absence of tumor suppressor gene methylation does not appear to be specifically associated with development of dysplasia in these lesions.[69-75] Although it remains controversial if *H. pylori* can induce fundic gland polyp regression, *H. pylori* infection is, in fact, rare in fundic gland polyps.[76,77]

### Pathologic Features

Fundic gland polyps are smooth, sessile, well-circumscribed lesions that occur exclusively in gastric oxyntic mucosa. They may be single or multiple, particularly in FAP patients. In one study, each patient with FAP had an average of four polyps, with a range from one to 11.[57] Fundic gland polyps are most often smaller than 1.0 cm, but lesions up to 2 to 3 cm have been reported. Histologically, these polyps are composed of cystically dilated and architecturally irregular fundic glands (Fig. 17-9). Fundic glands, which often assume a microcystic configuration or form prominent budding, are lined by flattened parietal and chief cells and, occasionally, mucinous foveolar cells. Inflammation is typically absent or minimal. The surface and foveolar epithelium in fundic gland polyps are atrophic and hypoplastic.

**TABLE 17-5** Fundic Gland Polyps: Comparison of Sporadic and Syndromic

| Feature | Sporadic | Syndromic |
|---|---|---|
| Number | Usually single (40% multiple) | Often multiple (90%) |
| Male-to-female ratio | F > M | M = F |
| Mean age | 52 | 40 |
| Mutations | β-catenin > APC | APC > β-catenin |
| Dysplasia risk | Low (<1%) | High (up to 48%) |
| Incidence | 0.8%-1.4% | 50%-90% |

*APC, adenomatous polyposis coli.*

### Natural History and Treatment

Although sporadic fundic gland polyps are considered benign lesions with no malignant potential, dysplasia may be present in up to 48% of FAP-associated lesions.[70-72,74,75,78-84] Most cases show only low-grade dysplasia, and the prevalence of high-grade dysplasia ranges from 0% to 12.5%. In contrast, dysplasia is detected in fewer than 6% of sporadic polyps.[63,79,80,84] Dysplasia in fundic gland polyps occurs primarily in the surface and foveolar compartment. Like dysplasia in adenomas and hyperplastic polyps, dysplasia in fundic gland polyps usually reveals elongated hyperchromatic nuclei, an increased nucleus-to-cytoplasm ratio, and nuclear pseudostratification that extends to the surface of the polyp (Fig. 17-10). When hyperchromaticity and nuclear enlargement are limited to proliferative zones of the polyp, and particularly in the setting of active inflammation, regenerative atypia should be considered. The risk of malignant transformation is rare. Only four cases of adenocarcinoma (all in FAP patients) have been reported in fundic gland polyps.

## PEUTZ-JEGHERS POLYP

### Clinical Features

Peutz-Jeghers syndrome is an autosomal dominant inherited syndrome characterized by the presence of mucocutaneous pigmentation and multiple GI hamartomatous polyps.[85,86] The disease occurs equally in men and women. Patients usually present in the second or third decade of life with abdominal pain, GI bleeding, or, less commonly, obstruction. Hamartomatous polyps in Peutz-Jeghers syndrome may occur in any portion of the GI tract, but they are most common in the small intestine. Gastric lesions are present in 25% to 50% of patients. Because of their small size, gastric Peutz-Jeghers polyps are usually asymptomatic.

Peutz-Jeghers syndrome is caused by a germline mutation in the serine-threonine kinase *STK11/LKB1* tumor suppressor gene.[87-89] The function of this gene product is related to the TGF-β signal transduction pathway.[90] Dysplasia and carcinoma are rare in gastric polyps, occurring at an estimated incidence of 2% to 3%.[91] However, they may develop at a young age. For example, in one series of Peutz-Jeghers syndrome patients with gastric cancer, carcinoma developed at a mean age of 27 years.[92]

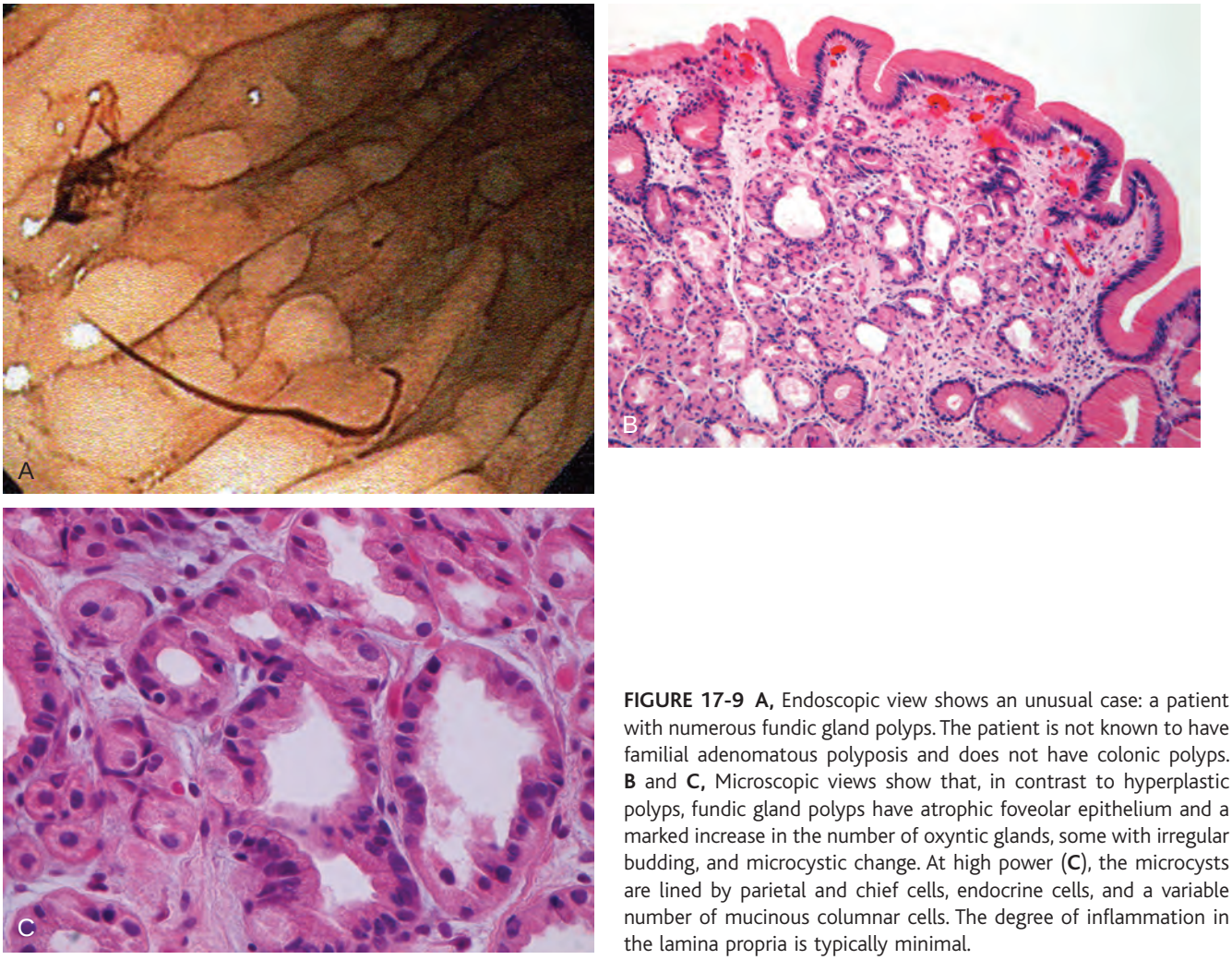



**FIGURE 17-9 A,** Endoscopic view shows an unusual case: a patient with numerous fundic gland polyps. The patient is not known to have familial adenomatous polyposis and does not have colonic polyps. **B** and **C,** Microscopic views show that, in contrast to hyperplastic polyps, fundic gland polyps have atrophic foveolar epithelium and a marked increase in the number of oxyntic glands, some with irregular budding, and microcystic change. At high power (**C**), the microcysts are lined by parietal and chief cells, endocrine cells, and a variable number of mucinous columnar cells. The degree of inflammation in the lamina propria is typically minimal.

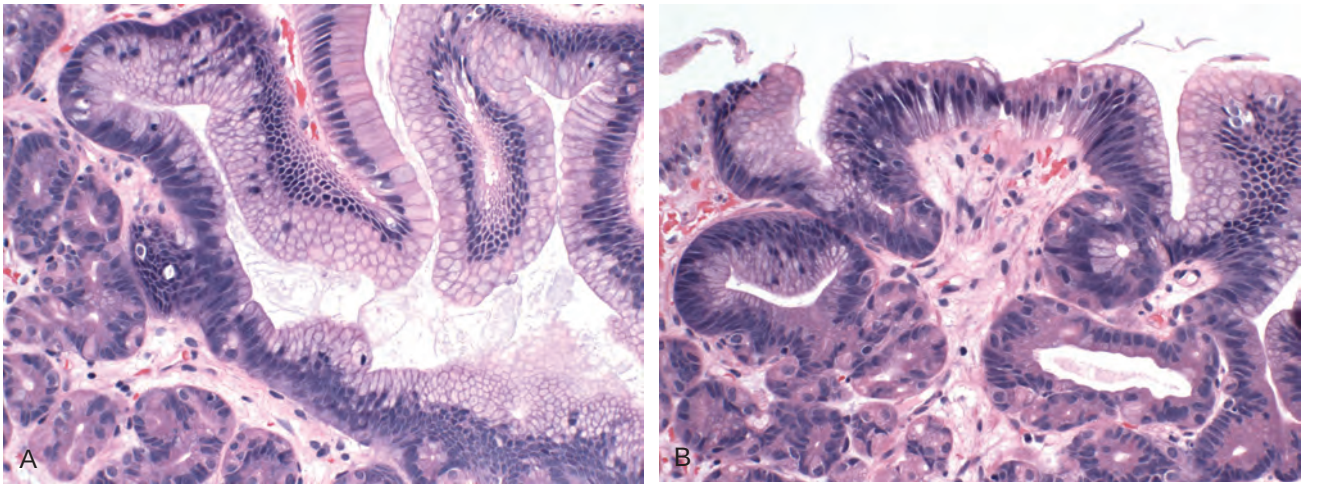
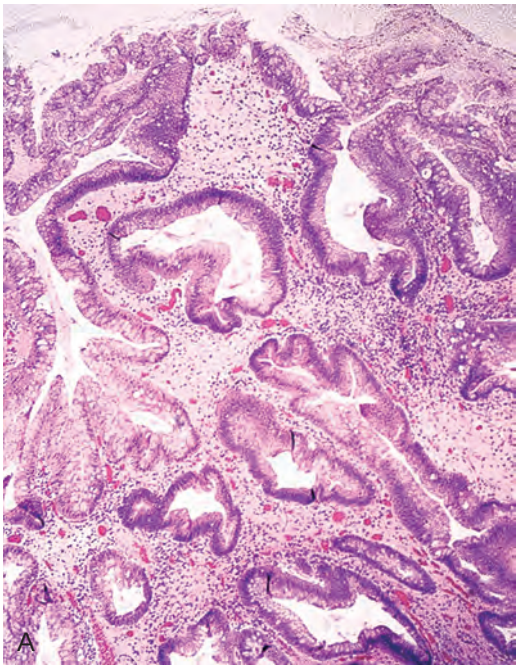



**FIGURE 17-10** Dysplasia arising in a fundic gland polyp associated with familial adenomatous polyposis. **A,** The *right* side of the photograph shows an area of surface and foveolar epithelial atypia consistent with low-grade dysplasia. **B,** The dysplastic epithelium shows a proliferation of cells containing hyperchromatic, pencil-shaped nuclei with clumped chromatin, pseudostratification, and increased mitoses. Dysplastic epithelium may be seen in the glandular or surface compartment of the polyps.

Interestingly, *Lkb1* knockout mice develop GI hamartomatous polyposis similar to that in Peutz-Jeghers syndrome.[93,94] Knockout mice represent a unique opportunity to investigate new therapeutic agents, such as specific kinase inhibitors. Some studies of *Lkb1* heterozygous mice and Peutz-Jeghers syndrome patients suggests that cyclooxygenase-2 inhibition may ultimately prove beneficial in chemoprevention of polyposis.[95]

### Pathologic Features

Peutz-Jeghers polyps may be sessile, but they are more commonly pedunculated and generally measure less than 1 cm. However, larger lesions may rarely develop. The gross appearance is similar to Peutz-Jeghers polyps in other portions of the GI tract and often includes a velvety papillary or villiform surface. They occur most commonly in the antrum but may develop in any part of the stomach. Microscopically, gastric Peutz-Jeghers polyps show a complex arborizing architecture of smooth muscle. Irregular bundles of smooth muscle extend from the muscularis mucosae into the lamina propria of papillary projections and extend to the surface of the polyp (Fig. 17-11). Marked surface and foveolar hyperplasia, with cystic change, is often present. Glandular atrophy is common, and a mild degree of lamina propria edema, congestion, and inflammation may also be apparent. The morphologic features are, essentially, similar to those of gastric hyperplastic polyps, with the exception that hamartomatous polyps often have a more fully developed and prominent smooth muscle component. Gastric Peutz-Jeghers polyps are usually clinically silent. However, rare examples of patients who have vomited large polyps, presumably as a result of autoamputation, have been reported.[96] Dysplasia can occur in Peutz-Jeghers polyps (Fig. 17-12), but is uncommon in the stomach. There is, presently, no consensus on appropriate surveillance or follow-up of gastric Peutz-Jeghers polyps, with or without dysplasia, although general guidelines have been proposed.[97]



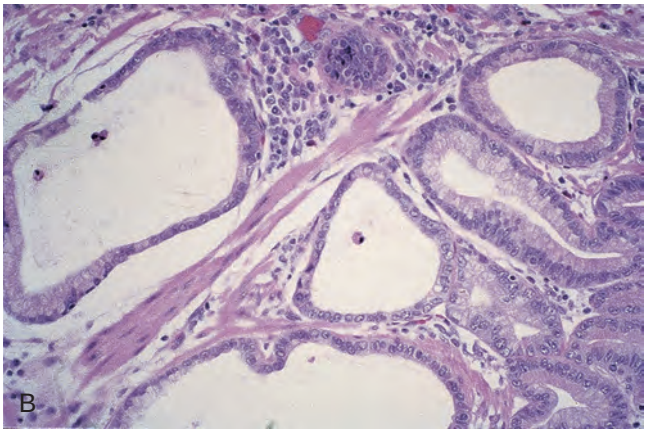




**FIGURE 17-11** Gastric Peutz-Jeghers polyp in a patient with Peutz-Jeghers syndrome. **A,** The low-power appearance of a Peutz-Jeghers polyp is similar to that of a hyperplastic polyp. It is composed of an irregular and architecturally distorted proliferation of foveolar epithelium with increased inflammation in the lamina propria. **B,** This Peutz-Jeghers polyp shows a more prominent muscularis proliferation.

## JUVENILE POLYP

### Clinical Features

Sporadic gastric juvenile polyps are rare. They may occur as part of generalized juvenile polyposis coli or as the rare gastric subtype of this syndrome.[98,99] Gastric juvenile polyps are present in 15% to 25% of patients with generalized juvenile polyposis coli. Twenty percent to 50% of patients with gastric juvenile polyps have a positive family history for juvenile polyposis coli. Juvenile polyposis coli is an autosomal dominant condition characterized by a genetic dysregulation of the TGF-β pathway. The mutation most commonly identified thus far involves the *SMAD4/DPC4* gene, which codes for a cytoplasmic intermediate in TGF-β signaling.[100-103] However, this mutation is present in only a minority of cases, so other as yet unidentified mutations are probably responsible for this disorder as well.[104-106] Possible gene candidates include *PTEN,* which is mutated in Cowden's syndrome.[107,108]

### Pathologic Features

The gross and microscopic features of gastric juvenile polyps resemble those of gastric hyperplastic polyps (Fig. 17-13). In some instances, juvenile polyps may show a less pronounced degree of muscularis hyperplasia and a more prominently inflamed lamina propria than hyperplastic polyps. However, because of significant overlap, this feature is not helpful in all cases. The essential features of juvenile polyps include surface and foveolar hyperplasia, cystic change, edema and inflammation of the lamina propria,

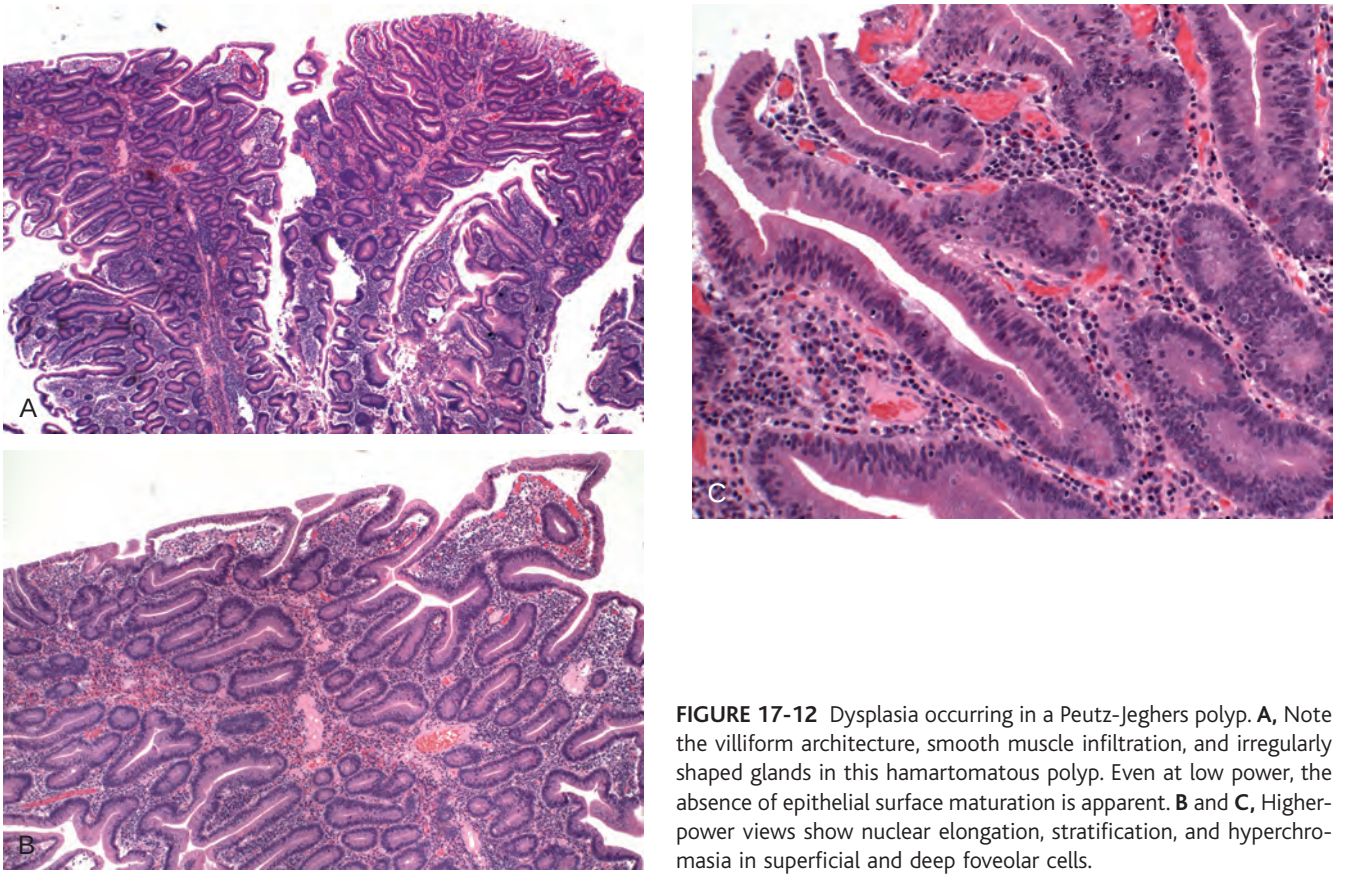



**FIGURE 17-12** Dysplasia occurring in a Peutz-Jeghers polyp. **A,** Note the villiform architecture, smooth muscle infiltration, and irregularly shaped glands in this hamartomatous polyp. Even at low power, the absence of epithelial surface maturation is apparent. **B** and **C,** Higher-power views show nuclear elongation, stratification, and hyperchromasia in superficial and deep foveolar cells.

smooth muscle hyperplasia, and a variable degree of intestinal metaplasia. The polyps may range from a few millimeters to several centimeters in size. Based on histology alone, it is not possible to reliably distinguish an isolated gastric juvenile polyp from a hyperplastic polyp. Therefore, knowledge of the clinical context, including family history, is essential in establishing a correct diagnosis.[99,109]

Dysplasia, and carcinoma, occur with increased frequency among patients with generalized juvenile polyposis coli. However, dysplasia is rare in gastric polyps. Dysplasia in juvenile polyps appears histologically similar to that which occurs in hyperplastic polyps; it consists of mucin-depleted surface and foveolar epithelium, hyperchromatic elongated nuclei with clumped chromatin, increased nucleus-to-cytoplasm ratio, loss of polarity, and pseudostratification. Of course, lack of surface maturation is a common feature of dysplasia. With increasing degrees of dysplasia, the nuclei become larger and show greater overlapping and loss of polarity, and the glands may take on a back-to-back or cribriform growth pattern.

## CRONKHITE-CANADA SYNDROME–ASSOCIATED POLYPS

### Clinical Features

Cronkhite-Canada syndrome is a nonhereditary, generalized polyposis disorder that involves the stomach, small intestine, and colorectum.[110-112] Unlike most syndromic polyposis disorders, Cronkhite-Canada syndrome typically appears in middle adulthood. It occurs equally in men and women. In addition to the presence of numerous GI polyps, patients with this disorder show alopecia, nail atrophy, skin hyperpigmentation, and vitiligo.[113] Common GI complaints include diarrhea, weight loss, abdominal pain, anorexia, weakness, and hematochezia.[111] The etiology of the syndrome is unknown.

Cronkhite-Canada syndrome is associated with a mortality rate of approximately 50%; most deaths are related to anemia and chronic wasting. Unfortunately, effective therapy for Cronkhite-Canada syndrome is not yet available. Treatment options include nutritional support, antibiotics, corticosteroids, anabolic steroids, histamine-receptor antagonists, and surgery, depending on the particular circumstances of the patient.[114-119] A combination of histamine-receptor antagonists, cromolyn sodium, prednisone, and suppressive antibiotics has recently been shown to be effective, but, as with other Cronkhite-Canada syndrome treatments, controlled therapeutic trials have not been reported. Up to 20% of patients with Cronkhite-Canada syndrome develop adenocarcinoma, which may occur in any portion of the GI tract, including the stomach.[120-123] Cancers may develop in polyps or nonpolypoid mucosa.[124]

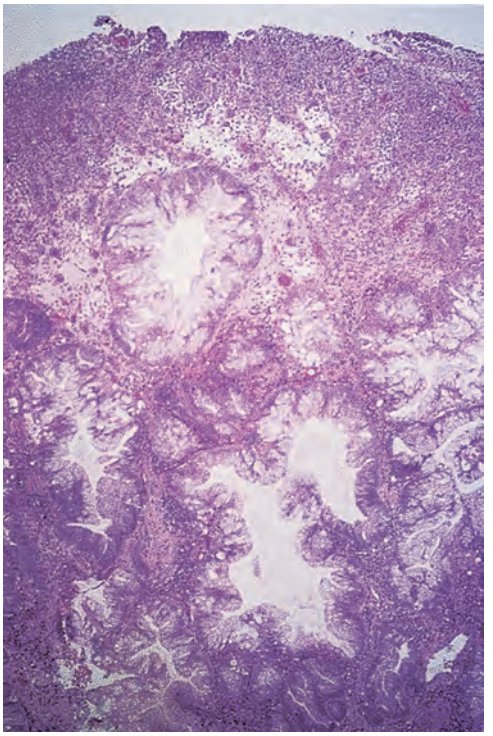


**FIGURE 17-13** Gastric juvenile polyp in a patient with generalized juvenile polyposis coli. Like hyperplastic polyps and Peutz-Jeghers polyps, juvenile polyps are composed of irregular, dilated, and tortuous foveolar and glandular epithelium with inflammation in the lamina propria. Diffuse ulceration is more common in gastric juvenile polyps than in hyperplastic or Peutz-Jeghers polyps.

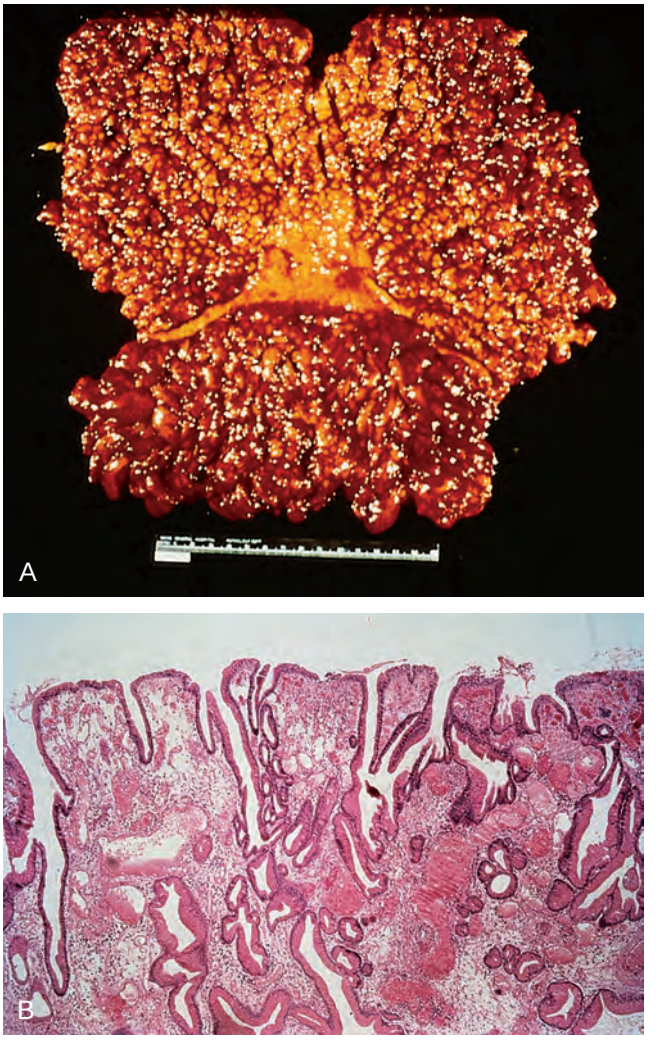



**FIGURE 17-14 A,** Resected stomach in a patient with Cronkhite-Canada syndrome. The fundus and the antrum show a carpet-like proliferation of small polyps and enlarged rugae. **B,** Both the polypoid and the interpolypoid mucosa show elongated, tortuous, and cystically dilated foveolar epithelium, as well as edema and hemorrhage, in the lamina propria. In contrast to hyperplastic polyps, Cronkhite-Canada syndrome–associated polyps typically do not show prominent inflammation or muscularis hyperplasia.

### Pathologic Features

Advanced cases of Cronkhite-Canada syndrome show diffuse irregular enlargement of the gastric rugae throughout the fundus and antrum. Numerous small to medium-sized polyps that typically measure between 0.5 and 1.5 cm in diameter may be superimposed on enlarged rugae (Fig. 17-14A). The endoscopic appearance is similar to Ménétrier's disease, except that the entire stomach is involved. Individual polyps may appear as elongated, papillary, or villiform lesions or, alternatively, as clusters of sessile nodules. Helpful in the diagnosis of this disorder is the fact that interpolypoid mucosa is typically abnormal.

Microscopically, changes in the stomach involve both the interpolypoid and polypoid mucosa (Fig. 17-14B). As in Ménétrier's disease, marked surface and foveolar hyperplasia with cystic change and atrophy of the glands are characteristic features. The lamina propria is often edematous and shows a mild to moderate degree of inflammation, but intestinal metaplasia is uncommon. The surrounding nonpolypoid mucosa shows alternating areas of atrophy and foveolar hyperplasia with microcystic change. Unfortunately, a single biopsy from a Cronkhite-Canada syndrome–associated polyp may look histologically identical to a juvenile or a hyperplastic polyp or even to Ménétrier's disease. However, knowledge of other clinical features of this disorder, particularly when combined with diffuse enlargement of gastric rugae and multiple polyps in all areas of the stomach, is helpful in establishing a correct diagnosis.

## Embryonic Rests and Heterotopia

### PANCREATIC HETEROTOPIA

#### Clinical Features

Ectopic rests of pancreatic tissue, also termed adenomyomas, may develop when fragments of pancreas separate

during embryonic rotation of the foregut. Foci of ectopic pancreatic tissue are most commonly found in the stomach, but they may also occur in the small intestine and colon. In one recent series, 4% of all benign gastric polyps were due to pancreatic heterotopia.[125] Men and women are affected equally, and the average age at diagnosis is 45 years. However, pediatric patients may be affected as well.[126] Heterotopic pancreatic tissue is susceptible to many of the same inflammatory disorders that affect the native pancreas, including acute and chronic pancreatitis and cancer,[126-128] although the latter complication is extremely uncommon.

## Pathologic Features

Pancreatic heterotopia most commonly occurs in the prepyloric and antral regions of the stomach, but may rarely occur in the corpus. The lesions usually measure less than 3 cm in size. Grossly, they consist of small submucosal nodules that protrude through the mucosa, often forming a central dimple or surface erosion, which represents a draining pancreatic duct. This finding offers an endoscopic clue to the diagnosis. Ulceration and bleeding are common. Clinical symptoms relate to the location and size of the lesion as well as the presence or absence of ulceration and bleeding.

Microscopically, heterotopic pancreatic tissue may be composed of any of the normal components of pancreatic parenchyma, either in isolation or in combination. Thus, exocrine (acinar tissue), endocrine (islet cells), and ductal epithelial elements, in combination with pancreatic stroma, may be present in a mixture in various proportions. Histologically, each component is similar to that which occurs in the normal pancreas (Fig. 17-15). Acini typically drain into ducts lined by tall columnar epithelium. However, squamous metaplasia is occasionally present. Thick disorganized bundles of hyperplastic smooth muscle are often admixed with acini and ducts. Endocrine elements, representing islets of Langerhans, are present in less than 50% of cases. Acute and chronic inflammation and necrosis, resembling acute and chronic pancreatitis of the native pancreas, may be present. Gastric mucosa overlying heterotopic pancreas often shows reactive changes, including foveolar hyperplasia, variable amounts of edema and congestion, and inflammation.

## Differential Diagnosis

The differential diagnosis of pancreatic heterotopia includes well-differentiated adenocarcinoma and gastritis cystica polyposa/profunda. Distinguishing between these entities may be difficult if pancreatic acini and endocrine cells are not readily identifiable. However, unlike well-differentiated carcinoma, pancreatic heterotopia does not show significant architectural or cytologic atypia, atypical mitoses, or other features of malignancy. In contrast to carcinoma, the ducts in pancreatic heterotopia are smooth, not irregular or jagged in contour. Furthermore, histologic foci of pancreatic heterotopia are normally present in an organoid,

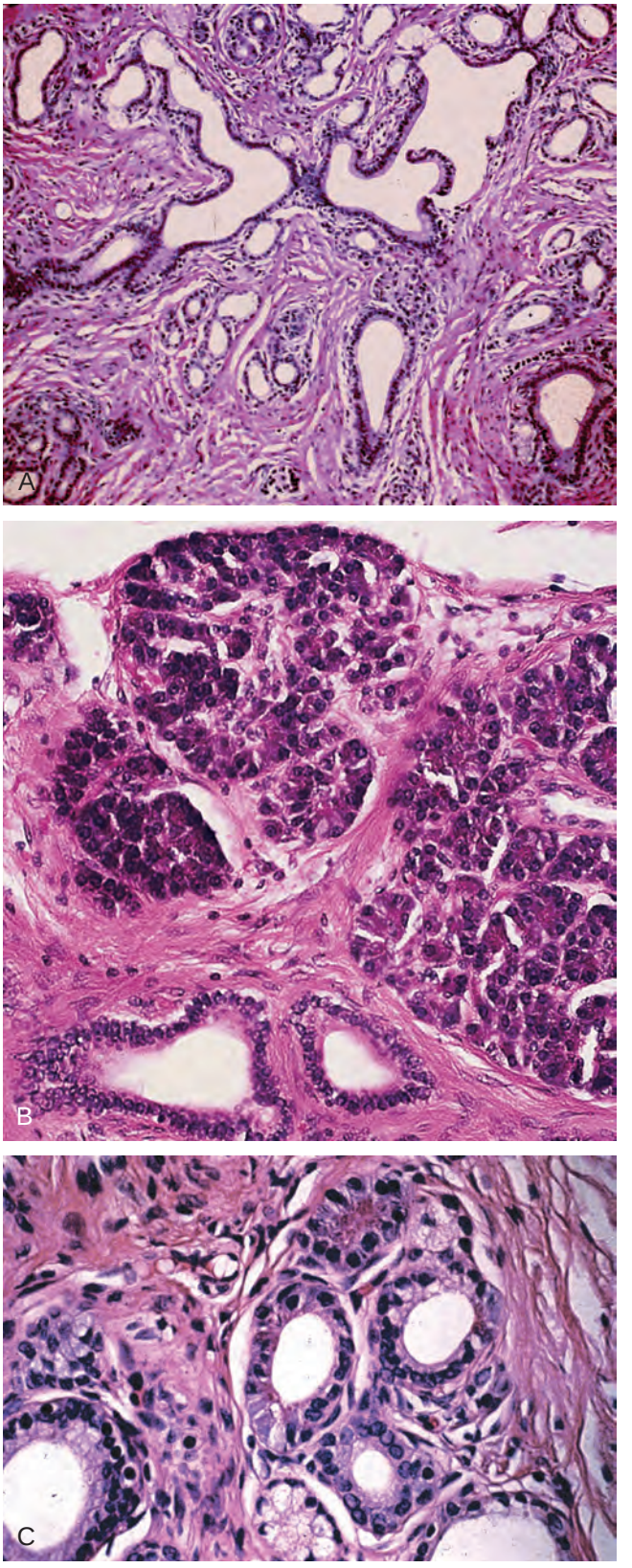



**FIGURE 17-15** Pancreatic heterotopia. **A,** Pancreatic heterotopia consists of variably sized ducts, acinar glands, and islet cells in a stroma characterized by muscularis hyperplasia. **B,** Prominent acinar glands, a few ducts, and marked muscularis hyperplasia are evident. **C,** At high power, another area from this patient highlights the bland cytologic features of the duct epithelium.

lobulated growth pattern. Smooth muscle hyperplasia associated with pancreatic heterotopia contrasts greatly with the desmoplasia often associated with invasive carcinoma.

Gastritis cystica polyposa/profunda may also resemble pancreatic heterotopia, but the former is associated with mucosal hyperplastic changes, inflammation, and erosions. In contrast to pancreatic heterotopia, the submucosal epithelium of gastritis cystica polyposa/profunda is composed of mucinous columnar epithelium, with or without gastric glands, in contrast to the pancreatic duct–type epithelium characteristic of pancreatic heterotopia.

## PANCREATIC ACINAR METAPLASIA

### Clinical Features

Pancreatic acinar metaplasia may occur in children or adults[129-132] and is detected in approximately 1% of gastric biopsies in both children and adults.[133] In adults, the mean age is 52 years, with a range of 18 to 89 years and a male-to-female ratio of 1:1.[134] Pancreatic acinar metaplasia occurs most often in antral and cardiac (gastroesophageal junction) mucosa on a background of either little or no inflammation, and often without glandular atrophy or intestinal metaplasia.[130,132] The cause of pancreatic acinar metaplasia is unknown. Some studies have shown an association with chronic gastritis.[133,135] However, others have shown no association with esophagitis, intestinal metaplasia, chronic gastritis, or *H. pylori* infection.[134] Thus, this condition has recently been proposed to represent either a congenital rest, particularly when it occurs at the gastroesophageal junction,[134] or a metaplastic consequence of chronic gastritis.[135]

### Pathologic Features

Pancreatic acinar–like cells are characterized by the presence of fine acidophilic granules in the apical cytoplasm and prominent basophilia of the basal portion of the cells. The cells are usually arranged in small nests or lobules, often in continuity with the surrounding gastric glands (Fig. 17-16).[136] Alternatively, lobules of pancreatic acinar cells may be separated from the surrounding gastric mucosa by connective tissue and smooth muscle.[136] When examined immunocytochemically or by electron microscopy, the cells are indistinguishable from pancreatic acinar cells. They contain exocrine secretory granules immunoreactive for exocrine pancreatic markers, such as lipase, trypsinogen, and pancreatic α-amylase.[130,132,133] Occasional cells may also be positive for neuroendocrine markers, such as chromogranin, somatostatin, gastrin, and serotonin. Some cells are positive for both exocrine and neuroendocrine markers.[130]

### Differential Diagnosis

The most common differential diagnosis is pancreatic heterotopia. The presence of ductal elements, pancreatic stroma, or well-defined islets effectively excludes pancreatic acinar metaplasia. Paneth cell metaplasia may also resemble pancreatic acinar metaplasia. However, the well-developed zymogen granules and small and fine apical granules are distinct from the larger more refractile granules characteristic of Paneth cells. Immunostains for trypsinogen and lipase may be helpful in diagnostically difficult cases, but this distinction has little clinical consequence.

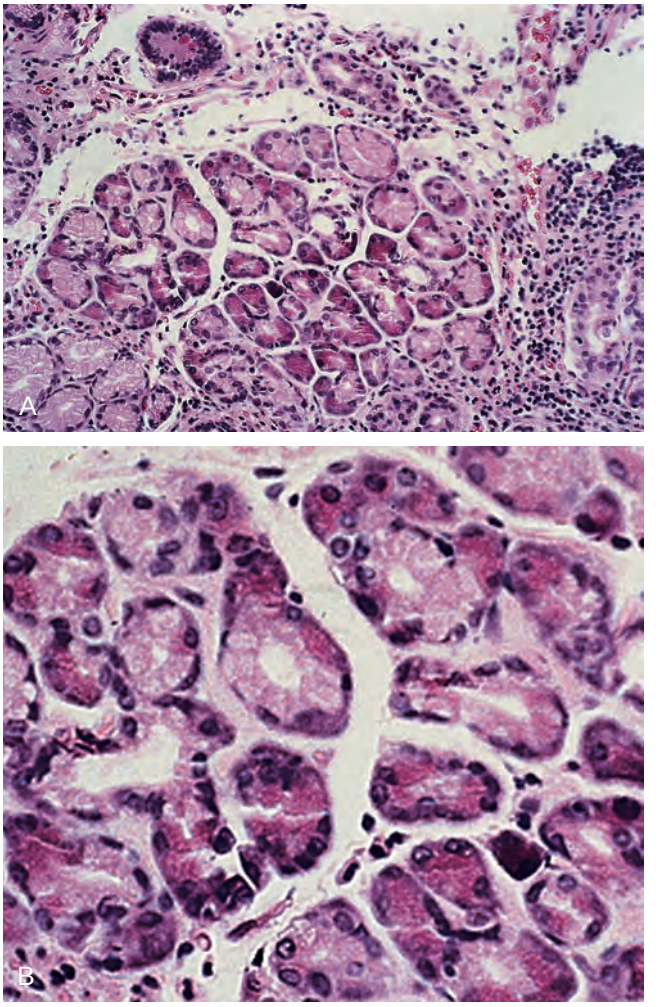



**FIGURE 17-16** Pancreatic acinar metaplasia in the gastric cardia of a patient with chronic gastritis. In contrast to pancreatic heterotopia, pancreatic acinar metaplasia is composed of a well-demarcated lobule of pancreatic acinar glands without islets of Langerhans or ducts. **B,** The granules of the acinar cells can be easily appreciated at higher power.

## BRUNNER'S GLAND NODULES

In the duodenum, Brunner's gland hyperplasia is usually related to chronic peptic duodenitis. In contrast, it is unclear if the presence of Brunner's glands in the prepyloric region represents a hamartomatous process, is the result of

proximal extension of hyperplastic duodenal Brunner's glands into the distal stomach because of hyperchlorhydria, or is a consequence of chronic *H. pylori* gastritis.[137-140] Histologically, Brunner's gland nodules are composed of densely packed, cytologically benign Brunner's glands that form a prominent submucosal nodule. In rare and extreme cases, pyloric obstruction may occur.

## Epithelial Polyps

### ADENOMA

#### Clinical Features

Sporadic adenomas account for 8% to 10% of all gastric polyps. Their incidence increases progressively with patient age.[11,12,21,141-143] However, there is marked variation in the incidence of adenomas in different geographic populations that, generally, parallels the incidence of adenocarcinoma. For example, gastric adenomas are more common in Japan, where the incidence of adenocarcinoma is high.[2,96,144-146] Affected patients are usually in the sixth to seventh decade of life, and the male-to-female ratio is 3:1. Adenomas are also increased in incidence in patients with familial adenomatous polyposis (1% to 15%). As in other forms of gastric dysplasia, adenomas often occur on a background of chronic gastritis with atrophy and intestinal metaplasia. This finding has led some authors to speculate that most, if not all, adenomas may actually represent polypoid areas of dysplasia that develop as a result of underlying chronic gastritis, similar to polypoid dysplasia in ulcerative colitis.[147] Sporadic adenomas in an otherwise normal stomach, are, in fact, quite rare. However, the pathogenesis of gastric "adenomas" is unresolved and remains to be studied in a rigorous systematic fashion. Interestingly, one study has shown that intestinal-type adenomas are more often associated with chronic gastritis than lesions composed of gastric-type epithelium, which supports the theory that the former may represent chronic gastritis-associated polypoid dysplasia.

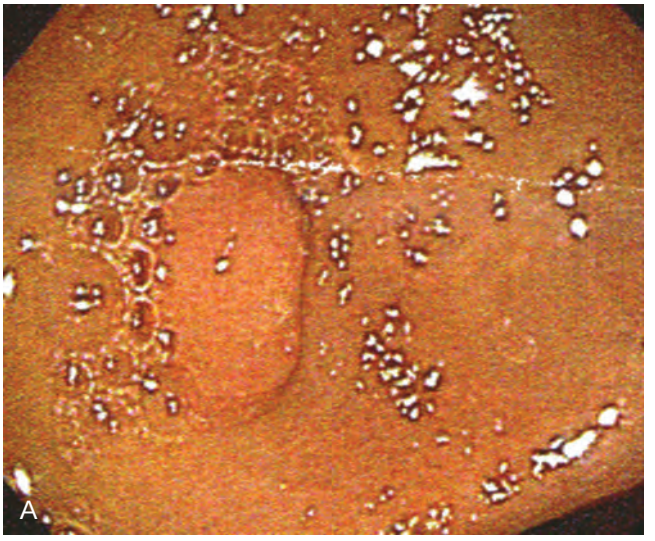
Gastric adenomas are associated with a high risk of malignancy. The risk is related to the size of the lesion and is particularly high in lesions that measure greater than 2 cm in diameter.[2,21,143] Overall, carcinoma may be present in up to 30% of gastric adenomas.[16,21,143,148] The molecular features of gastric adenomas are poorly understood. Microsatellite instability is present in a minority of lesions, but its incidence increases in adenomas that contain carcinoma.[149-153] In contrast, APC mutations occur more commonly in adenomas without carcinoma than in those with carcinoma.[153]

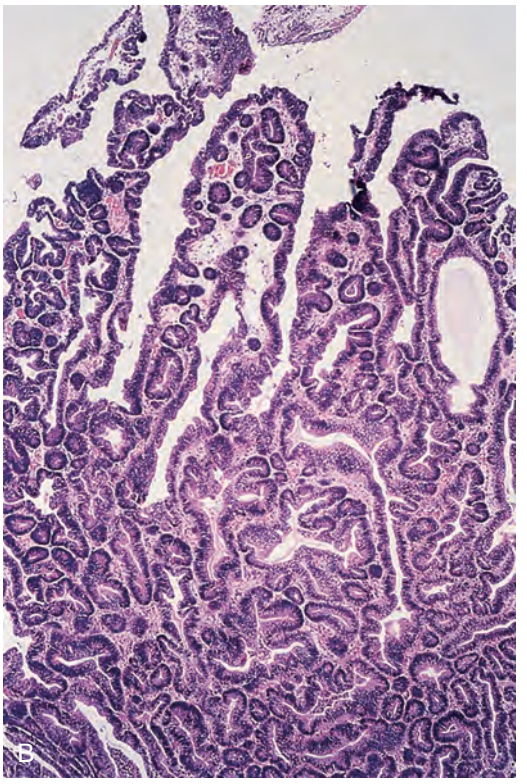
#### Pathologic Features

Adenomas occur most commonly in the antrum, but they may develop anywhere in the stomach.[154] More than 80% are solitary.[154] Grossly, adenomas are typically well-circumscribed sessile, or pedunculated lesions measuring less than 2 cm in diameter (Fig. 17-17A). The average size is 1 cm. Rarely, gastric adenomas may be flat or even depressed in shape. Papillary adenomas, those with a prominent tubulovillous or villous growth pattern, are often larger, with an average diameter of 4 cm. Papillary adenomas have a velvety surface contour and a lobulated gross appearance.

Microscopically, the majority of adenomas are composed of intestinal-type columnar epithelium (see Fig. 17-17) with goblet cells. Often, a distinct brush border is detectable that confirms intestinal differentiation in the dysplastic epithelium. Paneth cell and endocrine differentiation are also commonly present. A much smaller proportion of gastric adenomas are composed of dysplastic gastric-type mucinous columnar epithelium or a mixture of intestinal and gastric cell types. Adenomas composed of gastric-type epithelium are less likely to harbor high-grade dysplasia or carcinoma.[154] In contrast, adenomas that occur in corpus-predominant *H. pylori* gastritis were more prone to harbor adenocarcinoma in some studies.[155,156] Chronic gastritis is present more frequently in association with intestinal-type adenomas than with gastric-type adenomas. Adenomas with a prominent papillary or villous architecture (papillary adenomas) frequently display marked cellular pleomorphism and brisk mitotic activity, features that are uncommon in flat adenomas.

The classification of adenomas is controversial and differs among pathologists in different parts of the world.[157,158] For example, Western pathologists grade dysplasia (whether it be in adenomas or in flat mucosa) as either low or high grade.[159-161] The main advantage of a two-tiered grading system of classification compared to a three-tiered system (mild, moderate, severe) is that it has a higher degree of interobserver agreement and aligns more precisely with patient management options than do more complex grading systems.[161] Ultimately, the main difference in evaluation of dysplasia between Western and Japanese pathologists is that the former require unequivocal evidence of lamina propria invasion to establish a diagnosis of adenocarcinoma,[160] whereas the latter put emphasis on cytologic features in the assessment of malignancy. Thus, a lesion that is categorized as an adenoma with high-grade dysplasia by Western pathologists may be interpreted as carcinoma by Japanese pathologists.[160] Recognition of this discrepancy in grading has led to the establishment of four potential international systems for the classification of dysplasia and early cancer in the stomach (Table 17-6).[159,161-163] Regardless of the classification system, low-grade dysplasia is characterized by the presence of hyperchromatic, mucin-depleted, elongated cells with crowding and pseudostratification.[161] The architecture of low-grade dysplasia is composed of multiple small glands with little budding or branching.[159] Dysplasia, regardless of the grade, usually extends to the mucosal surface. This feature is helpful in differentiating dysplasia from epithelial regenerative lesions.



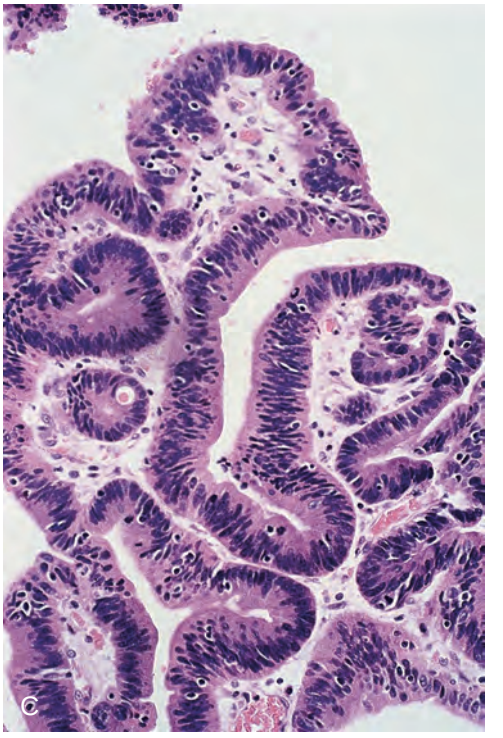
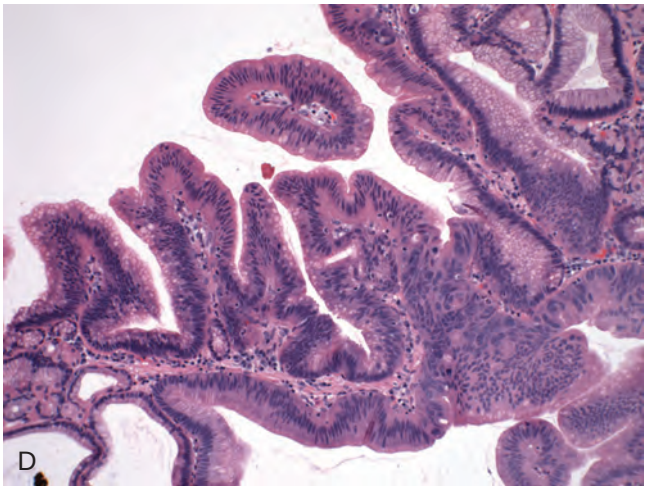



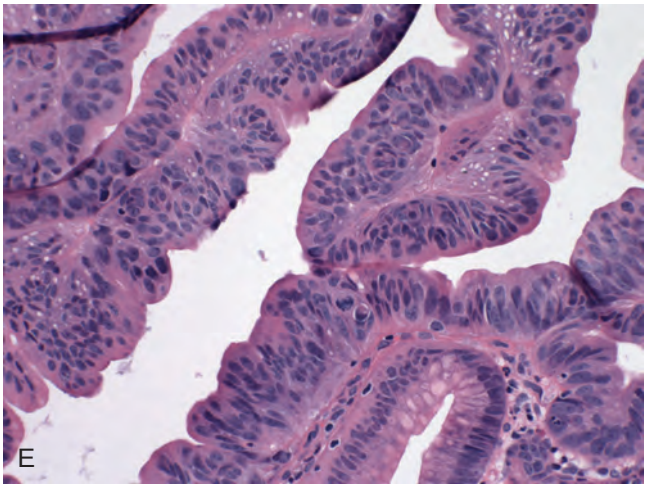

**FIGURE 17-17** Gastric adenoma. **A,** Adenomas are endoscopically similar to hyperplastic polyps (compare with Figure 17-1A). Note the slight reddish color, which is commonly present. Most gastric adenomas appear histologically similar to their colonic counterparts and are composed of cells with stratification, hyperchromatic pencil-shaped nuclei, and mucin depletion. **B,** This is an intestinal-type adenoma with a focus of high-grade dysplasia that is composed of architecturally distorted dysplastic epithelium without obvious invasion into the lamina propria. **C,** Higher-power examination of the adenoma in **B** shows clear cytologic evidence of dysplasia without surface maturation.

Adenomas with high-grade dysplasia show more complex architecture aberrations, and more severe cytologic atypia. These include irregularly shaped crowded glands with frequent budding and branching. Cribriform profiles may also be noted. Cell nuclei are enlarged, elongated, and hyperchromatic, similar to low-grade dysplasia, but they may show ovoid and vesicular changes with irregular nuclear contours, prominent nucleoli, and clumped chromatin. Loss of cellular polarity is also more pronounced in high-grade dysplasia, as is the degree of nuclear stratification.[159,161]

## Differential Diagnosis

The differential diagnosis of a gastric adenoma includes a hyperplastic polyp with dysplasia, fundic gland polyp with dysplasia, and polypoid carcinoma (see Polypoid Carcinoma, later). In contrast to adenomas, hyperplastic polyps with dysplasia contain foveolar hyperplasia, cystic change, and inflammation in the underlying polyp. In addition, dysplasia is often focal or patchy in hyperplastic polyps. The presence of cystically dilated fundic glands lined by parietal and chief cells beneath the area of dysplasia is helpful in diagnosing a dysplastic fundic gland polyp. In addition,



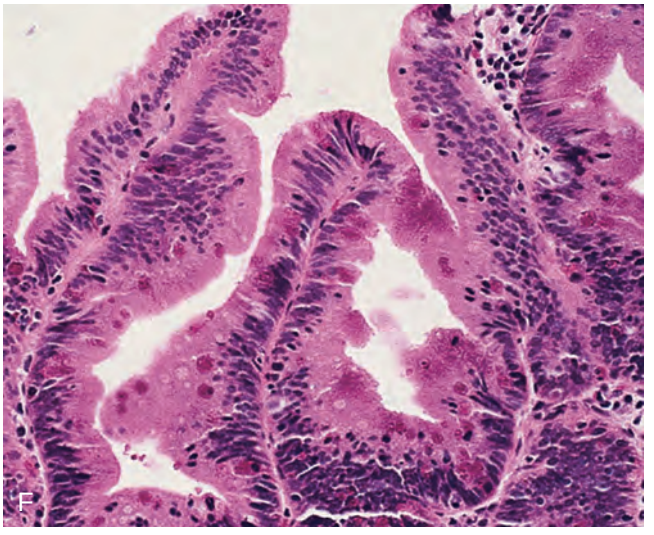




**FIGURE 17-17, cont'd D** and **E,** This adenoma shows an area of high-grade dysplasia that is composed of piled-up dysplastic epithelium without obvious invasion into the lamina propria. **F,** This adenoma shows prominent Paneth cell differentiation, which may be marked in some cases.

dysplasia is extremely uncommon in fundic gland polyps with the exception of FAP patients.

### Treatment

Treatment of adenomas is guided by endoscopic impression, polyp size, and grade of dysplasia. The risk of intramucosal carcinoma or invasive cancer in gastric adenomas is increased with polyp size greater than 2 cm.[164-167] However, carcinoma can be present in small lesions, prompting some authors to argue that all lesions greater than 0.5 cm be removed in their entirety.[4,19,168] Thus, evaluation of the entire adenoma is critical, since more advanced lesions may be present. The risk of carcinoma appears to be particularly increased elevated in flat or depressed adenomas.[169] As a result, adenomas with low-grade dysplasia are generally treated by complete endoscopic resection, careful evaluation of the entire stomach, and long-term endoscopic surveillance. The evaluation of nonpolypoid mucosa and careful follow-up are critical because a single gastric adenoma is a strong risk factor for subsequent, or even coincident, gastric neoplasia.[170] *H. pylori* eradication is also important.[171] In the past, open surgical resection was typically deemed necessary for adenomas with high-grade dysplasia and lesions too large to be removed by endoscopic resection. However, continuing advances in endoscopic mucosal resection,[172-175] laparoscopic procedures,[176] and even transgastrostomal endoscopic surgery[177] are providing many alternatives to traditional open abdominal surgery.[178]

## POLYPOID CARCINOMA

Polypoid carcinoma, also known as protruded or protuberant carcinoma, represents a malignant lesion that grows in a polypoid fashion into the gastric lumen. It may be associated with deeply invasive tumor. Polypoid carcinomas represent a minority of gastric cancers, accounting for less than 10% in most series. As in other types of gastric cancer, the peak incidence occurs in the sixth decade of life, with a male-to-female ratio of 2 to 3:1. A strong association has been noted with *H. pylori* infection as well as other forms of chronic gastritis.

Polypoid carcinomas are most prevalent in the lesser curvature of the stomach. They are often smaller than 1 cm. Histologically, polypoid carcinomas usually show intestinal-type dysplastic epithelium[154] with high-grade dysplasia and invasion of cells into the lamina propria (Fig. 17-18). Desmoplasia and increased microvessel density may be noted as well.[154,179,180]

## CARCINOID TUMOR

Carcinoid tumors are discussed more thoroughly in Chapter 25. Up to 30% of GI carcinoid tumors occur in the stomach. In fact, the incidence of gastric carcinoid tumors is on the rise.[181-184] They occur most commonly in the body and fundus. Not uncommonly, they grow as a polypoid

**TABLE 17-6** Classification of Gastric Dysplasia

| Western Classification | Japanese Classification | Padova Classification | Vienna Classification |
|---|---|---|---|
| Benign reactive | Benign, no atypia (Includes intestinal metaplasia, regenerative and hyperplastic epithelium) | 1. Negative<br>1.0 Normal<br>1.1 Reactive<br>1.2 Intestinal metaplasia (IM)<br>1.2.1 IM, complete type<br>1.2.2 IM, incomplete type | 1. Negative for neoplasia/dysplasia |
| Indefinite | Benign, with atypia (Frequently associated with active inflammation or found within hyperplastic polyp) | 2. Indefinite for dysplasia<br>2.1 Foveolar hyperproliferation<br>2.1 Hyperproliferative intestinal metaplasia | 2. Indefinite for neoplasia/dysplasia |
| Low-grade dysplasia | Borderline between benign and malignant (Dysplastic lesions with architectural and cytologic atypia) | 3. Noninvasive neoplasia<br>3.1 Low-grade dysplasia<br>3.2 High-grade dysplasia<br>3.2.1 Including suspect for carcinoma without invasion<br>3.2.2 Including carcinoma without invasion | 3. Noninvasive neoplasia, low grade |
| High-grade dysplasia | Highly suspect for carcinoma (Complex architecture) | 4. Suspect for invasive carcinoma | 4. Noninvasive neoplasia, high grade<br>4.1 High-grade adenoma-dysplasia<br>4.2 Noninvasive carcinoma (carcinoma in situ)<br>4.3 Suspect for invasive carcinoma |
| Carcinoma | Invasive carcinoma (Stromal invasion) | 5. Invasive adenocarcinoma | 5. Invasive neoplasia<br>5.1 Intramucosal carcinoma<br>5.2 Submucosal carcinoma or deeper |

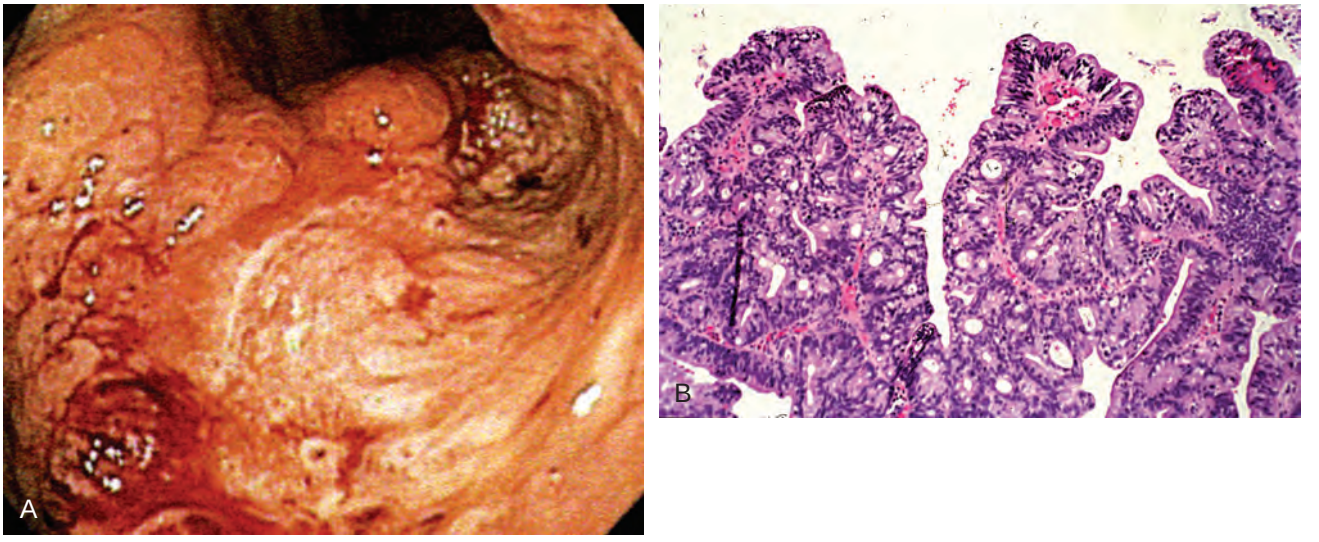



**FIGURE 17-18** Invasive adenocarcinoma. **A,** Note the central ulceration and heaped up border of this gastric cancer. Additional polypoid areas are visible at the periphery. **B,** In this case of polypoid intestinal-type adenocarcinoma (not the same case as **A**), foci of intramucosal adenocarcinoma are visible.

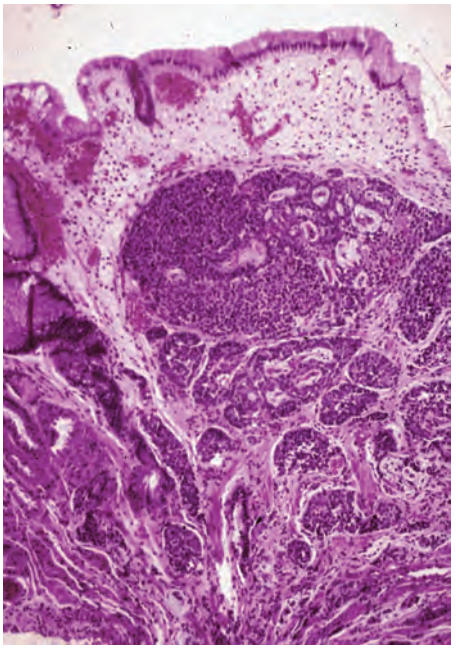
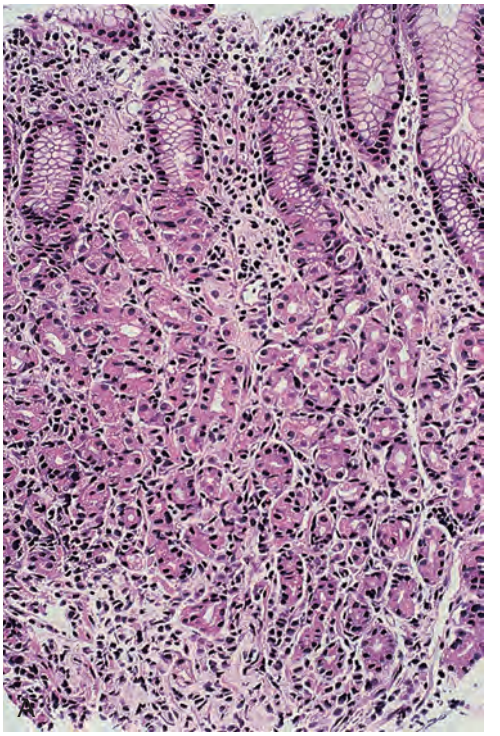


**FIGURE 17-19** The intramucosal portion of a well-differentiated carcinoid tumor is a small, sessile, well-circumscribed mucosal nodule.

lesion. Nodular proliferations of neuroendocrine cells may also be seen. Endocrine hyperplasia or dysplasia is diagnosed when the endocrine cell aggregates measure less than 150 μm or greater than 150 μm (but less than 500 μm) in diameter, respectively.[7,185,186] Nodules that exceed 500 μm in diameter represent true carcinoid tumors (Fig. 17-19).[7] Treatment of carcinoid tumors is dependent on the cause, size, and multiplicity of lesions and is discussed more thoroughly in Chapter 25.

## METASTATIC LESIONS

The stomach may be involved by distant metastasis, or by direct extension of tumors from the pancreas, lung, breast, transverse colon, and, in particular, distal esophagus (Fig. 17-20).[187-189] Most metastases to the stomach are located in the submucosa, where the vascular supply is richest. With growth, an ulcerated mucosal mass may form, and, especially in the case of melanoma, ulceration and bleeding may occur.[187-189] In some instances, metastases may appear as irregular polypoid lesions, but this is less common.



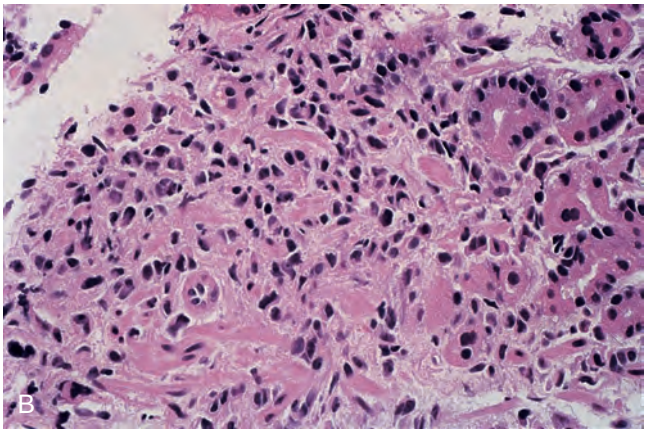



**FIGURE 17-20** Metastatic lobular carcinoma of the breast to the stomach. **A,** At low power, metastatic carcinoma cells may be mistaken for lymphocytes in association with chronic gastritis. **B,** However, at high power, the cells appear highly atypical, are epithelioid, and show a single-file arrangement of cells, unlike lymphocytes.

# Nonepithelial Polyps

## INFLAMMATORY FIBROID POLYP

### Clinical Features

Inflammatory fibroid polyps are mesenchymal proliferations composed of a mixture of stromal spindle cells, small blood vessels, and inflammatory cells, particularly eosinophils.[190-192] They may occur anywhere in the GI tract but are most common in the stomach and small intestine. In the stomach, inflammatory fibroid polyps usually occur in the sixth decade of life. Recent studies have reported a disproportionately large number of gastric inflammatory fibroid polyps in female patients.[193,194] Some have suggested an infectious etiology for inflammatory fibroid polyps.[191,192] However, no causative agent has ever been identified[195]; thus, most observers currently consider inflammatory fibroid polyps to be a form of reactive pseudotumor. When small, these tumors may be discovered incidentally at endoscopy. However, large lesions may cause obstructive symptoms such as nausea, vomiting, and

abdominal pain. In some cases, inflammatory fibroid polyps may contain a long stalk; these may prolapse through the pyloric sphincter and cause obstruction.[196] Some studies suggest that inflammatory fibroid polyps are more common among patients with atrophic gastritis and pernicious anemia.

## Pathologic Features

Inflammatory fibroid polyps are typically small, well-circumscribed, submucosally based, sessile lesions that may show ulceration of the overlying mucosa. Their median size is 1.5 cm, and, although most lesions are smaller than 3 cm in diameter, polyps that measure as large as 5 cm in diameter have been reported. In the stomach, they most commonly arise in the antrum, immediately proximal to, or overlying, the pyloric sphincter.

Microscopically, inflammatory fibroid polyps are submucosal tumors and often show an abrupt demarcation at the level of the muscularis propria. Mucosal involvement is common with gastric lesions. However, unlike small intestinal lesions, involvement of the muscularis propria is unusual in gastric polyps. Extension of the tumor into the mucosa causes separation of gastric glands, which results in a disordered and atrophic appearance. Inflammatory fibroid polyps are composed of a loose mixture of spindle-shaped, plump, cytologically bland stromal cells, inflammatory cells, and small, thin-walled blood vessels in an edematous or myxoid background (Fig. 17-21). In the stomach, stromal cells often proliferate in a concentric fashion around small and medium-sized blood vessels.[197,198] Mitotic figures are rare but may occasionally be present in deeper portions of the lesion. Atypical mitoses are never present. Eosinophils are a prominent inflammatory component and may also encircle vessels. Larger lesions may show collagen deposition and smooth muscle proliferation, or even giant cell formation.

Immunohistochemically, stromal cells have been reported to be positive for vimentin, CD34, fascin, CD35,

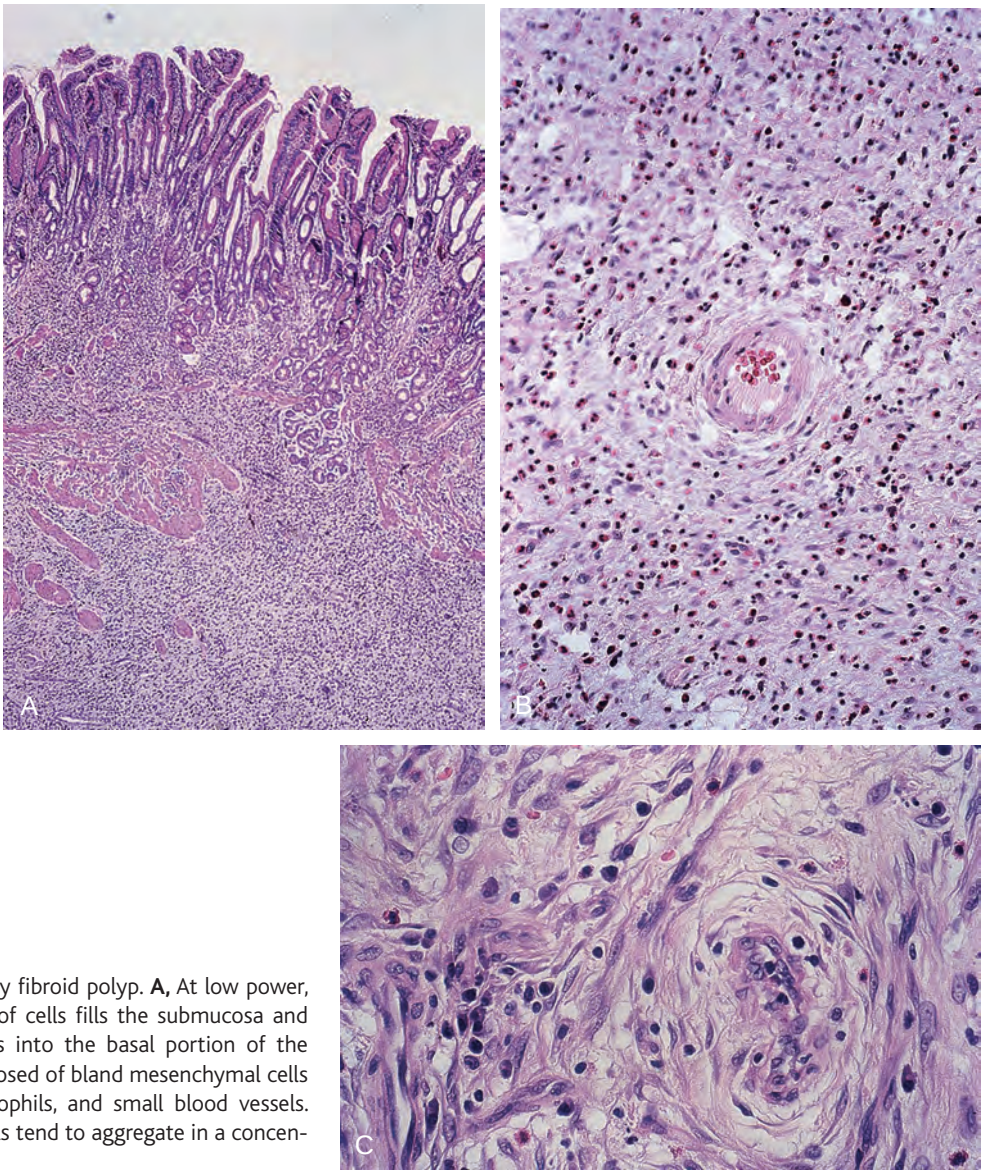



**FIGURE 17-21** Gastric inflammatory fibroid polyp. **A,** At low power, a loose mesenchymal proliferation of cells fills the submucosa and muscularis mucosae and penetrates into the basal portion of the mucosa. **B,** The proliferation is composed of bland mesenchymal cells combined with lymphocytes, eosinophils, and small blood vessels. **C,** Mesenchymal cells and eosinophils tend to aggregate in a concentric fashion around blood vessels.

cyclin D1, and calponin.[194,197-201] A smaller proportion are also positive for smooth muscle actin, HHF-35, KP-1, and Mac-387.[194,197-201] In contrast to stromal tumors of the GI tract, stromal cells in inflammatory fibroid polyps are negative for CD117 (c-kit).[194,197] Although the histogenesis of inflammatory fibroid polyps remains controversial, a possible origin in dendritic cells or CD34-positive perivascular cells has been proposed.[194,201] Differentiating between inflammatory fibroid polyps and inflammatory myofibroblastic tumors is discussed next.

## INFLAMMATORY MYOFIBROBLASTIC TUMOR

### Clinical Features

Inflammatory myofibroblastic tumors were originally termed inflammatory pseudotumor. This tumor was described in the small intestinal mesentery in preadolescent children.[202] Because of the abundance of mature plasma cells and lymphocytes in these lesions, the term *plasma cell granuloma* has also been used.[203] These tumors may occur in children and in adults.[202,204,205] Nearly one third occur in the stomach.[204-207] Patients usually present with nonspecific symptoms, including fever, growth retardation, and weight loss.[202,208] The cause of inflammatory myofibroblastic tumor is poorly understood. It is associated with gastric ulcers, chronic gastritis, use of nonsteroidal anti-inflammatory drugs, and ischemic disease. Abnormalities involving chromosome 2p are present in the majority of cases.[209-212] Genetic abnormalities frequently result in the development of a fusion protein that includes anaplastic lymphoma kinase, which is a putative growth factor receptor.[209-212] Gene rearrangements have been reported in up to 60% of inflammatory myofibroblastic tumors[209,210,213,214] and, interestingly, are more common in patients younger than 10 years of age.[209]

### Pathologic Features

Inflammatory myofibroblastic tumors average 8 cm in diameter. They typically appear as solid white lesions with infiltrative borders, and foci of myxoid change. Histologically, they are composed of spindle cells with features of myofibroblasts, mature plasma cells, and small lymphocytes (Fig. 17-22). The spindle cells, consistent with their proposed myofibroblastic origin, are immunohistochemically positive for smooth muscle actin, desmin, anaplastic lymphoma kinase, vimentin, muscle-specific actin, and cytokeratin.[209,210,213] Tumors may also be focally positive for CD34 and factor XIIIa.[215] The plasma cell component is polyclonal.[203] Although inflammatory myofibroblastic tumors were originally described as benign lesions,[202] it is now apparent that these tumors often recur locally.[206] At present, no specific histologic features have been associated with recurrence, but several studies suggest that aneuploidy may help identify particularly aggressive lesions.[206,209] An association between anaplastic lymphoma kinase expression and absence of distant metastases has been reported in extra-GI inflammatory myofibroblastic tumors.[209,216] Anaplastic lymphoma kinase expression may be present in tumors that recur locally,[216] and the general risk of local recurrence indicates that surgical excision and long-term follow-up are indicated in all patients with inflammatory myofibroblastic tumors.[216]

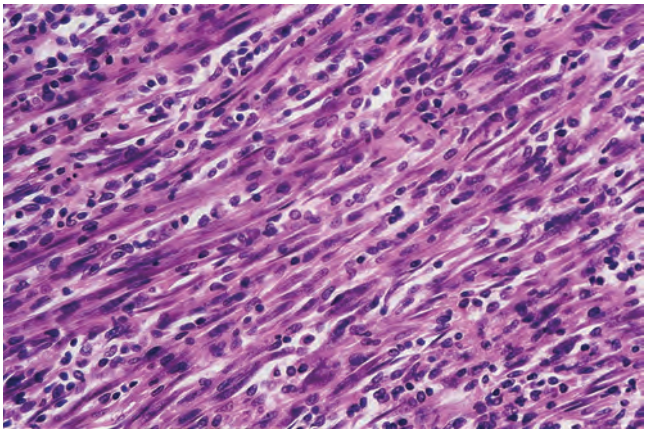


**FIGURE 17-22** High-power view of an inflammatory myofibroblastic tumor composed of mildly to moderately atypical mesenchymal cells in a stroma rich in lymphocytes. This tumor should be differentiated from a GI stromal tumor.

## GASTROINTESTINAL STROMAL TUMORS

GI stromal tumors (GISTs) are discussed in detail in Chapter 26. The stomach is the most common site. Rarely, when these tumors occur in the stomach, they appear as submucosal polyps.

## DIFFERENTIAL DIAGNOSIS OF STROMAL POLYPS

In some cases, the stromal cells in inflammatory fibroid polyps, inflammatory myofibroblastic tumors, and GISTs exhibit histologic similarities. However, some features of the inflammatory infiltrate can help differentiate between the entities. For example, the presence of eosinophils surrounding vascular spaces, with only rare plasma cells, are features suggestive of inflammatory fibroid polyp, whereas plasma cells are abundant in inflammatory myofibroblastic tumors. Furthermore, the absence of a significant inflammatory infiltrate suggests GIST. Patient age may be helpful as well. Inflammatory myofibroblastic tumors are common in children, whereas inflammatory fibroid polyps and GISTs typically appear in patients older than 50 years. Immunohistochemistry can also help: although all three types of lesions may be positive for smooth muscle actin, only inflammatory myofibroblastic tumors are positive for anaplastic lymphoma kinase and negative for both CD34 and CD117 (c-kit). In contrast, CD34 is positive (and anaplastic lymphoma kinase negative) in both inflammatory fibroid polyps and GISTs. With the exception of admixed mast cells, inflammatory fibroid polyps are negative for CD117, whereas GISTs are positive. In addition, calponin is often

positive in the majority of inflammatory fibroid polyps.[194] Thus, a simple panel of stains consisting of anaplastic lymphoma kinase, CD34, and CD117 allows discrimination between these three types of stromal tumors in most instances.

## VASCULAR TUMORS

Benign vascular tumors, such as hemangiomas and glomus tumors, may occur in the stomach and appear as intraluminal nodules or polyps (Fig. 17-23). These lesions are histologically similar to their counterparts in other areas of the body, such as the skin and elsewhere in the GI tract, and they are uniformly benign. On occasion, they may be confused with an epithelioid GIST. Vascular tumors are discussed more thoroughly in Chapter 10.

# Lymphoid Polyps

## LYMPHOID HYPERPLASIA

Lymphoid hyperplasia with germinal center formation, also known as follicular hyperplasia or chronic follicular gastritis, is usually a manifestation of chronic gastritis, and, in particular, *H. pylori* infection.[217,218] Consistent with the distribution of disease in *H. pylori* gastritis, reactive lymphoid nodules are most prevalent in the antrum, but they may also be present in the gastric body. Nodules are often multiple and are generally smaller than 0.3 cm in greatest diameter.[219] They are frequently umbilicated and can be visualized by double-contrast barium studies.[219] Eradication of *H. pylori* is associated with a decrease in the prevalence and density of lymphoid follicles.[220]

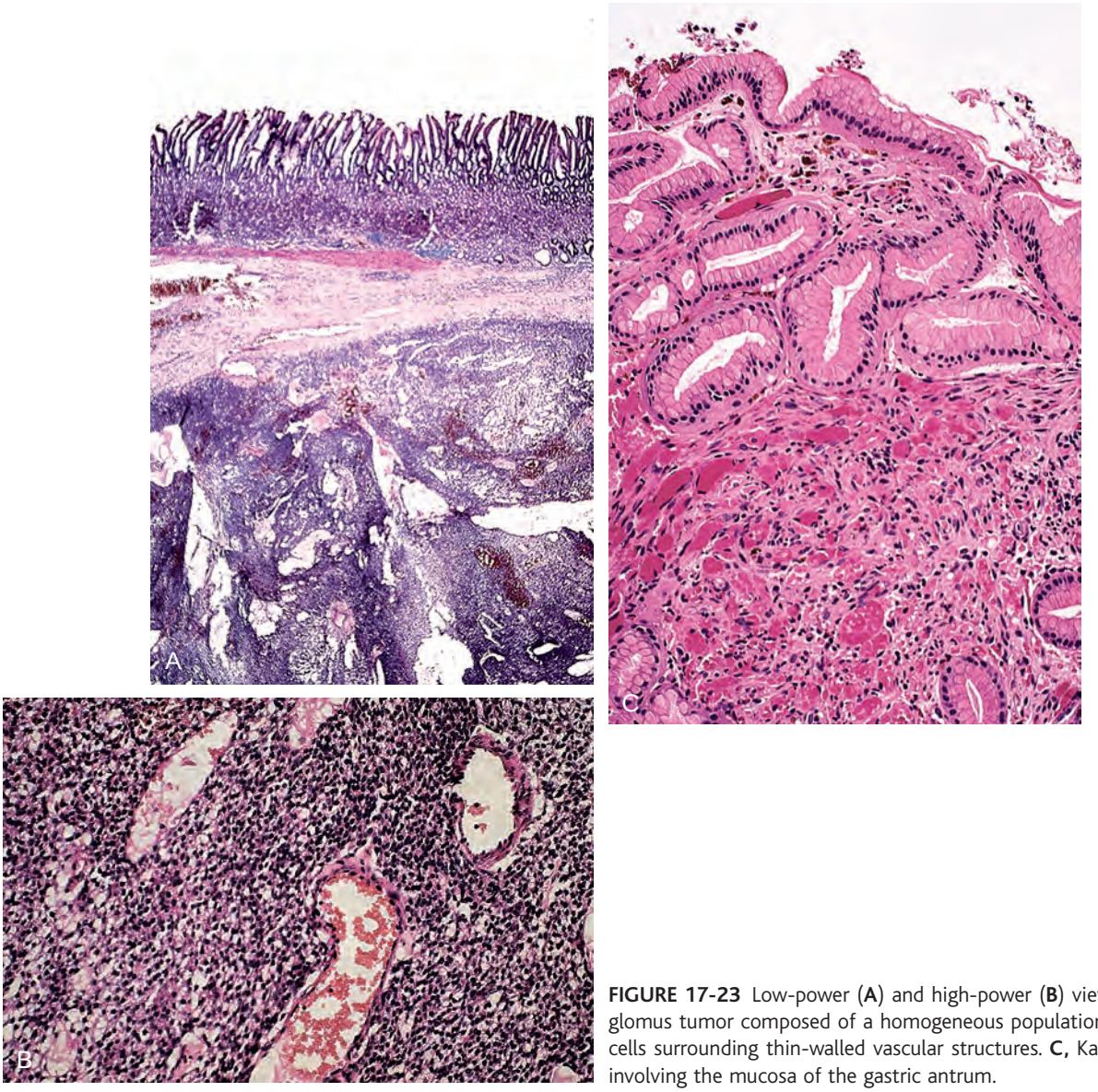



**FIGURE 17-23** Low-power (**A**) and high-power (**B**) views of a gastric glomus tumor composed of a homogeneous population of small blue cells surrounding thin-walled vascular structures. **C,** Kaposi's sarcoma involving the mucosa of the gastric antrum.

### LYMPHOMA

The GI tract is the initial site of presentation in 4% to 20% of all non-Hodgkin's lymphomas.[221] In fact, the majority of cases involve the stomach,[221] and many of these lesions initially present as polyps, either solitary or multiple. Gastric lymphoma is discussed in more detail in Chapter 27.

## Miscellaneous Rare Polyps and Polyp-Like Lesions

### OXYNTIC GLAND HYPERPLASIA/ADENOMA

Rarely, nodules composed exclusively of oxyntic gland parietal and chief cells have been described as being either sporadic, in the setting of chronic gastritis, or associated with familial adenomatous polyposis.[88-90] Less than five cases have been reported in the English literature. Etiologically, it is unclear if these lesions represent a form of hyperplastic reaction or, in fact, represent a low-grade neoplasm such as an adenoma. Some cases have been referred to as chief cell hyperplasia or oxyntic mucosa pseudopolyp. Histologically, these lesions are composed of tightly compact clusters of oxyntic-like glands, and irregular tubules and cords of atypical oxyntic epithelium composed of chief cells and parietal cells (Fig. 17-24). Both of these cell types show nuclear hyperchromasia, nucleomegaly, slight nuclear pleomorphism, anisonucleosis, and increased nucleus-to-cytoplasm ratio, with few mitotic figures. Cytoplasmic characteristics of chief cells and parietal cells are usually preserved with H&E staining. These lesions typically occur in the fundus, or in the fundic-antral transition zone. In the few reported cases, Ki67 has shown little increased staining. However, markers of parietal and chief cells, such as pepsinogen-I, are typically positive. By electron microscopy, the lesions are composed of cells with enlarged nuclei, irregular nuclear membranes, and disorganization and distortion of the intracellular organelles, such as the rough endoplasmic reticulum and zymogen granules. Some lesions may be composed predominantly of chief cells, whereas others show a mixture of chief and parietal cells. The natural history of these lesions is unknown.

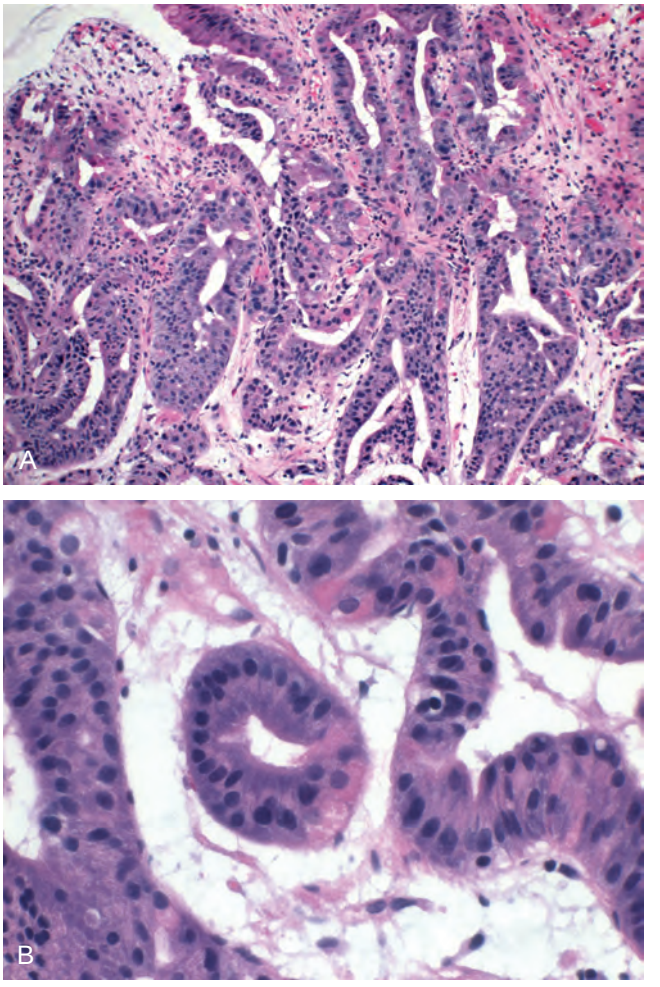



**FIGURE 17-24** Oxyntic gland hyperplasia/adenoma. **A,** At low power, this lesion, consisting of nodules of parietal and chief cells, may resemble a fundic gland polyp. **B,** At higher magnification, irregular tubules and cords are noted, with the epithelium focally appearing to be at least two cell layers thick. Cytologic nuclear atypia is also present.

### XANTHOMA

Xanthomas are small, sessile, yellow mucosal nodules composed of loose aggregates of lipid-laden macrophages in the lamina propria (Fig. 17-25). They are most often found in the body and fundus[222,223]; they are typically smaller than 3 mm in size and are frequently multiple in number. Xanthomas develop most commonly in association with chronic gastritis, especially after partial gastrectomy. It is believed that they develop as a form of reaction to tissue injury. The differential diagnosis of xanthoma includes benign muciphages, granular cell tumor, and signet ring cell carcinoma. Because xanthomas contain intracellular glycolipids normally lost during tissue processing, lesional macrophages are negative with the periodic acid–Schiff stain, whereas muciphages are usually strongly positive. The cytoplasmic granules of granular cell tumors stain positively with the periodic acid–Schiff stain, but they are also positive for the S100 protein with immunohistochemical staining. Signet ring cell carcinomas also contain cytoplasmic mucin, which can be demonstrated with periodic acid–Schiff or mucicarmine stain. However, in addition, signet ring cell carcinomas are normally easily differentiated because of their overt malignant nuclear cytologic features and cytokeratin immunoreactivity.

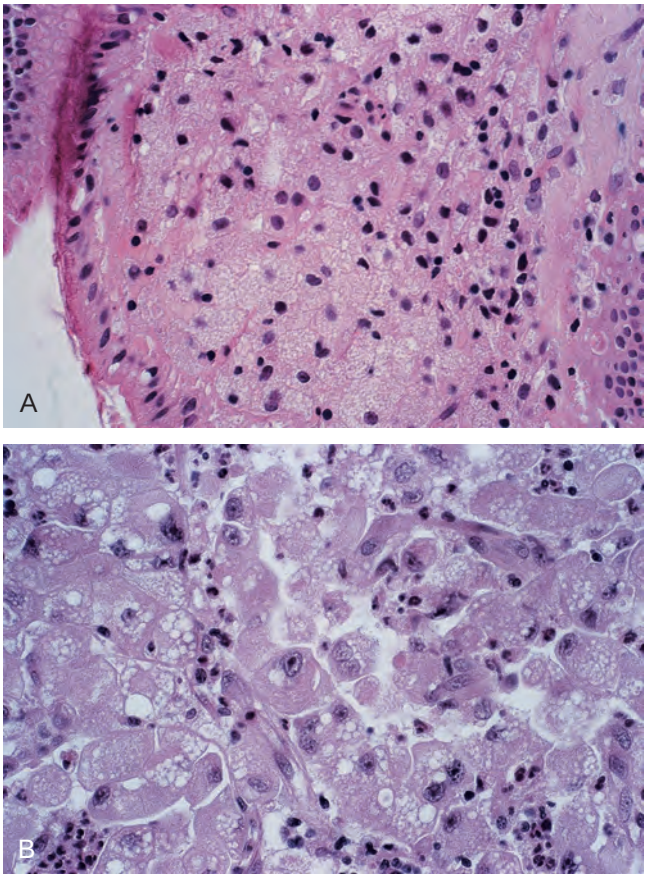



**FIGURE 17-25 A,** Gastric xanthoma. The mucosa is filled with foamy, lipid-laden macrophages that contain cytologically bland, round to oval-shaped nuclei without atypia. A mucicarmine stain was negative. **B,** In contrast to **A**, signet ring cell carcinoma shows variably sized mucin-filled cells with a vacuolated appearance and hyperchromatic, atypical, and eccentrically located nuclei with increased mitotic activity. A mucicarmine stain on this tissue was positive.

## HISTIOCYTOSIS X

Histiocytosis X, now more often known as Langerhans' cell histiocytosis, is primarily a disease of young children. Depending on the location of the disease, the terms *eosinophilic granuloma, Hand-Schüller-Christian disease*, and *Letterer-Siwe disease* are also applicable. *Eosinophilic granuloma* is the term generally applied to the solitary nodular form that is occasionally found in the stomach.[224,225] Histologically, these nodules are composed of tight clusters of cells with finely granular cytoplasm containing Birbeck granules. Scattered eosinophils may also be present in the nodule, but the mucosa is otherwise intact. The identity of the Langerhans' cells is confirmed by positive S100 protein and CD1a immunostains, and by electron microscopy, which shows the characteristic tennis racket–shaped intracytoplasmic Birbeck granules. When present as an isolated gastric nodule, eosinophilic granuloma is typically benign. In fact, they often regress without therapy.

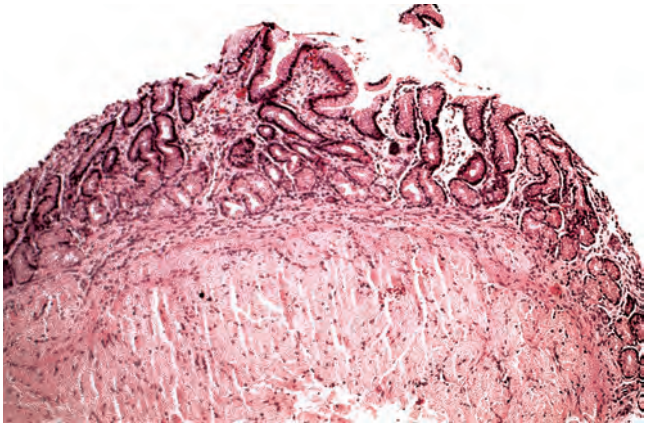


**FIGURE 17-26** $\beta_2$-Microglobulin amyloidosis resulting in elevation of the mucosa due to a nodular mass of amyloid in the submucosa.

## GRANULOMA

Granulomas may occur in the stomach from a number of different causes (see Chapter 6). They occur most frequently in the antrum. Pyloric obstruction may, rarely, occur as the result of granuloma-associated mucosal thickening.[226] Gastric granulomas may also be associated with systemic granulomatous diseases, including sarcoidosis, Crohn's disease, and, rarely, mycobacterial infection.[227-229] When all apparent causes of granulomatous inflammation have been excluded, a diagnosis of idiopathic granulomatous gastritis may be considered. This uncommon disorder occurs primarily in older patients and appears clinically as a slowly progressive type of partial gastric outlet obstruction. Of course, granulomas may be associated with *H. pylori* gastritis in up to 20% of cases (see Chapter 12).

## AMYLOIDOSIS

Amyloidosis is a heterogeneous group of systemic diseases discussed in detail in Chapter 6. When it involves the stomach, amyloidosis may cause ulceration or form a submucosal nodule or mass. Histologically, amyloid deposits in the stomach are most frequently concentrated in the wall of small to medium-sized blood vessels.[230] Perineural and interstitial deposits may also develop in the submucosa (Fig. 17-26). The condition may be associated with dysmotility, although this complication occurs frequently in other areas of the GI tract. Large interstitial amyloid deposits may be termed amyloidomas. One research group has suggested that AL-type amyloidosis occurs more frequently in the muscularis propria, whereas AA-type amyloidosis more often involves the lamina propria.[231] $\beta_2$-Microglobulin, or dialysis-associated amyloidosis, is most common in patients who have received hemodialysis for more than 10 years.[230] A diagnosis of amyloidosis can be confirmed by examination of Congo red–stained slides under polarized light.

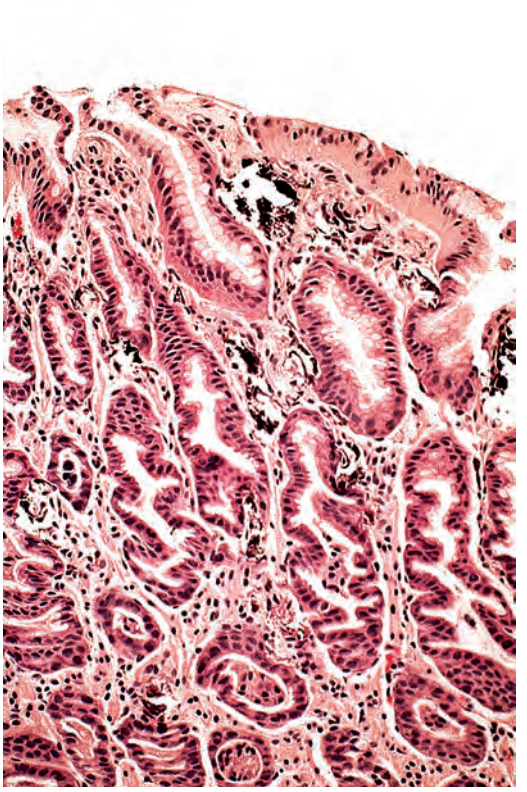


**FIGURE 17-27** Gastric antrum shows foveolar hyperplasia, mild chronic inflammation, and heterotopic calcifications in the mucosa as a result of chronic renal failure.

## CALCIUM DEPOSITS

Interstitial calcium deposits in the lamina propria (Fig. 17-27) may, rarely, impart an endoscopic impression of a small white plaque or sessile polyp. Deposits are typically found in patients with end-stage renal disease, but they may occur in patients with other diseases as well.[232] The surrounding mucosa is usually unremarkable but, on occasion, may be ulcerated. Some authors have proposed that such ulceration promotes induction of the calcium deposits, although direct evidence for this association is lacking.

## HEMOSIDEROSIS

Gastric mucosal hemosiderosis has been described in association with hemochromatosis as well as in alcoholics and patients taking oral iron-containing medications. Gastric mucosal hemosiderosis is present in approximately 2% of gastric biopsies when evaluated by Prussian blue stain.[233] A recent study of iron deposition in gastric biopsies described three histologic patterns of gastric mucosal hemosiderosis. Predominant iron deposition in stromal cells, including macrophages, with only focal epithelial deposition accounted for 60% of cases and was always patchy in its distribution. This pattern was frequently associated with gastric inflammation and may represent iron deposition from prior mucosal hemorrhage. A second pattern of patchy, mostly extracellular iron deposition and focal mild gastritis or reactive gastropathy–type changes was always associated with a history of oral iron-containing medications and was present in 20% of gastric mucosal hemosiderosis cases. The third pattern was a typically diffuse deposition predominantly in glandular epithelium (Fig. 17-28). This was associated with systemic iron overload or hemochromatosis.

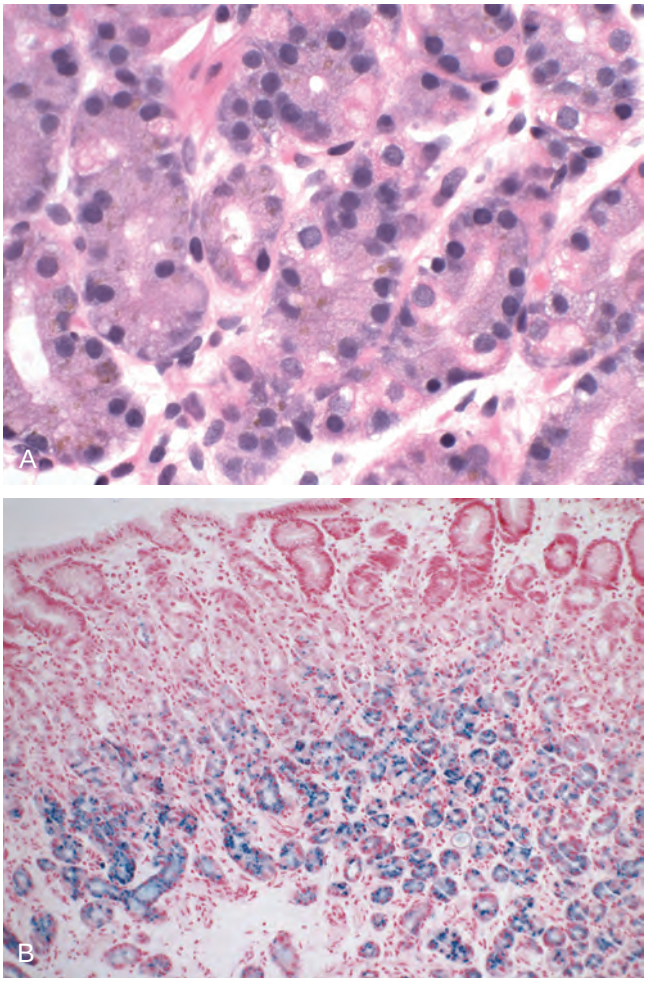



**FIGURE 17-28** **A,** High-power examination demonstrates the presence of brown pigment in glandular epithelium. **B,** Prussian blue stain shows that this represents diffuse iron deposition in glandular epithelium. This pattern of iron deposition is most commonly associated with systemic iron overload or hemochromatosis.

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*References, with PubMed access, are available in the online edition through Expert Consult.*

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