Gastric Epithelial Polyps

When to Ponder, When to Panic

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KEYWORDS

• Stomach • Gastric • Polyp • Polyposis • Hereditary • Dysplasia

Key points

- Gastric epithelial polyps comprise a wide spectrum of lesions with different cause, histology, malignant potential, and sometimes associations with tumor predisposition syndromes.
- Most gastric polyps are sporadic with no malignant potential, but clinical correlation is necessary, and pathologists should be familiar with the morphologic characteristics of gastric polyps as an indication for a search for an underlying genetic syndrome, such as familial adenomatous polyposis, Peutz-Jeghers syndrome, or juvenile polyposis syndrome.
- In the presence of a gastric polyp, preferably biopsies of background mucosa are taken of at least the antrum and corpus. Evaluation of the background nonpolypoid mucosa is essential in reaching a diagnosis that can characterize the condition in which the polyp developed and may have therapeutic consequences.

ABSTRACT

This review provides an overview of different types of gastric epithelial polyps. The polyps are classified based on their cell or epithelial compartment of origin. Some of these polyps can be considered reactive or nonneoplastic, whereas others are neoplastic in origin, are sometimes associated with a hereditary polyposis/cancer syndrome, and may have malignant potential. The aim of this review is to provide a pragmatic overview for the practicing pathologist about how to correctly diagnose and deal with gastric epithelial polyps and when (not) to ponder, and when (not) to panic.

OVERVIEW

Gastric polyps comprise a wide spectrum of lesions arising from different cell or epithelial compartments in the stomach and with different

causes, histology, malignant potential, and association with different tumor predisposition syndromes. Gastric polyps can be defined as lesions projecting above the plane of the surrounding gastric mucosa.¹ In about 1% to 6% of gastroscopies, polyps are found in the stomach.^{2,3} Most polyps are of epithelial origin and asymptomatic.² Less frequently found subepithelial lesions presenting as gastric polyps include neuroendocrine tumors, pancreatic heterotopia, mesenchymal polyps (eg, inflammatory fibroid polyp, gastrointestinal stromal tumor, leiomyoma, schwannoma, inflammatory myofibroblastic tumor) as well as lymphomas.⁴

Large geographic differences have been observed in the occurrence of gastric polyps, mainly caused by differences in *Helicobacter pylori* (*H pylori*) infection rate.⁵ In areas with high rates of *H pylori* infection, hyperplastic polyps (HPs), with or without dysplasia, are most prevalent. In contrast, fundic gland polyps (FGPs) are the most frequently encountered type of polyps

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in areas with a low prevalence of *H pylori* infection as well as high use of proton-pump inhibitory therapy, for example, western countries.^{3,4} Gastric polyps often arise in association with an inflammatory background or a polyposis syndrome. Careful attention to the background mucosa and awareness of syndromic gastric polyps are therefore important for correct interpretation and diagnosis of gastric polyps.

Gastric polyps can be classified based on their cell or epithelial compartment of origin (Table 1). The stomach consists of the following anatomic

regions: cardia, fundus, body, antrum, and pylorus. These areas have variable histologic appearances, which reflect differences in physiologic functions. Gastric pits or foveolae, lined by mucus-secreting foveolar cells, comprise the whole luminal surface of the stomach. Underneath these pits, the mucous neck cells as well as deep gastric glands are located, of which the cellular composition is region-dependent. The glands in the fundus and body consist of parietal cells, chief cells, and enterochromaffin-like cells. In the cardia, antrum, and pylorus, mainly mucus cells with

Table 1 Overview of gastric epithelial polyps classified by cell or epithelial compartment of origin			
Origin	Nonneoplastic		Neoplastic
<i>Foveolar layer</i>	<i>Hyperplastic polyp</i>	<i>Foveolar-type adenoma</i>	<i>Intestinal-type adenoma</i>
Characteristics	Polyp consisting of dilated, branched, and elongated glands in edematous stroma Background of chronic gastritis	Polyp with atypical foveolar cells (at least low-grade dysplasia) No background of inflammation, atrophy, or metaplasia Expression of MUC5AC; usually no expression of MUC2	Polyp with intestinal-type columnar epithelium containing absorptive cells, goblet cells, endocrine cells, and/or Paneth cells with at least low-grade dysplasia Background of intestinal metaplasia and/or inflammation or atrophy. Variable expression of MUC2; no or slight expression of MUC5AC and MUC6
Of note	Histopathologically indistinguishable from hamartomatous polyp/ polyposis syndrome Reasonable risk of malignancy (background)	Association with FAP Low risk of malignant transformation	Association with FAP (although rare) Relatively high risk of malignant transformation
<i>Glandular layer</i>	<i>Fundic gland polyp</i>	<i>Pyloric gland adenoma</i>	<i>Oxyntic gland adenoma</i>
Characteristics	Polyp consisting of dilated glands with parietal and chief cells and some mucous cells	Polyp with atypical pyloric-type glands (at least low-grade dysplasia) No background of inflammation, atrophy, or metaplasia Expression of MUC6; usually no expression of MUC2	Polyp with atypical oxyntic glands, consisting of chief cells or combination of chief and parietal cells (at least low-grade dysplasia) In general, no background of inflammation, atrophy, or metaplasia
Of note	Sporadic (association with PPI therapy) or in the context of FAP Low risk of malignant transformation	Association with several polyposis/tumor predisposition syndromes Relatively high risk of malignant transformation	Low risk of malignant transformation

clear cytoplasm line the deep glands with a small mixture of neuroendocrine cells. In the transitional zones, small numbers of parietal and chief cells are present. Familiarity with these histologic features will aid in gastric polyp recognition and diagnosis.

FUNDIC GLAND POLYP

INTRODUCTION

FGPs are the most common type of gastric polyp, comprising almost 80% of all gastric polyps, and seem to be more common in areas with low *H pylori* infection rates.^{3,4} Sporadic FGPs are strongly related to the use of proton-pump inhibitors (PPIs). Long-term use leads especially to increased risk of developing FGPs. PPI therapy gives acid suppression, which elevates serum gastrin, a growth factor for oxyntic mucosa and a downstream target of Wnt signaling. Patients on PPI therapy have hyperplasia and protrusions of parietal cells in their gastric biopsy, which is thought to be an initial step in the development of an FGP. After this, there is development of small and subsequently larger fundic gland cysts. The glands dilate because of increased intraglandular pressure, probably because of the parietal cell hyperplasia that gives increased outflow resistance.

In younger patients with multiple FGPs (>20), that is, fundic gland polyposis, or FGPs with dysplasia, an underlying familial adenomatous polyposis (FAP) syndrome (owing to a germline mutation in the *Adenomatous Polyposis Coli* [*APC*] gene) or *MUTYH* polyposis should be considered, and colonoscopy is advised, in particular if there are also duodenal adenomas.

GROSS FEATURES

FGPs are typically less than 5 mm and have a smooth surface. Sporadic FGPs are usually solitary or few in number (**Fig. 1**). However, FGPs can be numerous in patients using PPIs and in patients with familial polyposis syndrome (**Fig. 2**).^{5,6}

MICROSCOPIC FEATURES

FGPs are characterized by cystically dilated oxyntic glands mainly lined by parietal and chief cells and variable numbers of mucous neck cells (**Fig. 3**). The overlying foveolar surface is usually normal. Surface erosion can be present with resulting reactive changes of the foveolar epithelium, which may be misinterpreted as dysplasia. Sporadic single FGPs rarely show dysplasia; however, in some FGPs, dysplasia of the overlying foveolar epithelium is observed. Dysplasia in FGPs is of foveolar type, characterized by low columnar cells resembling foveolar cells with round to oval nuclei (**Fig. 4**). The cytoplasm contains a MUC5AC-positive mucin cap. The surrounding mucosa of FGPs is normal or shows signs of PPI use. There is no background of atrophy or intestinal metaplasia.

(DIFFERENTIAL) DIAGNOSIS

In general, FGPs are straightforward to diagnose both endoscopically and microscopically. Some FGPs can be difficult to differentiate from pyloric or oxyntic gland adenomas (OGAs), depending on the degree of cystic changes and pyloric or oxyntic differentiation, respectively. *GNAS* mutations are often present in pyloric gland adenomas

Fig. 1. Sporadic FGP: gross features. Several sporadic FGPs in the cardiac region of the stomach.

Fig. 2. FAP-associated FGP: gross features. Numerous FGPs and foveolar adenomas throughout the stomach of a patient with FAP syndrome.

(PGAs) and absent in FGPs, and this may be used to differentiate between PGA and FGP.⁷ Very large FGPs can pose a differential diagnosis with HPs. The key difference between FGPs and HPs is

that the cystically dilated glands in FGPs are lined by a mixture of cell types, including parietal and foveolar cells, whereas in HPs, the glands are lined by hyperplastic foveolar epithelium. FGPs with

Fig. 3. FGP: microscopic features. (A) Low-power view of an FGP, consisting of cystically dilated glands lined by parietal and chief cells and variable numbers of mucous neck cells. (B) High-power view of the same polyp. The polyp is lined by nondysplastic foveolar epithelium at the surface.

Fig. 4. FGP with high-grade dysplasia. (A) This FGP from a patient with FAP shows a focus of high-grade dysplasia of the overlying foveolar epithelium, characterized by columnar cells showing severe nuclear atypia with round to oval, vesicular nuclei with prominent nucleoli and loss of polarity as well as some architectural atypia with crowding and branching of glands. (B) The dysplastic cells show p53 overexpression.

dysplasia can be difficult to distinguish from foveolar-type adenomas with low-grade dysplasia, but this is of little clinical significance because both lesions carry a low risk of neoplastic progression.⁸

PROGNOSIS, WHEN TO PONDER, WHEN TO PANIC

FGPs are generally regarded as nonneoplastic lesions, either hamartomatous or hyperplastic/functional in nature, because they are retention cysts caused by corpus gland secretion impairment. However, the frequent finding of mutations in the Wnt pathway (*APC* and *CTNNB1* genes) indicates that FGPs are neoplastic growths as well. Most (60%–90%) sporadic FGPs without dysplasia

have somatic *CTNNB1* mutations.^{9,10} Dysplastic sporadic FGPs may have a somatic *APC* mutation without *CTNNB1* (β -catenin) mutation.⁹ In contrast, FGPs in FAP show somatic second-hit inactivation of the *APC* gene that precedes dysplasia, but lacks *CTNNB1* mutations.¹¹ The type of second-hit *APC* mutation may play a role in the chance of progression to high-grade dysplasia in FAP-associated FGPs.¹²

Dysplasia in sporadic FGPs is extremely rare and has an indolent nature.^{13–17} In general, sporadic FGPs do not progress to cancer and tend to regress when PPI therapy is stopped. Presence of FGPs is inversely correlated with *H. pylori* infection, active gastritis, and gastric neoplasia.¹⁸

FAP is an autosomal-dominant polyposis syndrome caused by a germline mutation in the *APC*

gene. It is characterized by hundreds to thousands of adenomatous polyps (≥ 100) throughout the colorectum and inevitable development of colorectal cancer if left untreated by colectomy. In addition, FAP patients develop several benign and malignant extracolonic lesions. In the stomach, most patients with FAP have multiple FGPs (polyposis). Low-grade dysplasia is often seen in FGPs in FAP, but the risk of malignant progression is low.^{5,19} Based on older literature, western FAP patients are considered not to carry an increased risk of gastric cancer compared with the general population,²⁰ whereas a 3 to 4 times increased risk of gastric cancer was reported in FAP patients from South Korea and Japan.^{21,22} The increased risk of gastric cancer in Asian populations likely results from higher prevalence of *H pylori* infection and associated atrophic gastritis and intestinal metaplasia in these populations.

However, several recent reports of FAP patients with gastric cancer suggest an increased incidence of gastric cancer in western patients.^{23,24} Interestingly, these gastric cancers are almost exclusively located in the proximal stomach and are associated with extensive carpeting fundic gland polyposis, and a large size (>20 mm) of polyps and dysplasia.²⁵ One study reported an association between gastric cancer and desmoid tumors in FAP patients, suggesting a genotype-phenotype correlation for gastric cancer.²³ In addition, gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is characterized by carpeting proximal fundic gland polyposis of the stomach with antral sparing, increased risk of gastric cancer, and no or a small number of duodenal and colorectal adenomas. Because it is caused by a point mutation in exon 1B of *APC*, it is now considered a variant of FAP with a unique gastric phenotype, further supporting that gastric cancer risk may depend on the genotype.^{26–28} GAPPS patients with gastric cancer more often have gastric adenomas, FGPs, and PGAs with high-grade dysplasia.²⁵ Thus, although low-grade gastric foveolar-type dysplasia is not very alarming in FAP patients, extensive proximal gastric polyposis and possibly also the presence of PGAs (see later discussion) may be markers of an increased risk of proximal gastric cancer in FAP. In addition, it remains important to detect FAP patients with *H pylori* infection, gastric atrophy, and intestinal-type adenomas because these patients seem to be at increased risk for distal intestinal-type adenocarcinomas.²⁹

Pathologic Key Features

- Cystically dilated oxyntic glands lined by parietal and chief cells
- Lined by nondysplastic foveolar epithelium
- Rarely foveolar-type dysplasia (mainly in FAP)

Differential Diagnosis

- Pyloric or oxyntic gland adenomas
- Large FGPs can be difficult to distinguish from HPs
- FGPs with dysplasia versus foveolar-type adenomas

Pitfall

! Multiple FGPs (fundic gland polyposis) are associated with FAP and GAPPS.

HYPERPLASTIC POLYP/INFLAMMATORY POLYP/HAMARTOMATOUS POLYP

INTRODUCTION

Gastric HPs are among the most common epithelial polyps of the stomach; incidences vary among populations and range between 15% and 75% of all gastric polyps.³⁰ HPs are localized, nonneoplastic mucosal expansions consisting of elongated, tortuous, and cystically dilated foveolae supported by an edematous lamina propria with distended vessels. In contrast to colonic HPs, which are neoplastic polyps, gastric HPs are reactive lesions resulting from reparative and regenerative responses to mucosal injury. First, there is an ongoing healing and reparative response in the form of foveolar hyperplasia after mucosal injury and erosion. This hyperplastic reaction can end or persist and progress with the formation of an

HP. Mostly the initial inflammation is caused by *H pylori* or autoimmune gastritis, although any agent causing chronic gastritis or mucosal erosion may lead to the formation of an HP. In addition, mucosal prolapse can result in HPs.³¹ HPs can be multiple, which is the case in 20% of patients.³⁰ Gastric “inflammatory polyp” is a commonly used misnomer for an HP and should not be used in the stomach to avoid confusion with an inflammatory fibroid polyp. Hamartoma defines an overgrowth of normal tissue elements in their own native location. Hamartomatous gastric polyps are rare in the stomach and are, from a histopathological point of view, indistinguishable from HPs because they share the same morphology. Hamartomatous gastric polyps occur in the context of Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and Cowden (*PTEN* hamartoma tumor) syndrome.³²

GROSS FEATURES

HPs are mostly small, generally less than 2 cm, although sizes of up to 12 cm are reported. The polyps are usually solitary, smooth or lobulated, and can be sessile or pedunculated. There is often surface erosion. HPs cannot reliably be distinguished from small adenomas endoscopically. HPs are most common in the antrum (60%), but may arise throughout the stomach, including the cardia and gastroesophageal area.^{30,33}

MICROSCOPIC FEATURES

HPs have a polypoid form and show elongated, branching, and cystically dilated foveolar glands (Fig. 5). The foveolar cells have a hyperplastic appearance with abundant mucinous cytoplasm. The glands may contain prominent globoid cells. There is crowding of foveolar cells, and glands may be tortuous or have a corkscrew appearance. The lamina propria can be edematous and moderately to heavily infiltrated by immune cells. In other cases, the lamina propria is more fibrotic with or without chronic inflammatory infiltrate. The surface of the polyp can be eroded and have a regenerative appearance with nuclear enlargement and depletion of cytoplasmic mucin.³⁰ Small lesions may be best addressed as polypoid foveolar hyperplasia.³¹

(DIFFERENTIAL) DIAGNOSIS

HPs have an overlapping morphology with polyps arising in juvenile polyposis, Peutz-Jeghers (PJ) polyposis, and Cowden/*PTEN* hamartoma tumor syndrome (see Overview).³² Many of the hamartomatous syndrome polyps lack specific histology,

and to distinguish them from each other and from sporadic HPs based on only histology is unreliable. Therefore, one should think of the possibility of an underlying hamartomatous polyposis syndrome in the case of multiple gastric hyperplastic-type polyps but at the same time be cautious to establish a diagnosis of a polyposis syndrome based on gastric polyp pathologic condition alone.^{5,32} The syndromes in which they can occur are now briefly discussed.

PJS is an autosomal-dominant inherited disorder caused by a germline mutation in *LKB1* (*STK11*). Intestinal PJ polyps have characteristic features with an arborizing pattern of smooth muscle proliferating between mucosal epithelial components.³⁴ However, this is less pronounced in gastric PJ polyps (Fig. 6). Thus, in gastric polyps, there are mostly only foveolar hyperplastic features without the characteristic arborizing smooth muscle fibers. Therefore, clinical correlation and information on previous gastrointestinal polyps are necessary.³⁵ A classic clinical feature of PJS is perioral hyperpigmentation, and patients also are at high risk of developing malignancies in the gastrointestinal tract, pancreas, lung, breast, and gynecologic tract.³⁶ Diagnostic criteria for PJS are as follows: (1) 3 or more morphologically defined PJ polyps; (2) a personal diagnosis in combination with a family history of PJ polyps; and (3) characteristic mucocutaneous hyperpigmentation with a personal or family history of PJ polyps. Gastric cancer risk is increased with a cumulative lifetime risk of 29% from age 15 to 64 years.³⁶ Interestingly, polyps in PJS are likely not the obligate precursor lesion in PJS, but an epiphenomenon owing to mucosal prolapse. In this regard, it is interesting to note that mucosal prolapse also plays a role in the pathogenesis of a subset of sporadic gastric HPs.³¹ Dysplasia is rare in gastric PJ polyps.^{5,37}

JPS is caused by germline mutation in *SMAD4* or *BMPR1A* and characterized by a few to multiple juvenile polyps throughout the gastrointestinal tract. Because germline mutations are only found in 50% to 60% of JPS patients, the diagnosis is made when a patient fulfills any of the following criteria: (1) 3 or more colorectal juvenile polyps; (2) juvenile polyps throughout the gastrointestinal tract; or (3) any number of juvenile polyps in combination with a family history of juvenile polyposis.^{38,39} Gastric juvenile polyposis may be quite extensive, in particular, in patients with *SMAD4* germline mutations, and can simulate Ménétrier disease. Polyps are described being more “stroma-rich” with elongated filiform projections, smooth outer surfaces, and prominent stroma with edema and mixed inflammation (Fig. 7).⁴⁰

Fig. 5. HP. (A) Low-power view of an HP, showing elongated, branching, and cystically dilated foveolar glands with abundant mucinous cytoplasm. The lamina propria is edematous and infiltrated by immune cells. (B) High-power view of the same polyp.

On the other hand, “epithelium-rich” juvenile gastric polyps have little stromal edema, but tightly packed glands and surface epithelium with hyperplasia.⁴⁰ Immunohistochemistry for SMAD4 can

be used because polyps from carriers of a *SMAD4* germline mutation can show decreased or absent staining compared with normal epithelium.^{5,40,41} Massive gastric polyposis, associated

Fig. 6. PJ polyp (hamartomatous polyp). A PJ hamartomatous polyp showing an arborizing pattern of smooth muscle proliferation between the epithelial components. This characteristic arborization pattern is often less pronounced in gastric polyps compared with intestinal PJ polyps. Therefore, these polyps generally cannot be reliably distinguished from gastric HPs based on histopathological characteristics.

Fig. 7. Juvenile polyp (hamartomatous polyp). (A) Hamartomatous polyp in the context of JPS (juvenile polyp). Juvenile polyps are described as being more “stroma-rich” with smooth outer surfaces and prominent edematous and inflamed stroma. However, these polyps generally cannot be reliably distinguished from gastric HPs based on morphologic characteristics, although SMAD4 immunohistochemistry may be of help because juvenile polyps show decreased or absent staining compared with normal epithelium and (sporadic) HPs (B).

with *SMAD4* germline mutation, is often impossible to control endoscopically, and partial or complete gastrectomy is often necessary.³⁸ High-grade dysplasia and gastric cancer can develop in juvenile polyposis patients. Estimates of gastric cancer risk vary between 10% and 30%.^{5,38,40}

Phosphatase and tensin homolog (*PTEN*) hamartoma tumor syndrome comprises a heterogeneous group of disorders, including Cowden (most cases), Bannayan-Riley-Ruvalcaba, and Proteus syndromes, all of which result from various germline mutations in *PTEN*. Clinical features of Cowden syndrome include mental retardation, macrocephaly, mucocutaneous lesions (facial trichilemmoma, acral keratoses, papillomatous papules), esophageal glycogenic acanthosis, thyroid lesions, fibrocystic disease, breast cancer, and a spectrum of gastrointestinal polyps, including hamartomatous polyps, adenomas, lipomas, and ganglioneuromas.^{42,43} The World Health Organization (WHO) defined diagnostic criteria based on the International Cowden Consortium, which is based on the presence of one or more of the mentioned diseases that can occur in Cowden syndrome. Gastric Cowden syndrome polyps are multiple and small and simulate sporadic HPs.^{44,45} Probably there is an increased gastric cancer risk, but no definite estimates are available.^{43–45}

Biopsies in patients with Ménétrier disease show hyperplastic foveolar epithelium, which on biopsies may be impossible to differentiate from HPs. The clinical and endoscopic information and biopsies of surrounding mucosa are especially needed to distinguish HPs from the protein-losing gastropathy in Ménétrier disease. This condition typically involves the oxyntic area (fundus and body) of the stomach, whereas HPs are more commonly situated in the antrum. In Ménétrier disease, there is diffusely oxyntic glandular atrophy and prominent foveolar hyperplasia.⁴⁶

PROGNOSIS, WHEN TO PONDER, WHEN TO PANIC

Gastric HPs were thought to be generally benign and banal polyps, but most HPs arise in a background of mucosal disease with a strong association with chronic gastritis with atrophy and intestinal metaplasia, which are the main risk factors of gastric cancer. Intestinal metaplasia can be observed in around 15% of HPs, dysplasia in less than 5%, and cancer in less than 1%.³⁰ There should be a thorough search and sampling for dysplasia in large polyps, because especially in polyps with a diameter greater than 2 cm, the risk of malignancy increases. Patients with HPs

are at increased risk of gastric cancer, because of background of chronic (atrophic) gastritis in which HPs arise. Preferably, HPs are removed endoscopically in order to determine their nature and prove that the lesions are benign. Because HPs are important markers for an abnormal gastric mucosal background and are not isolated preneoplastic lesions, endoscopic evaluation with biopsies of the background mucosa is necessary to look for concomitant conditions like *H pylori* inflammation, intestinal metaplasia, atrophy, dysplasia, and malignancy.⁴⁷

Pathologic Key Features

- Elongated, branching, and dilated foveolar glands with a hyperplastic appearance with abundant mucinous cytoplasm
- Edematous stroma and chronic (active) inflammation

Differential Diagnosis

- Syndromic hamartomatous polyps
- Ménétrier disease

Pitfalls

- ! The histology of gastric hamartomatous polyps arising in the context of PJS, JPS, and Cowden syndrome is not specific, and reliable distinction between syndromic hamartomatous polyps and HPs is impossible.
- ! An underlying hamartomatous polyposis syndrome should be considered in the case of multiple gastric hyperplastic-type polyps. Clinical correlation is pivotal because these syndromes have typical clinical characteristics and a family history.
- ! Sporadic HPs are associated with *H pylori* chronic gastritis. Therefore, biopsies of the background mucosa are necessary to look for intestinal metaplasia, dysplasia, and malignancy.

GASTRIC FOVEOLAR-TYPE ADENOMA

INTRODUCTION

Gastric foveolar-type adenomas are epithelial polyps consisting of neoplastic foveolar epithelium.³⁹ Foveolar-type adenomas are rare and show an equal sex distribution.^{8,48,49} The mean age of diagnosis is 44 years.^{48,49} These adenomas can occur sporadically, but there is also an association with FAP and GAPPS.⁸

GROSS FEATURES

Gastric foveolar-type adenomas are typically solitary lesions, usually less than 1 cm in diameter, and occur more frequently in the body and fundus than in the antral region.^{39,48,49} In patients with FAP or GAPPS, these polyps usually coexist with multiple FGPs (see above).⁸

MICROSCOPIC FEATURES

Gastric foveolar-type adenomas are composed of gastric epithelial mucin cells with a pink or pale apical mucin cap and show at least low-grade dysplasia (**Fig. 8**).^{5,48,49} These polyps can be distinguished from the background mucosa by an abrupt transition from normal to atypical foveolar cells with hyperchromatic, crowded, and slightly disorganized nuclei, extending to the epithelial surface. Immunohistochemical expression for MUC5AC (gastric mucin marker) can confirm gastric differentiation, whereas expression of MUC6 (pyloric mucin marker), MUC2, and CDX2 (intestinal markers) are generally absent in these lesions.^{48,49} Foveolar-type adenomas typically

occur in normal gastric mucosa without metaplasia, atrophy, or inflammation.^{5,48,49} Moreover, they rarely show high-grade dysplasia (characterized by severe nuclear atypia, loss of polarity, and/or architectural atypia) (**Fig. 9**) or carcinoma (**Fig. 10**).^{5,48,49}

(DIFFERENTIAL) DIAGNOSIS

Differential diagnostic considerations include other types of gastric adenomas (intestinal-type adenomas and PGAs). The cytoplasmic feature of the foveolar cells as described above helps to distinguish foveolar-type adenomas from the other types, although distinction may become more challenging in high-grade dysplasia. Intestinal-type adenomas show at least focal goblet cell or Paneth cell differentiation. Gastric foveolar-type adenomas rarely show high-grade dysplasia or carcinoma, whereas this is more common in intestinal-type adenomas. Moreover, the background mucosa of intestinal-type adenomas typically shows inflammation, atrophy, and/or intestinal metaplasia, whereas the background mucosa of foveolar-type adenomas is normal.⁴⁸ No statistically significant differences in genetic mutations have been found between foveolar-type and intestinal-type adenomas.⁵⁰ Foveolar-type adenomas in the context of FAP show biallelic *APC* inactivation, whereas sporadic variants infrequently harbor *APC* or *KRAS* mutations.³⁹ PGAs are characterized by an apical neutral mucin cap, show expression for MUC6 rather than MUC5AC, and harbor *GNAS* mutations not found in gastric foveolar-type and intestinal-type adenomas (see later discussion).^{51,52}

Fig. 8. Foveolar-type adenoma with low-grade dysplasia. High-power view of a foveolar-type adenoma with low-grade dysplasia, showing atypical foveolar cells at the surface with hyperchromatic, crowded, and slightly disorganized nuclei.

Fig. 9. Foveolar-type adenoma with high-grade dysplasia. High-power view of a foveolar-type adenoma with high-grade dysplasia, showing foveolar cells at the surface with more severe nuclear atypia as compared with Fig. 8, with round to oval, hyperchromatic nuclei with prominent nucleoli, loss of polarity, high nuclear-to-cytoplasmic ratio, and some architectural atypia with crowding and branching of glands. This case was from a patient with FAP syndrome.

Fig. 10. Foveolar-type adenoma with invasive carcinoma. (A) This foveolar-type adenoma shows intramucosal and superficial submucosal invasion with atypical back-to-back glands. (B) The neoplastic and invasive glands can be easily detected in this p53 staining, as they show p53 overexpression.

PROGNOSIS, WHEN TO PONDER, WHEN TO PANIC

For foveolar-type adenomas, the rate of progression to high-grade dysplasia or cancer is exceedingly low (irrespective of sporadic or familial setting).^{8,48} A genetic background of FAP syndrome can be found in 68% of foveolar-type adenomas.⁸ Foveolar-type adenomas are the most frequent type of gastric adenomas in western FAP patients (85%). It should be noted, however, that distinguishing a gastric foveolar-type adenoma and an FGP with low-grade dysplasia can be difficult, but this is of little clinical significance because both lesions harbor a low risk of malignant transformation.⁸ Similar to sporadic cases, the background mucosa of FAP patients with a foveolar-type adenoma is typically normal. Western FAP patients likely do not carry an increased risk of gastric cancer, although recently several cases of gastric cancer were reported in western patients with FAP and GAPPS^{23,24,53} (see also above, Prognosis of fundic gland polyps).

Pathologic Key Features

- Lesion composed of foveolar cells with a clear or pale apical mucin cap
- Per definition, at least low-grade dysplasia
- Immunohistochemistry: expression of MUC5AC; negative for MUC2, CDX2, and MUC6
- In general, normal background gastric mucosa

Differential Diagnosis

- Intestinal-type adenoma (at least focal presence of goblet cells and/or Paneth cells, expression of MUC2, background gastric mucosa with inflammation, atrophy, and intestinal metaplasia)
- Pyloric gland adenoma (pyloric-type glands, expression of MUC6)
- FGP with dysplasia (cystically dilated glands lined by parietal and chief cells)
- Reactive atypia (more gradual gradient in atypia, background of inflammation/erosion)

Pitfall

! Association with FAP and GAPPS (low risk of malignant transformation)

GASTRIC INTESTINAL-TYPE ADENOMA

INTRODUCTION

Gastric intestinal-type adenomas are localized polypoid lesions composed of dysplastic intestinalized epithelium and are the most frequent type of all gastric adenomas.³⁹ They occur more commonly in men than women (ratio 3:1), and usually in patients 60 to 80 years of age.⁴⁸ Risk factors for developing this type of adenoma are any cause of gastric intestinal metaplasia (eg, *H pylori* infection, autoimmune atrophic gastritis).³⁹

GROSS FEATURES

Gastric intestinal-type adenomas are usually single, well-circumscribed, sessile or pedunculated lesions, measuring less than 2 cm³. They are mostly found in the antral and pyloric region (about 60%) where intestinal metaplasia is most prevalent.⁵⁰

MICROSCOPIC FEATURES

Gastric intestinal-type adenomas show an intestinal-type columnar epithelium containing absorptive cells, goblet cells, endocrine cells, and/or Paneth cells (although they may be sparse) and show by definition at least low-grade dysplasia (**Fig. 11**). These lesions show columnar cells with hyperchromatic, elongated nuclei with pseudostratification and crowding, extending to the surface, similar to tubular adenomas in the colon and rectum. There is increased mitotic activity. Often, a distinct brush border is present that confirms intestinal differentiation in the dysplastic epithelium. Because of an abrupt transition from the background mucosa with striking hyperchromasia, these lesions can usually be easily detected at low power, although reactive epithelial changes in surrounding mucosa can cause diagnostic challenges. Architectural complexity (cribriform, branching, budding, or crowding glands) as well as severe cytologic atypia (rounded nuclei with loss of polarity, clumped chromatin, and prominent nucleoli) are features of high-grade dysplasia.

Fig. 11. Intestinal-type adenoma. High-power view of an intestinal-type adenoma with low-grade dysplasia, showing columnar cells with hyperchromatic, elongated nuclei and pseudostratification, extending to the surface. Several goblet cells and Paneth cells can be seen.

Almost all intestinal-type adenomas occur in background gastric mucosa with *H pylori* infection (42%), background gastritis and atrophy (environmental atrophic metaplastic gastritis [52%], autoimmune metaplastic atrophic gastritis [19%]), and/or intestinal metaplasia.^{5,48} Intestinal-type adenomas show variable expression of intestinal markers MUC2 and CD10. There is no or slight expression for gastric mucins MUC5AC and MUC6.

(DIFFERENTIAL) DIAGNOSIS

Differential diagnostic considerations include other types of gastric adenomas (foveolar-type adenomas and PGAs; see Differential diagnosis section of Gastric foveolar-type adenomas). Another diagnostic difficulty can be caused by reactive epithelial changes due to inflammation or erosion, which is frequently present in chronic gastritis. In contrast to intestinal-type adenomas, reactive atypia is characterized by a gradual gradient in atypia from the background mucosa with slight hyperchromatic nuclei and no nuclear crowding.

PROGNOSIS, WHEN TO PONDER, WHEN TO PANIC

It is important to realize that intestinal-type adenomas have a reasonable risk of malignant transformation. Approximately 40% of lesions show high-grade dysplasia, and approximately 25% progress to adenocarcinoma.^{48,50} Therefore, complete (endoscopic) excision is important, and the lesions should be processed entirely for

microscopic examination to identify potential areas of high-grade dysplasia or carcinoma. Moreover, these adenomas are also associated with separate foci of intestinal metaplasia (97%), flat dysplasia (6%), and adenocarcinoma (16%) elsewhere in the stomach.⁴⁸ Therefore, biopsies of the background mucosa are crucial.

Intestinal-type adenomas are very rare in western FAP patients (1%–2% of gastric adenomas in FAP) but more common in Asian FAP patients, probably related to differences in prevalence of *H pylori* infection and atrophic gastritis.^{8,54} FAP patients with intestinal-type adenomas with additional *H pylori* infection and gastric atrophy especially seem to have an increased risk of developing intestinal-type gastric adenocarcinoma.^{29,54}

Pathologic Key Features

- Localized lesion composed of dysplastic intestinalized epithelium with at least focal presence of goblet cells and/or Paneth cells
- Per definition, at least low-grade dysplasia
- Immunohistochemistry: expression of MUC2; negative for MUC5AC and MUC6
- Background gastric mucosa often shows inflammation, atrophy, and/or intestinal metaplasia

Differential Diagnosis

- Foveolar-type adenomas (foveolar-type cells with pale or clear mucin cap, no goblet cells or Paneth cells)
- Pyloric gland adenoma (pyloric-type glands, positive for MUC6)
- Reactive atypia (more gradual gradient in atypia)

Pitfalls

- ! Reasonable risk of malignant transformation (high-grade dysplasia or carcinoma in same lesion, or presence of synchronous lesions with high-grade dysplasia or carcinoma)
- ! Association with FAP syndrome, especially in non-western populations
- ! FAP patients with intestinal-type adenoma together with *H pylori* infection and gastric atrophy are especially at risk for developing gastric adenocarcinoma

GASTRIC GLANDULAR ADENOMAS: PYLORIC GLAND ADENOMA AND OXYNTIC GLAND ADENOMA

INTRODUCTION

PGA and OGA are rare polyps. They are the most recently recognized gastric epithelial polyps, characterized by closely packed pyloric or oxyntic glands, respectively. Of these polyps, PGAs are the more common. Sporadic PGAs are found in patients with conditions resulting in pyloric metaplasia, such as autoimmune atrophic gastritis or chronic *H pylori* gastritis. More than 30% of PGAs arise in a background of autoimmune atrophic gastritis.^{49,55} Nevertheless, PGAs remain a rare finding, even in patients with autoimmune atrophic gastritis, and most polyps in patients with autoimmune atrophic gastritis are HPs (80%), oxyntic mucosa pseudopolyps (10%), or intestinal adenomas (10%).⁵⁶ Of note, PGAs were recently also described in FAP patients, where

they arise in nonatrophic background mucosa.⁸ PGAs have also been reported in Lynch syndrome, McCune-Albright syndrome, and JPS.^{57–59} Various terms have been used in the literature for gastric neoplasms with oxyntic gland differentiation. Most such lesions are best addressed as OGA, whereas rare cases with atypia and submucosal invasion may be better addressed as gastric adenocarcinoma of fundic gland type (GA-FG).⁶⁰ Neoplasms with oxyntic gland differentiation are exceedingly rare, and most cases have been reported in Japanese literature. Gastric glandular adenoma has been suggested as an appropriate unifying diagnostic term for polyps arising from the glandular compartment, as opposed to gastric foveolar and intestinal type adenomas.⁷

GROSS FEATURES

Most PGAs form polypoid lesions or masses varying from a few millimeters to 10 cm, with an average of 2 cm. OGAs tend to be smaller in size (usually <1 cm), whereas GA-FG are larger (1.5–4 cm).

MICROSCOPIC FEATURES

Histologically, PGA is characterized by densely packed cuboidal to low columnar epithelium resembling pyloric gland cells (**Fig. 12**). Immunohistochemically, PGAs are positive for both MUC6 (strong) and MUC5AC (slight or partially). PGAs typically lack expression of intestinal markers MUC2 and CDX2, although MUC2 is sometimes positive in areas with transition to intestinal metaplasia.⁶¹ High-grade dysplasia has been reported in about half of PGAs and is characterized by disturbed architecture and loss of nuclear polarity. Ki-67 immunohistochemistry can be helpful to identify high-grade dysplasia in PGAs (**Fig. 13**). Activating *GNAS* mutations are relatively specific for PGA because it is found in most PGAs but not in gastric foveolar-type or intestinal-type adenomas or FGPs.^{7,51,52}

Gastric neoplasms with oxyntic gland differentiation are characterized by closely packed oxyntic gland with either a monotonous proliferation of chief cells or an admixture of chief cells and parietal cells resembling fundic glands (**Fig. 14**).^{60,62} Most of these tumors have only very mild atypia and are restricted to the mucosa. These lesions are benign and best addressed as OGA. Some of these lesions show superficial submucosal involvement (<0.1 cm). Larger lesions (>1.5 cm) can show more aggressive histologic features with deeper submucosal invasion, atypical cellular differentiation (ie, mucus neck or foveolar

Fig. 12. PGA. (A) Low-power view of a PGA showing densely packed, sometimes cystically dilated, monotonous pyloric-type glands. (B) High-power view of the same polyp showing cells with ground-glass cytoplasm. PGAs show strong expression of MUC6 (not shown).

differentiation), and mild to moderate nuclear atypia and may be best addressed as GA-FG.⁶⁰ In contrast to PGA, OGAs arise in oxyntic mucosa without atrophy or pyloric metaplasia.⁶⁰

(DIFFERENTIAL) DIAGNOSIS

The differential diagnosis is mainly with other gastric glandular polyps, such as FGP. In contrast to GA-FG, dysplastic changes in FGP are only present in the superficial foveolar layer, whereas the glandular part of the lesion lacks atypia and architectural complexity. Depending on the background mucosa, distinction between PGA and OGA can be challenging.⁷ There is a morphologic continuum between OGA and GA-FG, if these are indeed considered as separate entities.⁶³

PROGNOSIS, WHEN TO PONDER, WHEN TO PANIC

Up to half of PGAs harbor high-grade dysplasia, but submucosal invasion is rare (<10%).^{49,64} Therefore, radical local excision is indicated. After radical resection, recurrence rate is low (<10%).⁶⁴ Although submucosal invasion is commonly found in OGA, these lesions have a very low malignant potential. Lymphovascular invasion has only been found in lesions fulfilling criteria of GA-FG. Even in those cases with invasion, lymph node metastasis is extremely rare, and complete (endoscopic) resection of GA-FG seems adequate treatment.^{60,63,65}

In contrast to sporadic cases, PGAs in FAP patients develop in nonatrophic mucosa and show

variable presence of parietal cells, making differentiation from OGA sometimes very difficult or even impossible. Based on these observations and the common *GNAS* mutations in OGA and PGA, it has been hypothesized that PGA and OGA are likely the same lesions within a spectrum with subtle histologic differences depending on the background mucosa in which they arise.⁷

Pathologic Key Features

- Pyloric gland adenoma: densely packed pyloric-type glands
- OGA: closely packed oxyntic glands (can be chief cell-predominant or an admixture of chief cells and parietal cells)

Differential Diagnosis

- FGPs
- Distinction between PGA and OGA can be difficult and may depend on type of background mucosa (eg, atrophic mucosa with pseudopyloric metaplasia or nonatrophic oxyntic mucosa)
- OGA versus GA-FG is a histologic continuum

HOW TO RECOGNIZE EARLY INVASION IN GASTRIC POLYPS (INTRAMUCOSAL CARCINOMA)

INTRODUCTION

Most gastric polyps, such as adenomas, HPs, FGPs, and PGAs, are sporadic with no significant malignant potential; however, it is important to search for areas of high-grade dysplasia and infiltrative growth. Early gastric cancer, defined as carcinoma confined to the mucosa or submucosa, may be encountered in endoscopically benign-appearing polyps.⁶⁵ Especially in the Japanese population, there is experience with the risks that intramucosal cancers exhibit. Patients with well-differentiated early gastric cancer

limited to the mucosa or the upper submucosa (SM1, up to a depth of 500 μ m) and without lymphovascular invasion generally have a very low risk of lymph node metastases.^{65,66} Therefore, surgery is not necessary in most early gastric cancers, and these may be treated effectively with endoscopic resection or endoscopic polypectomy.

MICROSCOPIC FEATURES

Polyps with low-grade dysplasia are characterized by mild to moderate nuclear atypia and crowding of nuclei with mild pseudostratification. There is no complex architecture. Features of high-grade dysplasia are cribriform architecture, marked glandular crowding, full-thickness nuclear stratification, and severe nuclear atypia. Intramucosal carcinomas are defined by invasion into the lamina propria. It is difficult to distinguish nuclear features of intramucosal carcinomas from high-grade dysplasia. Features in favor of carcinoma are syncytial growth pattern, effacement of normal architecture with back-to-back glands, and single cells infiltrating the lamina propria (see Fig. 10). Often there are cystic glands. Desmoplastic stroma is often lacking or difficult to detect in intramucosal cancer. Intramucosal cancer should be classified and graded. Classification is preferably according to the WHO classification scheme.³⁹ Grading applies only to tubular and papillary gastric cancers. A tumor can be designated as poorly differentiated if there are marked architecturally distorted glands and single cells are present. Tumors with signet ring cells or diffuse growth are classified as poorly cohesive cancers; these gastric cancers often have a higher stage with consequently a poor prognosis. Therefore, limited endoscopic resection is often inferior for the treatment of these tumors, especially in a western population. Assessing the extent of invasion into the mucosa and/or submucosa is essential to determine whether the patient requires a (partial) gastrectomy.⁶⁵ As for all gastric polyps, the nonneoplastic surrounding epithelium should be assessed for features predisposing to neoplasia, such as intestinal metaplasia, atrophic mucosa, and *H pylori* infection.

CONCLUDING REMARKS

In this review, the authors provide an overview of different types of gastric epithelial polyps, based

Fig. 13. High-grade dysplasia in a PGA. (A) High-grade dysplasia in a PGA characterized by complex architecture and loss of nuclear polarity. (B) High-power view showing loss of nuclear polarity and mitotic activity.

Fig. 13. (continued). (C) Increased Ki-67 immunolabeling in high-grade dysplasia in a PGA. Note Ki-67 negativity in the low-grade glands at the bottom.

Fig. 14. OGA. High-power view of an OGA showing densely packed oxyntic glands with a monotonous proliferation of parietal and chief cells.

on their cell or epithelial compartment of origin. Most gastric polyps are sporadic with no malignant potential, but clinical correlation is necessary, and pathologists should be familiar with the morphologic characteristics of gastric polyps as an indication for a search for an underlying genetic syndrome, such as FAP, PJS, or JPS. Moreover, in the presence of a gastric polyp, preferably biopsies of background mucosa are taken of at least the antrum and corpus. Evaluation of the background nonpolypoid mucosa is essential in reaching a diagnosis that can characterize the condition in which the polyp developed, which may have therapeutic consequences.

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The authors have nothing to disclose.

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