Gastric polyps and polyposis syndromes

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Abstract
Gastric polyps show significant morphologic overlap, and some polyps defy classification altogether. Nevertheless, gastric polyps, particularly when profuse, should prompt further clinical and endoscopic investigation, as it may lead to the diagnosis of a polyposis syndrome. This review summarizes the common gastric polyps that are found in familial and non-inherited polyposis syndromes of the gastrointestinal tract. Examples of the gastric polyps are illustrated, and a discussion of polyp morphology and distribution is paired with a discussion of relevant clinical features and diagnostic criteria of polyposis syndromes. This information provides pathologists guidance for further patient workup, genetic testing, and cancer surveillance.

Keywords Cowden syndrome; Cronkhite—Cananda syndrome; familial adenomatous polyposis; fundic gland polyposis; hamartomatous intestinal polyposis; juvenile polyposis syndrome; Peutz—Jeghers syndrome

Introduction

Gastric polyps are far less common than colonic polyps. As a result, we know much less about gastric polyps than colonic polyps, and the literature tends to be more recent and sparse. With the increasing use of endoscopy, however, gastric polyps are encountered more often. Found in 6% of upper endoscopies, gastric polyps are a heterogenous group of lesions, the most common of which are fundic gland polyps and hyperplastic/polypoid foveolar hyperplasia (with a prevalence of 77 and 17%, respectively).[1] Other less common epithelial and stromal proliferations represent the remainder of the polyps.

Gastric polyps may be categorized in various ways, but for the pathologist, a pattern-based approach is best. Table 1 lists the most common gastric polyps as categorized by their main proliferative compartment. Among these, the easiest neoplasms to classify are those comprised of a single developmental compartment quickly recognized histologically. For example, the epithelial neoplasms are readily identifiable as epithelial proliferations, and the mesenchymal neoplasms typically show obvious spindle cell proliferations. Even those entities listed in the miscellaneous category normally show proliferation of only one cell type, allowing for easy classification.

Hamartomatous polyps, on the other hand, are mucosal-based and can be derived from any of the three embryonic layers, resulting in significant histologic heterogeneity. These polyps result from disordered growth of tissues indigenous to the site, and are frequently associated with a clinical syndrome. Unfortunately, hamartomatous polyps in the gastric mucosa have nonspecific histology and may be indistinguishable from hyperplastic polyps even in a patient with a known polyposis syndrome.[2] When profuse, gastric polyps should prompt further clinical and endoscopic investigation, as it may lead to the diagnosis of a polyposis syndrome.[3]

This review summarizes the common gastric polyps found in familial and non-inherited polyposis syndromes of the gastrointestinal tract. Examples of the gastric polyps are illustrated, and a discussion of polyp morphology and distribution is paired with a discussion of relevant clinical features (Table 2) and diagnostic criteria (Table 3) of polyposis syndromes. This information provides pathologists guidance for further patient workup, genetic testing, and cancer surveillance.

Familial adenomatous polyposis and associated polyps

Familial adenomatous polyposis (FAP) is an autosomal dominant disease caused by mutations in the adenomatous polyposis coli (*APC*) gene, which is located on chromosome 5q21-q22. FAP occurs in approximately 1 out of 10,000—30,000 live births, and accounts for less than 1% of the total colon cancer risk in the United States. World Health Organization criteria for the diagnosis of FAP are: (1) 100 or more colorectal adenomas, or (2) a disease-causing germline mutation of the *APC* gene, or (3) family history of FAP and any number of adenomas at a young age.[4] The spectrum of disease caused by mutations in the *APC* gene includes classic FAP (more than 100 adenomatous colorectal polyps) and attenuated forms of the disease (less than 100 adenomas, by definition, but frequently less than 30). In addition to colorectal carcinoma, patients with FAP are at risk for extraintestinal disease manifestations (Table 2) and extracolonic malignancies including duodenal ampullary carcinoma, follicular or papillary thyroid carcinoma, hepatoblastoma, gastric carcinoma, and central nervous system tumours (primarily medulloblastomas).

Polyps occur commonly in the upper gastrointestinal tract of patients with FAP (up to 100%).[5,6] Fundic gland polyps are the most common gastric lesion found in patients with FAP (prevalence 80—93%), followed by adenomatous polyps. Fundic gland polyps are typically located in the proximal stomach, tend to be <1 cm, and can be profuse.[7—9] Histologically, fundic gland polyps are characterized by dilated cystic oxyntic glands with distorted glandular architecture admixed with normal appearing glands. Parietal cells balloon into the lumen and exfoliated anucleated structures with eosinophilic granules clog the gland outlets (Figure 1).[10] The finding of dysplasia in a fundic gland polyp (Figure 2) should raise one's suspicion for FAP syndrome,

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Gastric polyps categorized by proliferative compartment

Epithelial

- Hyperplastic polyps, polypoid foveolar hyperplasia, foveolar polyp
- Heterotopic polyps
  - Pancreatic acinar metaplasia
  - Pancreatic heterotopia
  - Brunner's gland hyperplasia
- Adenomatous polyps
  - Intestinal type
  - Gastric type, foveolar adenoma
  - Gastric type, pyloric gland adenoma
  - Gastric type, oxyntic gland adenoma
- Carcinomatous polyp, primary or metastatic
- Neuroendocrine tumours

Hamartomatous

- Fundic gland polyp[a]
- Peutz–Jeghers polyp[a]
- Juvenile polyp[a]
- Cronkhite–Canada syndrome-associated polyp[a]
- Cowden's syndrome-associated polyp[a]
- Bannayan–Riley–Ruvalcaba syndrome associated polyp[a]

Mesenchymal

- Inflammatory fibroid polyp
- Gastrointestinal stromal tumour
- Leiomyoma
- Vascular lesions
- Granular cell tumour

Other

- Lymphoid hyperplasia
- Lymphoma
- Xanthoma
- Granuloma
- Amyloidosis
- Hemosiderosis
- Calcium deposit

[a] Polyps associated with clinical syndromes.

Table 1

as the prevalence of dysplasia in sporadic fundic gland polyps is exceptionally low (0.2% in one study of 100,000 patients) compared to FAP patients (38–44% low-grade dysplasia, 3% high grade dysplasia).[11–13] Despite the frequent rate of dysplasia in fundic gland polyps from FAP patients, only rare reports of malignant degeneration exist.[12,14–16] As such, these lesions are generally not considered to have significant malignant potential.[11] Sampling of fundic gland polyps is recommended in patients with FAP to confirm their histology, along with complete polypectomy of large or irregular appearing polyps to assess for malignancy. In contrast to fundic gland polyps, antral polyps in FAP patients are usually adenomatous (Figure 3), the finding of which is associated with severe duodenal adenomatosis; these polyps should be completely removed endoscopically as they harbour greater malignant potential.[5,17–20] Rates of gastric cancer in FAP patients vary based on country, ranging from 0.6% in the United States to 7% in Japan, and gastric cancer exceeds duodenal cancer in the East Asian FAP population.[5,21,22] Characteristics of gastric cancer in patients with FAP include a long duration between occurrence of gastric cancer and colectomy, metachronous cancers, and multicentricity.[23] In summary, when faced with profuse fundic gland polyposis or dysplasia in a fundic gland polyp, suggestion for clinical evaluation of FAP syndrome is appropriate. If diagnostic clinical features are lacking, further *APC* gene mutation testing for attenuated FAP, and *MutYH* genetic testing should be considered.

MutYH-associated polyposis

MutYH-associated polyposis (MAP) is the only known autosomal recessive hereditary colon cancer syndrome and is caused by biallelic mutations in the *MutYH* gene.[24] The two most common *MutYH* gene mutations found in MAP in the Caucasian population are Y179C and G396D, but about 20% of cases with biallelic mutations have neither of these mutations.[25] The clinical spectrum of MAP is variable, with early descriptions similar to attenuated FAP and classic FAP.[26–28] Subsequently, other patients with biallelic *MutYH* gene mutations were reported with early onset (age <50 years) cancer without polyposis.[26–28] Large-scale meta-analysis shows a 28-fold increase in colon cancer risk in biallelic mutation carriers.[29] Extracolonic features, such as gastroduodenal polyps, are described but are far less common than in FAP.[30] In parallel with FAP, recognition and classification of gastric polyps can provide initial clues to identify patients at risk for this inherited polyposis syndrome, and thus prompt early screening and genetic counselling.

Peutz–Jeghers syndrome and Peutz–Jeghers polyps

Peutz–Jeghers syndrome is an autosomal dominant condition characterized by hamartomatous polyps (Peutz–Jeghers type) of the gastrointestinal tract and melanocytic mucocutaneous hyperpigmentation.[31] Primarily considered an inherited syndrome, 80% of affected families harbour a germline mutation in the *STK11/LKB1* gene; however, up to 25% of documented cases are sporadic.[32,33] Patients with Peutz–Jeghers syndrome have a 93% cumulative lifetime risk for cancer, including carcinomas of the gastrointestinal tract, breast, ovary, and testis.[34–36] In this context, early diagnosis of the syndrome allows for appropriate screening and surveillance. WHO criteria for the clinical diagnosis of Peutz–Jeghers syndromes are: (1) detection of three or more histologically confirmed Peutz–Jeghers polyps, or (2) the presence of any number of Peutz–Jeghers polyps in a patient with a family history of the syndrome, or (3) detection of characteristic, prominent mucocutaneous pigmentation in the patient with a family history of the syndrome, or (4) detection of any number of Peutz-Jheghers polyps in a patient with prominent mucocutaneous pigmentation.[37] It follows that the pathologic identification of a Peutz–Jeghers polyps is integral to diagnosis of this syndrome.

Although patients are more likely to have small bowel (64% of patients) or colonic polyps (53% of patients), about 15–30%