Chapter 17
Syndromic Gastric Polyps: At the Crossroads of Genetic and Environmental Cancer Predisposition

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Introduction

Gastric polyps are found in 1–4 % of all gastroscopies in the general population [1]. The vast majority are epithelial polyps. Other polypoid lesions, including neuroendrocrine tumors, pancreatic heterotopia, lymphoma, and mesenchymal polyps such as inflammatory fibroid polyp and gastrointestinal stromal tumor are relatively rare [2].

Mainly caused by differences in *Helicobacter pylori* (HP) infection, great geographical differences in prevalence of different gastric polyps are observed. In general, hyperplastic polyps and adenomas are much more prevalent in countries with high rates of HP infection. In Western countries, with low prevalence of HP infection,

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fundic gland polyps (FGP) are the most common polyp type comprising up to 77 % of all gastric polyps [1, 2]. Fundic gland polyps are usually <0.5 cm and characterized by cystically dilated oxyntic glands lined by parietal and chief cells. Sporadic FGPs are usually single or few in number but can be numerous in patients using proton pump inhibitors (PPI). Dysplasia in sporadic fundic polyps is very rare. Multiple fundic gland polyps (polyposis) are a frequent manifestation of familial adenomatous polyposis (FAP) and in this context low-grade dysplasia is often seen, although the risk of malignant progression is low.

Hyperplasic polyps, the second most common type of gastric polyps in Western populations, comprise almost 15 % of all gastric polyps [2]. Hyperplastic polyps are a hyperproliferative response to tissue injury and typically occur in patients with *Helicobacter pylori* or autoimmune chronic gastritis, atrophy and intestinal metaplasia. In addition, mucosal prolapse can result in hyperplastic-type polyps [3]. Gastric hyperplastic polyps are often multiple and most frequently found in the antrum. These polyps vary from 0.5 to 1.5 cm, but can be very large causing gastric obstruction. Gastric hyperplastic polyps are characterized by hyperplastic, dilated, elongated, distorted, and branching foveolae with edematous stroma, lined by reactive foveolar epithelium. Large polyps may become eroded and cause chronic blood loss and iron deficiency anemia. Intestinal metaplasia as well as dysplasia has been reported in 1–20 % of these polyps [1, 4].

Gastric adenomas are the third most common type of polyp in the Western population, but only account for <1 % of all gastric polyps [2]. Histologically, gastric foveolar-type adenoma, intestinal-type adenoma, and pyloric gland adenoma can be distinguished [5, 6]. Whereas background gastric mucosa in gastric foveolar-type adenomas is usually normal, intestinal-type adenomas typically occur in a background of *Helicobacter pylori* infection, chronic gastritis, atrophy, and intestinal metaplasia. The more recently recognized pyloric gland adenoma (PGA) is characterized by densely packed cuboidal to low columnar epithelium resembling pyloric gland cells and typically occurs in association with autoimmune atrophic gastritis. Moreover, activating mutation of *GNAS* seems to be specific for this type of adenoma since it was found in 65 % of PGAs but not in gastric foveolar-type or intestinal-type adenomas [7]. Recently, PGAs were also described in FAP and Lynch syndrome, although the lesions reported in Lynch syndrome arose in a population that differed from the one associated with FAP [8, 9]. Both intestinal-type adenomas and PGAs carry a higher risk of neoplastic progression than gastric-foveolar type adenomas, which typically harbor low-grade dysplasia [5, 6].

True hamartomatous polyps in the stomach are rare and exclusively occur in the setting of hamartomatous polyposis syndromes. However, as opposed to colonic hamartomatous polyps, gastric hamartomatous polys lack specific histology and are difficult, if not impossible, to differentiate from gastric hyperplastic polyps. Clinical context is essential to make a diagnosis of a gastric hamartomatous polyp [10].

Several recent studies shed new light on the pathology of gastric polyps occurring in the setting of gastrointestinal polyposis and other syndromes (Table 17.1). Although morphology of gastric polyps is less specific than of colonic polyps, in particular in the case of hamartomatous polyposis syndromes, knowledge of polyp

Table 17.1 Syndromes associated with gastric polyps

Syndrome	Genes	Mode of inheritance	Incidence of gastric polyps	Number of gastric polyps	Histological type of gastric polyps	Gastric cancer lifetime risk
(Attenuated) familial adenomatous polyposis	*APC*	Autosomal dominant	>66 % [8]	Multiple	FGP (predominant), gastric foveolar adenomas, pyloric gland adenoma	Not increased in Western patients [27] (<1 %)
MUTYH-associated polyposis	*MUTYH (MYH)*	Autosomal recessive	10–30 % [32, 33]	Unclear	FGPs (predominant), adenomas	Not increased [14]
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2,* or *EpCAM*	Autosomal dominant	Rare	Few	Pyloric gland adenoma	5–8 % [12]
Peutz–Jeghers syndrome	*LKB1 (STK11)*	Autosomal dominant	25 % [40]	Few to numerous	Hamartomatous polyps	29 % [42]
Juvenile polyposis syndrome	*SMAD4* (~30 %) *BMPR1A* (~20 %)	Autosomal dominant	60–83 % [55, 56]	Few to numerous	Hamartomatous polyps	11–21 % [46, 52, 58]
Cowden (PTEN hamartoma tumor syndromes)	*PTEN*	Autosomal dominant	Up to 100 % [66, 67]	Few to multiple	Hamartomatous and hyperplastic polyps	Not increased as far as known
Gastric adenocarcinoma and proximal polyposis of the stomach	Unknown	Autosomal dominant	100 % [70]	Numerous (polyposis)	FGPs (primarily). Few hyperplastic polyps and adenomas	Unknown
Neurofibromatosis type 1	*NF1*	Autosomal dominant	<2 % [75]	1–3 (Mostly) to multiple	Inflammatory/hyperplastic polyps	Not increased
McCune–Albright syndrome	*GNAS*	Noninherited postzygotic mutation	unknown	2 to multiple	Hamartomatous polyps, FGP, hyperplastic, adenoma	Not increased
Cronkhite–Canada syndrome	n/a	Non inherited	100 %	Numerous	Inflammatory/hamartomatous polyps	Not increased

FGP fundic gland polyp

n/a: not applicable

types occurring in different syndromes may help to recognize a patient with syndromic polyps. In addition, studying tumorigenesis in hereditary syndromes can increase our understanding of gastric tumorigenesis in general.

This chapter will review the prevalence, histopathology, and genetics of gastric polyps in the well-established gastrointestinal polyposis syndromes. In addition, the recently recognized hereditary syndrome Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS), and gastric polyps in other not primarily gastrointestinal syndromes such as McCune–Albright syndrome and neurofibromatosis type 1, will be discussed.

Familial Adenomatous Polyposis Syndrome

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome caused by germline mutation in the *Adenomatous Polyposis Coli* (*APC*) gene. Classic FAP is characterized by development in teenage years of hundreds to thousands adenomatous polyps (≥100) throughout the colorectum. About 50 % of patients develop adenomas by age 15 and 95 % by age 35. If left untreated, CRC is diagnosed at an average age of 39 years (range 35–43 year) [11, 12]. Attenuated FAP (AFAP) is defined by the presence of oligopolyposis; on average patients have 30 polyps. The diagnosis should be considered in patients 40–50 year old with 10–99 adenomas cumulatively. Patients with AFAP have a 70 % lifetime risk of CRC, presenting about 12 years later than classic FAP. Of note, oligopolyposis can be an expression of a germline *APC* mutation or a biallelic *MUTYH* mutation (see next section) [12–14].

A variety of benign and malignant extracolonic manifestations have been described in FAP, of which duodenal adenomas and cancer and desmoids tumors are clinically now the most challenging [12, 15]. Duodenal adenomas are present in 30–70 % of FAP patients with a lifetime risk of almost 100 %. The lifetime risk of duodenal adenocarcinoma is 4–10 % [12].

More than two-thirds of FAP patients have gastric polyps [8, 16] (Fig. 17.1). The vast majority (nearly 80 %) of gastric polyps in FAP are benign fundic gland polyps occurring in the gastric fundus and body [8]. Typically, FAP patients have multiple FGPs presenting as gastric polyposis [17]. Of note, sporadic fundic gland polyposis can occur, but this phenomenon is always associated with PPI, as are most single sporadic fundic gland polyps. Also, both sporadic single FGPs and sporadic fundic gland polyposis rarely show dysplasia, harbor *β-catenin* mutations, lack *APC* mutations, and never progress to cancer [18–20].

FGPs vary in size from a few millimeters to a centimeter. Microscopically, these polyps have dilatation and cystic changes of the fundic glands. Low-grade dysplasia is present in up to a third of FGPs in FAP, but high-grade dysplasia and malignant transformation in FGPs in FAP is exceedingly rare [8, 21, 22]. Genetically, fundic gland polyps in FAP frequently show a somatic second hit inactivation of the wild-type *APC* allele that precedes dysplasia [23]. In contrast, sporadic FGPs without

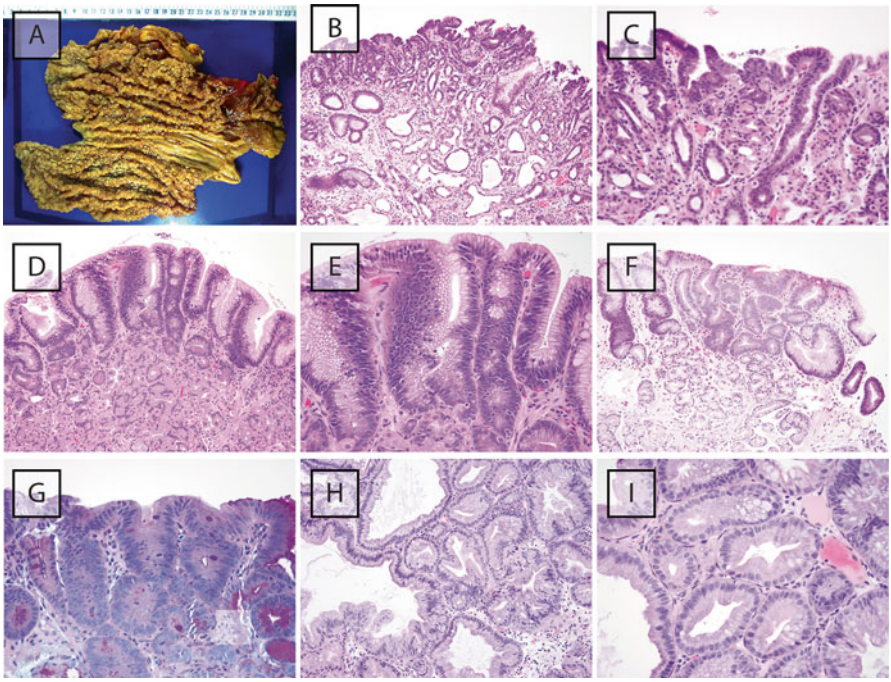

Fig. 17.1 (**a**) Familial adenomatous polyposis, gross specimen. Numerous fundic gland polyps and gastric foveolar-type adenomas were identified. (**b**) Familial adenomatous polyposis, fundic gland polyp with surface low-grade foveolar-type dysplasia. Such lesions are unlikely to progress to carcinoma. Note the dilated oxyntic glands beneath the surface. (**c**) Familial adenomatous polyposis, fundic gland polyp with surface low-grade foveolar-type dysplasia. This is a higher magnification of the lesion depicted in (**b**). (**d**) Gastric adenoma, gastric foveolar type in familial adenomatous polyposis. This lesion is from a Western patient and lacks background gastritis. (**e**) Gastric adenoma, gastric foveolar type in familial adenomatous polyposis. At high magnification note that each surface cell has a droplet like well marginated neutral mucin cap. This is a higher magnification of the lesion depicted in (**d**). F. Gastric adenoma, intestinal type in familial adenomatous polyposis. This lesion arose in the antrum but note that there is no background intestinal metaplasia such that this lesion, like gastric foveolar adenomas in FAP patients, is more akin to a sporadic colorectal adenoma as opposed to a colitis-associated dysplastic polypoid lesion. (**g**) Gastric adenoma, intestinal type in familial adenomatous polyposis, PAS/AB stain. Note the goblet cells within the lesion. (**h**) Pyloric gland adenoma in familial adenomatous polyposis. These lesions usually arise in the setting of pyloric metaplasia in the sporadic setting but in FAP they arise in uninflamed oxyntic mucosa. Note the ground glass cytoplasm and compare it to the appearance of the cytoplasm of the foveolar adenoma in (**e**). I. Pyloric gland adenoma in familial adenomatous polyposis. The nuclei are round and form a monolayer

dysplasia typically show a single *β-catenin* mutation. Although sporadic FGPs with dysplasia are extremely rare they often harbor an *APC* mutation [19, 24].

Up to 20 % of gastric polyps in Western FAP patients are adenomas [8]. Most of these (85 %) occur in the gastric body and are gastric foveolar-type adenomas with low-grade dysplasia. Distinction between a FGP with low-grade dysplasia and a gastric foveolar-type adenoma can be difficult. Background gastric mucosa in FAP

patients with gastric foveolar-type adenomas is typically normal. This type of adenoma, therefore, seems to represent an isolated lesion caused by the germline *APC* mutation, similar to colonic adenomas in FAP. Gastric foveolar-type adenomas have a low risk of progression to high-grade dysplasia [5].

About 2–3 % of all gastric polyps (14 % of all adenomas) in FAP are classified as pyloric gland adenomas. These polyps are characterized by densely packed cuboidal to low columnar epithelium with round nuclei without prominent nucleoli and pale or eosinophilic, "ground glass" cytoplasm, resembling pyloric gland cells. PGAs are found in the gastric body and fundus and high-grade dysplasia is seen in about 10–15 % [6]. In the general population, PGAs are typically found in association with autoimmune atrophic gastritis and pseudopyloric metaplasia (or antralization) although even in this setting PGAs are still very rare with a prevalence of just 1 % and comprise 15 % of all gastric adenomas (the vast majority being intestinal-type adenomas) [25]. Interestingly, PGAs in FAP occur in undamaged background gastric mucosa but seem to be more prevalent in FAP than in autoimmune atrophic gastritis since PGAs were found in 6 % of FAP patients [6, 8].

Intestinal-type adenomas are very rare in Western FAP patients (1–2 % of gastric adenomas in FAP) [8]. Interestingly, a higher prevalence of gastric adenomas of 40–50 % has been found in Asian FAP patients, compared to 10–20 % in Western patients. This higher prevalence is likely caused by more widespread *Helicobacter pylori* infection and chronic atrophic gastritis and intestinal-type adenomas. Indeed, a strong correlation between presence of gastric adenomas (subtype not specified) and *Helicobacter pylori* associated atrophic gastritis has been shown in Japanese FAP patients [26].

Western FAP patients do not carry an increased risk of gastric cancer, which is consistent with the low malignant potential of the gastric-foveolar-type adenomas seen in most Western FAP patients [27]. In contrast, a 3–4 times higher risk of gastric cancer is seen in FAP patients in Asian countries where gastric cancer is also more prevalent in the general population. This difference is best explained by higher prevalence of *Helicobacter pylori* infection and associated atrophic gastritis and intestinal metaplasia in these populations [28, 29]. Therefore, presence of *Helicobacter pylori* infection, gastric atrophy, and intestinal-type adenomas seem to be particularly important to identify FAP patients at increased risk of gastric cancer [30]. Also, presence of pyloric gland adenomas in FAP may be relevant for an increased cancer risk, but this needs further studies. Gastric foveolar-type dysplasia, as long as it is low grade, may be ignored with regard to an increased risk of gastric cancer.

Screening for upper gastrointestinal tumors in Western FAP is thus mainly directed at duodenal/ampullary adenomas and cancer. Screening endoscopy should start at age 25–30 years and be repeated every 0.5–4 years depending on Spigelman stage of duodenal polyposis [15]. Examination of the stomach should include random sampling of fundic gland polyps and larger suspicious looking polyps with biopsies from surrounding flat mucosa. Gastric surgery should be reserved for high-grade dysplasia or cancer [12].

MUTYH-Associated Polyposis

MUTYH-associated polyposis (MAP) is an autosomal recessive disorder caused by biallelic germline mutation in the *MUTYH* gene [14]. Most patients have between 10 to a few hundred colorectal adenomas, mimicking the colonic phenotype of attenuated FAP. However, MAP can also present with early onset CRC with few to zero polyps [14]. Most colorectal polyps in MAP are adenomas, but serrated polyps can occur [31]. The risk of CRC in MAP is 19 % by age 50 and 43 % by age 60. The average age of CRC onset is 48 years. Relatives of MAP patients with a heterozygous *MUTYH* mutation have a risk of CRC comparable to that of first-degree relatives of patients with sporadic CRC [14]. Compared to the general population, MAP patients have an almost doubled risk of extraintestinal malignancies, including ovarian, bladder, skin, and possibly breast cancer [32].

Gastric polyps are found in about 10–33 % of MAP patients and mainly include fundic gland polyps, sometimes with low-grade dysplasia, and less frequently pure adenomas [32, 33]. The histological spectrum of polyps in MAP is thus similar to FAP. Analogously, there seems to be no increased risk of gastric cancer in MAO, but an increased lifetime risk of duodenal cancer of about 4 % [14, 32].

Lynch Syndrome

Lynch syndrome (LS) (also known as hereditary nonpolyposis colorectal cancer; HNPCC) is an autosomal dominantly inherited syndrome caused by germline mutation in one of the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or the *EpCAM* gene [11]. Colorectal cancer is the major clinical consequence of LS with a lifetime risk as high as 75 %, depending on the mismatch repair (MMR) gene mutated [12]. The average age of CRC diagnosis in LS patients is 44–61 years compared to 69 years in sporadic CRC. The histopathology of LS colorectal cancer is often poorly differentiated, with signet cell histology, abundant extracellular mucin, tumor infiltrating lymphocytes, and a Crohn's like lymphoid host response to tumor [34].

In addition to colorectal cancer, patients with Lynch syndrome have an increased risk for many extracolonic malignancies. Endometrial cancer is the second most common malignancy in LS patients with a lifetime risk between 15 and 71 %, depending on the specific MMR gene mutation. Other neoplasms with lifetime risks ranging from 4 to 25 % are urothelial cell carcinoma; adenocarcinomas of the ovary, stomach, hepatobiliary tract, and small bowel; brain cancer (glioblastoma); and cutaneous sebaceous neoplasms. The lifetime risk of gastric cancer is about 5 % in female and 8 % in male LS patients [12]. As in colorectal carcinomas, gastric carcinomas in LS are characterized by microsatellite instability and are usually of intestinal type [9, 35, 36].

Compared to patients with attenuated FAP or MAP, LS patients develop few colorectal adenomas (usually <3 adenomas). But the adenoma–carcinoma sequence appears accelerated in LS with polyp to cancer intervals estimated at 35 months compared to 10–15 years in sporadic cancer [37]. Also gastric polyps are rare which complicates surveillance strategies for gastric cancer [38]. A recent study showed MSI and loss of MMR protein expression in pyloric gland adenomas in 3 of 15 patients with LS and gastric cancer suggesting that pyloric gland adenomas may be a precursor to gastric cancer in LS [9]. However, the vast majority of patients in this study had atrophic gastritis and intestinal metaplasia and, based on the illustrations in this article, the reported lesions may have not have wholly conformed to pyloric gland adenomas as initially described [6]. Further studies are needed to confirm this observation. Better understanding of gastric cancer carcinogenesis and identification of biomarkers or precursor lesions may lead to more effective screening methods to prevent gastric cancer in LS.

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome (PJS) is an autosomal dominant syndrome caused by germline mutation of the *LKB1/STK11* gene. PJS is characterized by gastrointestinal polyposis, perioral pigmentation, and a moderate or high risk of a diversity of malignancies with an overall lifetime risk of any cancer of 81 % by age 70 [12, 39]. Patients are particularly at increased risk for gastrointestinal malignancies, including colorectal, gastric, small bowel, and pancreatic cancer. In addition, increased risk for a variety of extraintestinal malignancies exists, including lung, breast, and gynecological cancer [12].

Polyps most frequently occur in the small intestine in about 95 % of PJS patients. The colon and stomach each are affected in about 25 % of patients [40]. Guidelines recommend that upper and lower gastrointestinal endoscopies are performed first at age 8 years and repeated at least every 3 years when polyps are found. Small bowel imaging should be done at least every 3 years starting at age 8 years. Clearing of all polyps is recommended when possible [12].

Small bowel and colon polyps are typically pedunculated, whereas, gastric polyps are often sessile. Polyps vary in size from 0.1 to 5 cm. These large polyps make patients prone to small bowel intussusception [12].

Colorectal Peutz–Jeghers polyps have a distinct morphology characterized by villous architecture and arborizing smooth muscle. Also, characteristic lobulated clusters of colonic crypts have been described in syndromic PJS polyps which may discriminate them from other polyps such as hyperplastic, prolapse type, or juvenile polyps [41]. In contrast, gastric Peutz–Jeghers polyps are difficult to distinguish from gastric juvenile or hyperplastic polyps [10]. Sometimes, lobulated clustering of gastric foveolae/pits can be seen (Fig. 17.2), but the diagnostic value of this finding in the stomach has not yet been addressed. Without knowledge of the clinical

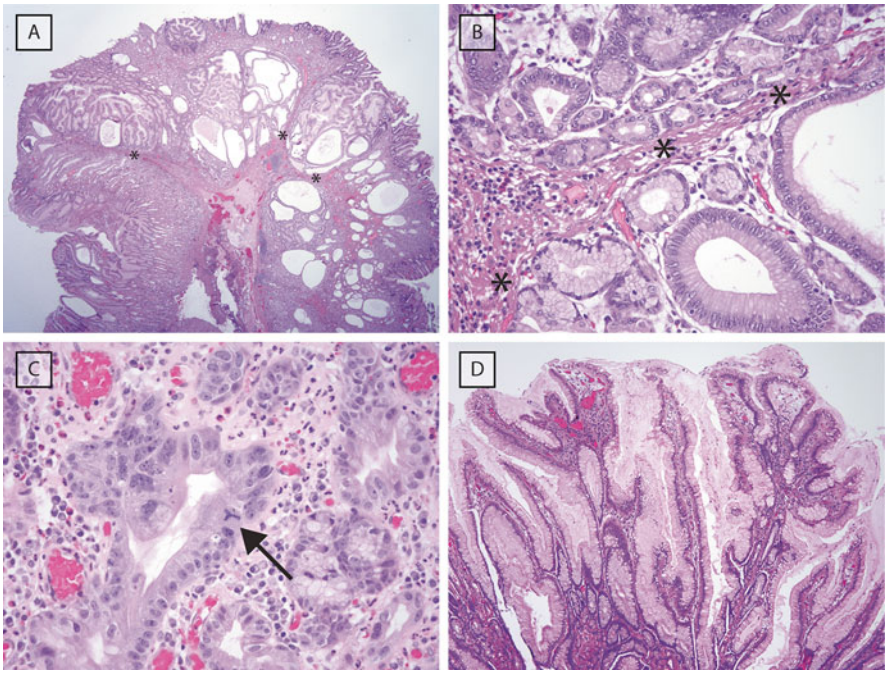

Fig. 17.2 (**a**) Gastric Peutz–Jeghers polyp. Note the cords of smooth muscle that partition the lesion into sections (asterisks). In a large sample such as this, it can be possible to prospectively suggest the diagnosis but in superficial samples, it can be impossible to separate these from hyperplastic polyps. (**b**) Gastric Peutz–Jeghers polyp. Note the strand of smooth muscle in the center of the field (asterisks). (**c**) Gastric Peutz–Jeghers polyp. Dysplasia is rare in such polyps but is encountered. This example of high-grade dysplasia arose in a patient with many gastric Peutz–Jeghers polyps. Note the atypical mitotic figure (triaster mitosis) (*arrow*). (**d**) Gastric Peutz–Jeghers polyp. This polyp arose in a patient with known Peutz–Jeghers syndrome and normal flat gastric mucosa. In isolation it is not possible to separate it from a hyperplastic polyp. A clue is the smooth surface

context one should be cautious when gastric polyps are used to establish a new diagnosis of PJS [10]. Additional endoscopic examination and sampling of polyps in the small intestine or colon, as well as genetic testing should be recommended.

PJS is associated with a lifetime risk of gastric cancer of 29 % [42, 43]. Whether the Peutz–Jeghers polyp is the actual precursor to gastrointestinal cancer is a matter of debate. Dysplasia in a Peutz–Jeghers polyp is very rare (Fig. 17.2). It has been suggested that Peutz–Jeghers polyps are in fact an epiphenomenon to the cancer prone condition and not obligate malignant precursors [44]. Studies in the colon show a protracted clonal evolution in normal colonic crypts from PJS patients. This allows a greater number of mutations to be retained in the crypt which accelerates somatic evolution and can explain the increased risk of colorectal cancer in PJS. Pretumor progression has not yet been studied in gastric mucosa of PJS patients [45].

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is an autosomal dominant disorder characterized by multiple juvenile polyps primarily in the colorectum but also elsewhere in the gastrointestinal tract. Juvenile polyposis syndrome is diagnosed in patients with five or more juvenile polyps in the colorectum, juvenile polyps throughout the gastrointestinal tract, or any number of juvenile polyps and a positive family history of juvenile polyposis [46]. A germline mutation in the *SMAD4* or *BMPR1A* gene can be identified in about 50–60 % of JPS patients [47]. A variant of JPS (juvenile polyposis of childhood) which shows phenotypic overlap with PTEN hamartoma syndromes (next section) is caused by contiguous deletion of the *BMPR1A* and *PTEN* genes which are both located on chromosome 10q23 [46, 48–50].

Patients with JPS have an increased risk of several gastrointestinal malignancies. The lifetime risk of colorectal cancer has been calculated to be 38 % but may be as high as 70 % [46, 51]. In addition, JPS patients appear to be at increased risk of stomach, duodenal, and pancreatic cancer, but no formal risk analysis for these malignancies exists [52]. Evaluation of literature reports suggests that gastric and small bowel carcinoma, together, occur at about one-fifth the frequency of colorectal cancers in this patient group [51]. *SMAD4* mutations are associated with a more aggressive gastrointestinal phenotype, involving higher incidence of colonic adenomas and carcinomas and more frequent upper gastrointestinal polyps and gastric cancer [53, 54].

Polyps in JPS predominantly occur in the colorectum, varying in number from five to several hundreds. In addition, polyps can be found in the stomach (Fig. 17.3), duodenum, jejunum, and ileum, but few studies examined upper gastrointestinal tract involvement in juvenile polyposis systematically [55–58]. The incidence of gastric polyps in JPS varies between 60 and 85 % and the incidence of duodenal polyps between 14 and 33 % [55, 57, 58]. JPS patients with a germline *SMAD4* mutation seem to have more severe gastric polyposis than patients with a *BMPR1A* mutation or those with no germline mutation identified [53, 59, 60]. One study found a significantly higher frequency of gastric polyposis in *SMAD4* mutations carriers (73 %) than BMPR1A mutation carriers (8 %) and all seven cases of gastric cancer occurred in families with *SMAD4* mutations [54].

A recent study evaluated upper gastrointestinal tract pathology in 41 juvenile polyposis patients. Twenty-two patients had upper gastrointestinal endoscopy with biopsies and 13 of these patients (59 %) developed gastric polyps. Almost 25 % of patients had profuse gastric polyposis for which gastrectomy or long-term parenteral feeding was indicated [56]. The youngest patient diagnosed with gastric polyps was 7 years old and had a *SMAD4* mutation. Gastric polyp morphology was characterized by irregular hyperplastic glands mostly lined by foveolar epithelium (Fig. 17.4). Dysplasia was found in 8 of 56 gastric juvenile polyp biopsies (14 %) in two patients, four of which contained high-grade dysplasia. Two of the polyps with dysplasia showed intestinal differentiation, and 6 showed both intestinal and pyloric gland differentiation, intermixed with foveolar epithelium. Pyloric gland differentiation was only observed in gastric juvenile polyps with dysplasia, whereas intestinal

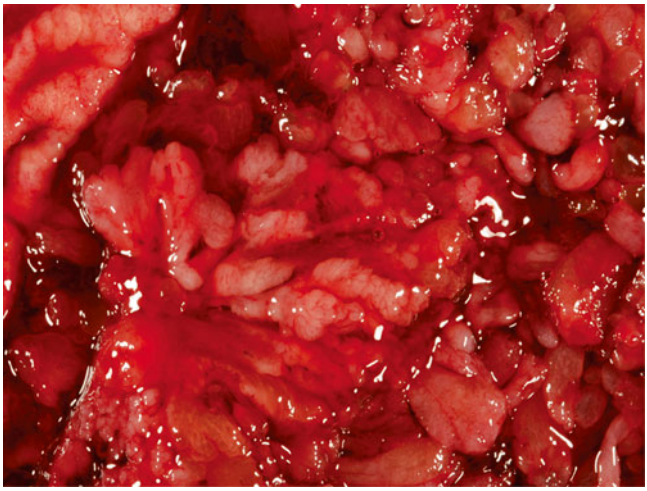

Fig. 17.3 Gastric juvenile polyposis, gastrectomy specimen, macroscopic. The stomach is carpeted with polyps in this case. One of them contained a carcinoma

differentiation was also seen in four gastric JP without dysplasia. However, the vast majority of gastric juvenile polyps only showed foveolar epithelium without dysplasia (44 of 56) with unremarkable background mucosa [56]. High-grade dysplasia and gastric cancer arise in gastric juvenile polyps and these polyps are thus bona fide precursor lesion for gastric cancer in JPS [61].

Importantly, distinction between gastric hyperplasic, juvenile, or Peutz–Jeghers polyps is difficult or impossible. Without knowledge of the clinical context the pathologist should be cautious to call a gastric polyp a juvenile polyp. Rather it is advisable to use a broader term such as hamartomatous polyp, not otherwise specified [10, 55]. Additional endoscopic examination and sampling of polyps in the small intestine or colon, as well as genetic testing are recommended [10]. In this regard, however, loss of SMAD4 immunostaining in colonic juvenile polyps is specific for an underlying *SMAD4* germline mutation and can be used as an adjunct in the molecular diagnosis of JPS [62]. Although the value of SMAD4 loss in gastric juvenile polyps has not been investigated, we have observed loss of SMAD4 protein expression in gastric polyps from a patient with JPS and a germline *SMAD4* mutation (Fig. 17.4).

To conclude, gastric polyps occur in 60 and 85 % of patients with JPS, can develop at young age, and can be profuse requiring parenteral feeding or gastrectomy. In addition, dysplasia can be found in almost 15 % of gastric polyps in JPS and patients seem to be at increased risk of gastric cancer, although the exact magnitude is unclear. Upper gastrointestinal tract endoscopy is, therefore, strongly recommended for patients with JPS. Current guidelines recommend upper endoscopy with removal of polyps >5 mm, starting at age 12 or earlier in case of symptoms and should be repeated every 1–3 years, depending on the severity of upper gastrointestinal polyposis [12].

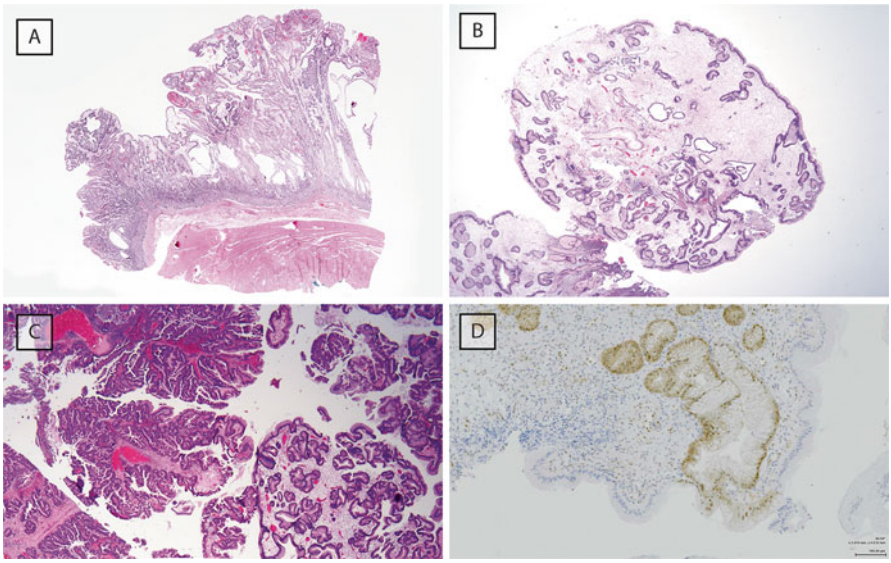

Fig. 17.4 (**a**) Gastric juvenile polyposis, gastrectomy specimen, low magnification. Note the cystically dilated glands. Additionally, one can imagine that a superficial biopsy of any of the lesions would be impossible to distinguish from a hyperplastic polyp. (**b**) Gastric juvenile polyposis, endoscopic biopsy. The prominent lamina propria edema and the smooth surface are clues that this is a juvenile polyp rather than a hyperplastic polyp. (**c**) Gastric juvenile polyposis with dysplasia. The nondysplastic component is present in the right half of the image whereas the left half shows extensive dysplasia. (**d**) SMAD4 immunohistochemistry in a gastric juvenile polyp showing loss of SMAD4 immunostaining consistent with the presence of a germline *SMAD4* mutation in this patient with juvenile polyposis syndrome

Cowden Syndrome (PTEN Hamartoma Tumor Syndrome)

PTEN hamartoma tumor syndrome (PHTS) is a heterogeneous group of autosomal dominant disorders caused by germline mutation of *PTEN* gene and includes Cowden syndrome, Bannayan–Riley–Ruvalcaba syndrome (BRRS), and Proteus syndrome. Most PHTS cases correspond to Cowden syndrome and the terms are often used interchangeable. Clinical features of CS include mucocutaneous lesions (facial trichilemmoma, acral keratoses, papillomatous papules and mucosal lesions are pathognomic) increased risks for malignancies (breast, thyroid, endometrial, colorectal, kidney, and melanoma) as well as benign hamartomatous overgrowth of tissues, including gastrointestinal polyposis, and macrocephaly. The lifetime risk of colorectal cancer is about 10–15 % [12]. The primary clinical features of BRRS include macrocephaly, hamartomatous intestinal polyps, lipomas, and pigmented macules on the penis [63].

Gastrointestinal polyps are almost universally present in CS patients. Polyps in CS occur throughout the entire gastrointestinal tract and typically represent a mixture of histologies [64]. In the colon hyperplastic polyps, hamartomatous/juvenile

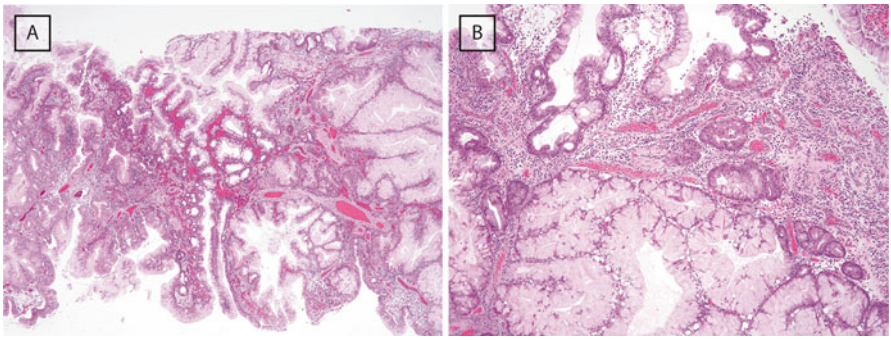

Fig. 17.5 (**a**) Gastric polyp from a patient with Cowden's syndrome. The appearances are similar to those seen in polyps in the setting of juvenile polyposis and similarly difficult to distinguish from those of hyperplastic polyps. (**b**) Gastric polyp from a patient with Cowden's syndrome. Note the hyperplastic appearing foveolar type epithelium and disorganized glands

polyps, adenomas, ganglioneuromas, and lymphoid follicles are most frequent [65]. Of note, colonic hyperplastic polyps are not considered part of the diagnostic criteria of PHTS [63]. Duodenal polyps are mainly hamartomas and some ganglioneuromas and adenomas [65]. More than 80 % of CS patients have diffuse esophageal glycogenic acanthosis which, in combination with colonic polyposis, may be diagnostic for CS [63, 66, 67].

Gastric polyps are usually numerous and can be found in almost all patients with Cowden syndrome (Fig. 17.5) [66, 67]. The polyps range in size from 0.1 to 2 cm. Histologically most are diagnosed as hyperplastic or hamartomatous [66, 67]. Dysplasia has not been reported in gastric polyps in Cowden syndrome. Nevertheless, a few cases of gastric cancer have been reported in this syndrome, but no formal risk analysis exists that shows an increased risk [64, 68, 69]. Interestingly, two of these gastric cancers were poorly differentiated or of signet cell histology, and one patient presented with two synchronous gastric carcinomas [64, 68].

The diversity of gastrointestinal polyps, including hamartomatous and ganglioneuromatous polyps and diffuse glycogen acanthosis in the esophagus suggests the diagnosis of Cowden syndrome [63–65]. Currently, it is unclear whether gastric polyps in CS are neoplastic and if CS patients are at increased risk of gastric cancer. Endoscopic upper gastrointestinal tract surveillance is recommended every 2–3 years starting at 15 years of age [12].

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is a recently described autosomal dominant syndrome with an unknown genetic cause [70]. Presently, only 6 families have been reported in the literature [70–72].

The following diagnostic criteria have been proposed: (1) gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis; (2) >100 polyps carpeting the proximal stomach in the index case or >30 polyps in a first-degree relative of another case; (3) predominantly FGPs, some having regions of dysplasia (or a family member with either dysplastic FGPs or gastric adenocarcinoma); and (4) an autosomal dominant pattern of inheritance. Importantly, patients with other heritable gastric polyposis syndromes and those on acid-suppressive therapy (i.e., sporadic fundic gland polypsis [18]) are excluded. In patients on acid-suppressive therapy, endoscopy should be repeated when the patient is off therapy [70].

Phenotypically, GAPPS is mainly characterized by fundic gland polyposis with areas with dysplasia. Polyps are typically small and carpet the gastric body and fundus. Gastric polyposis can be observed as young as 10 years of age. Occasional hyperplastic, adenomatous, and mixed polyps can be present also. A recent study of one Australian GAPPS family with 15 patients also described hyperproliferative aberrant pits, polypoid foveolar hyperplasia, predominantly gastric and/or hybrid dysplasia [72]. The gastric cancers in GAPPS are typically intestinal-type adenocarcinoma and can occur at a young age (median age 50 years; range 33–75 years) [70, 71].

Neurofibromatosis Type 1

Neurofibromatosis type 1 (NF1; von Recklinghausen disease) is an autosomal dominant hereditary syndrome caused by germline mutation of the *NF1* gene. Because the *NF1* gene is large, routine genetic testing is impractical. Therefore, NF1 is traditionally defined by clinical criteria (Table 17.2).

The gastrointestinal tract is commonly involved in NF1 (Fig. 17.6) [73]. Gastrointestinal stromal tumors (GIST) represent the most frequent gastrointestinal tract manifestation of NF1 occurring in up to 25 % of patients. NF1 associated GISTs typically lack mutations in *KIT* or *PDGFRA* [74]. Although much less frequent, peripheral nerve sheet tumors of different histological subtypes, including solitary or plexiform neurofibroma and diffuse neurofibromatosis or ganglioneuromatosis, also occur in the gastrointestinal tract of NF1 patients. Lastly, neuroendocrine tumors, particular in the periampullary region, are common in NF1 [73]. Coexistence of GIST and peripheral nerve sheath tumors in the gastrointestinal tract and/or GIST and (peri)ampullary neuroendocrine neoplasm are almost pathognomonic for NF1 [73].

Recently, inflammatory mucosal gastrointestinal polyps have been suggested as another manifestation of NF1 [75]. Although most polyps occur in the colon or small intestines, four of 15 patients had a gastric polyp and two patients had a polyp at the gastroesophageal junction/Z-line. Most patients had between 1 and 3 polyps, but four patients had ten or more (two of these patients had multiple or diffuse polyposis). Unfortunately, genetic testing to exclude other polyposis syndromes was not performed. Histologically these polyps had a variable appearance ranging from juve-

Table 17.2 Diagnostic criteria for neurofibromatosis type 1

Two or more of these criteria are required for diagnosis:
Six or more café au lait macules (>0.5 cm in children or >1.5 cm in adults)
Two or more cutaneous or subcutaneous neurofibromas or one plexiform neurofibroma
Axillary or groin freckling
Optic pathway glioma
Two or more Lisch nodules (iris hamartomas seen on slit lamp examination)
Bony dysplasia (sphenoid wing dysplasia, bowing of long bone +/– pseudoarthrosis)
First-degree relative with NF1

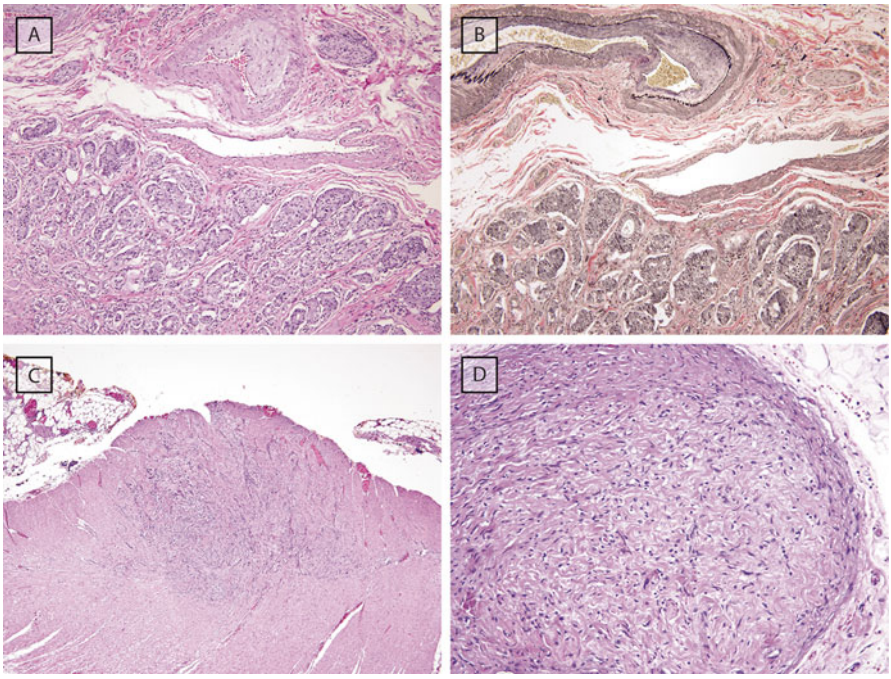

Fig. 17.6 (**a**) Gastrointestinal findings in patients with neurofibromatosis 1. This patient had a somatostatinoma, shown here. This field lacks the characteristic psammoma bodies but shows the vascular intimal hyperplasia accompanying such tumors. (**b**) Gastrointestinal findings in patients with neurofibromatosis 1. This Movat highlights the vascular intimal hyperplasia seen adjacent to the somatostatinoma quite nicely. (**c**) Gastrointestinal findings in patients with neurofibromatosis 1. This field is from the same Whipple operation in which the somatostatinoma in Fig. 17.3a, b was detected. This is a minute gastrointestinal stromal tumor. (**d**) Gastrointestinal findings in patients with neurofibromatosis 1. This field is from the same Whipple operation in which the somatostatinoma in Fig. 17.3a, b was detected. This is a minute neurofibroma

nile-like to granulation tissue rich predominantly inflammatory and hyperplastic. The gastric polyps showed mainly hyperplastic features. There was no dysplasia in any of these polyps which is consistent with the observation that NF1 patients are not at increased risk for colorectal or gastric adenocarcinoma. Based on a pathology database search, the authors estimated the frequency of inflammatory polyps in NF1 to be less than 2 %, the same magnitude as the incidence in the general population [2, 75]. It is therefore questionable whether these polyps are a specific manifestation of NF1 and the true nature and association of these polyps with NF1 remains to be further studied. As an aside, and a source of further confusion, children born with constitutional (biallelic) mismatch repair deficiency can manifest café-au-lait spots seen in neurofibromatosis [76].

McCune–Albright Syndrome

McCune–Albright syndrome (MAS) is a rare sporadic disorder caused by postzygotic activating mutation in the *GNAS* gene. The classical triad of McCune–Albright syndrome consists of polyostotic fibrous dysplasia, skin hyperpigmentation (café-au-lait spots), and endocrine dysfunctions, notably precocious puberty, hyperthyroidism, growth hormone excess, hyperprolactemia, and hypercortisolism. These manifestations usually present during infancy and childhood. Because patients with MAS display mosaicism of activating somatic *GNAS* mutations, the clinical presentation of each individual depends on the particular distribution of affected cells [77].

Recently, upper gastrointestinal polyps were identified as another frequent phenotypic expression of MAS [78]. Duodenal polyps were present in all four patients that were studied and gastric polyps were found in two of these four patients. No colonic polyps were found. Morphologically duodenal polyps showed arborizing smooth muscle fibers in the lamina propria. Gastric polyps showed elongated gastric pits and a mixture of fundic, pyloric, and Brunner's glands. The authors concluded that the polyps in MAS most closely resembled Peutz–Jeghers type hamartomatous polyps, but germline *LKB1* mutations were excluded. Importantly, activating *GNAS* mutations were found in these polyps, confirming the association with MAS molecularly [78]. Another study confirmed the presence of various upper gastrointestinal mass lesions in three patients with MAS [79]. One patient had a circumferential cardiac polypoid gastric adenoma (Fig. 17.7), fundic gland polyps were present in two patients, and a gastric hyperplastic polyp and foveolar hyperplasia were both found in one patient. Multifocal gastric heterotopia in the duodenum was found in two patients. Interestingly, two of these patients received upper endoscopy for evaluation of a pancreatic cyst, likely representing an IPMN, which has been described in MAS before [80]. No high-grade dysplasia was reported and no cases of gastrointestinal cancer in MAS are known. To further define the association between MAS and gastrointestinal polyps, routine endoscopy is recommended for patients with MAS [78, 79].

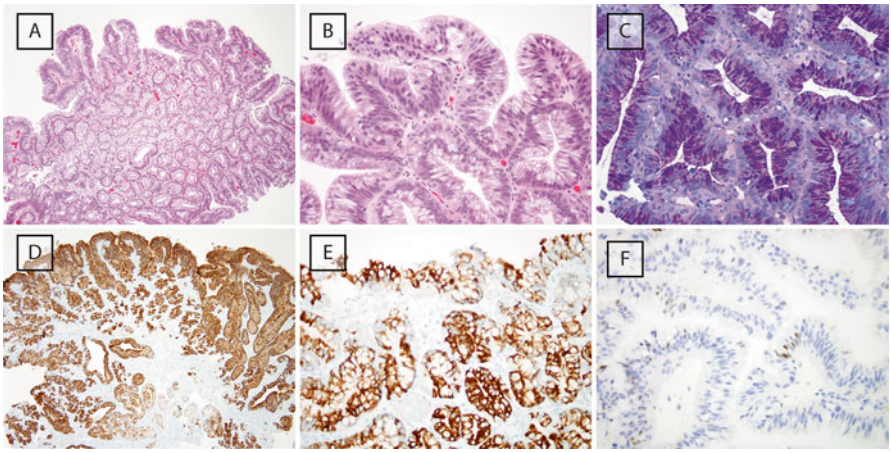

Fig. 17.7 (**a**) Unusual adenoma from a patient with McCune–Albright syndrome. On H&E, the lesion is reminiscent of both foveolar and pyloric-type adenomas but not typical of either. (**b**) Unusual adenoma from a patient with McCune–Albright syndrome. At high magnification there is a suggestion of intestinal differentiation as well as pyloric and foveolar differentiation. (**c**) Unusual adenoma from a patient with McCune–Albright syndrome, PAS/AB stain. Note the presence of goblet cells as well as neutral mucin and the ground glass appearance that characterizes pyloric type differentiation. (**d**) Unusual adenoma from a patient with McCune–Albright syndrome, MUC5AC stain. This confirms gastric foveolar differentiation. (**e**) Unusual adenoma from a patient with McCune–Albright syndrome, MUC6 stain. This confirms pyloric gland differentiation. (**f**) Unusual adenoma from a patient with McCune–Albright syndrome, CDX2 stain. This confirms intestinal differentiation

Cronkhite–Canada Syndrome

Cronkhite–Canada syndrome (CCS) is a rare protein-losing enteropathy typically characterized by diffuse gastrointestinal polyposis and typical ectodermal changes, such as hair loss and nail dystrophy. Although recent studies favor an autoimmune etiology, the precise cause of CCS has not been elucidated [81]. More than 80 % of patients are diagnosed at age 50 or older. The prognosis is poor. Less than 5 % of patients have complete remission and a 5-year mortality rate of 55 % is noted due to gastrointestinal bleeding, sepsis, and congestive heart failure. There is no standard therapy but limited success has been reported with antibiotics, steroids, and partial gastrectomy [81, 82].

Typically polyposis in CCS is diffuse throughout the entire gastrointestinal tract. The esophagus is uninvolved. The polyps are broad based and sessile and are a few millimeters to 1.5 cm in size. In the upper gastrointestinal tract, diffuse mucosal thickening rather than polyposis can be the main endoscopic picture (Fig. 17.8), which may be more suggestive for gastric malignancy (lymphoma of linitis plastica) or gastric infection than CCS polyposis [83].

Microscopically polyps in CCS show marked foveolar hyperplasia with cystically dilated glands, abundant stromal edema, and a predominantly mononuclear inflammatory infiltrate (Fig. 17.8). Eosinophils can be prominent. Especially in the stomach, the

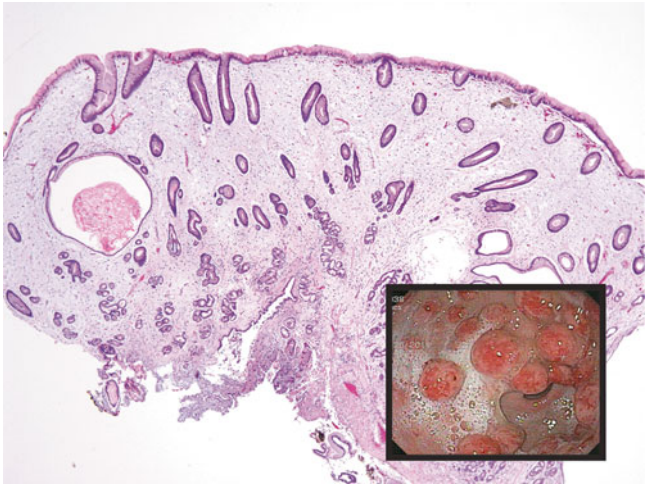

Fig. 17.8 Gastric Cronkhite–Canada polyposis. The polyps appear very similar to juvenile and hyperplastic polyps. The main clue is that flat mucosa is abnormal and the patients are very ill from profuse protein loss. Inset: endoscopic appearance of gastric Cronkhite–Canada polyposis. Numerous polyps are encountered throughout the gastrointestinal tract, sparing the esophagus. The flat mucosa is also abnormal

polyps can be difficult to discriminate from hyperplastic, juvenile or Peutz–Jeghers polyps [84]. Of key diagnostic importance for this differential diagnosis is that the intervening endoscopically nonaffected mucosa in CCS is also affected and shows marked lamina propria edema, inflammatory infiltrate, and gland distortion, which is not seen in JPS or PJS [81, 84]. In addition, correlation with clinical manifestations, in particular the typical ectodermal changes in CCS, is key to a correct diagnosis [84]. Ménétrier's disease is another important differential diagnosis, both clinically as well as histologically. However, the hyperplastic pathology in Menetrier disease is normally limited to the foveolar compartment of the body and fundus with unremarkable antral mucosa and without lamina propria edema [81].

Polyps in CCS are nonneoplastic but coexisting adenomas and adenocarcinomas have been reported. Patients may be at increased risk of colorectal cancer, possibly secondary to chronic mucosal inflammation. However, assessment of gastrointestinal cancer risk is limited by the rarity of this syndrome, and it remains inconclusive whether CCS patients are truly at increased risk of gastrointestinal malignancy [81].

Conclusion

Gastric polyps are found in 1–4 % of gastroscopic procedures. Most of these polyps are sporadic lesions, but polyps in the stomach can also indicate an underlying syndrome (Table 17.1). Polyps in a syndromic setting are often multiple, as in FAP, JPS, or PJS, but can also be few in number such as in Lynch syndrome. Different

histologic types of polyps can be found in different syndromes, which can help establish a syndromic diagnosis. However, the histology of gastric polyps is less specific compared to colonic polyps, and one should be careful to establish a diagnosis of a polyposis syndrome solely based on the gastric polyp pathology [10, 83, 84].

Some of the syndromes described in this chapter are associated with an increased risk of gastric cancer (e.g., LS, PJS, and JPS), whereas others are not (e.g., FAP, MAP, MAS). Interestingly, the assumption that the polyp is the precursor lesion of gastric cancer in these syndromes is not always true. For instance, whereas proof exists that juvenile polyps can be precursor lesions of gastric cancer in JPS, this is not the case in PJS. Moreover, Western FAP patients typically have numerous gastric polyps, mostly fundic gland polyps and some gastric foveolar adenomas, but do not have an increased risk of gastric cancer [27].

Prevention of upper gastrointestinal cancer is one of the major reasons for endoscopic surveillance of patients with syndromic polyps. Well-defined precursor lesions of gastric cancer that can be screened for and treated are a sine qua non for successful endoscopic surveillance. In syndromes where polyps are the (only) precursor lesions of gastric cancer it is likely effective to remove these polyps to prevent cancer development. However, screening for gastric cancer is more difficult in syndromes with an increased risk of gastric cancer but without a well-defined precursor lesion (such as LS or PJS) and other biomarkers are needed. Studying tumorigenesis in these syndromes will increase understanding of gastric cancer carcinogenesis and may identify new biomarkers or precursor lesions leading to more effective screening methods. As such, gastric polyric gland adenomas were recently suggested to be precursor lesions of gastric cancer in Lynch syndrome [9].

Moreover, the neoplastic potential of Peutz–Jeghers polyps is a matter of debate. Dysplasia in a Peutz–Jeghers polyp is very rare and it has been suggested that Peutz–Jeghers polyps are in fact an epiphenomenon to the cancer prone condition and not obligate malignant precursors [44]. Indeed, a protracted clonal evolution has been shown in normal colonic crypts from PJS patients. This allows a greater number of mutations to be retained in the crypt which accelerates somatic evolution and can explain the increased risk of colorectal cancer in PJS [45]. These alterations in stem cell dynamics in morphologically nonneoplastic mucosa may ultimately be used as a biomarker for cancer risk. Pretumor progression has not yet been studied in gastric mucosa.

To conclude, studying genetic syndromes that lead to disturbed epithelial homeostasis, polyp formation, and sometimes gastric cancer can greatly increase our understanding of gastric tumorigenesis. This will improve patient care and can lead to new biomarkers that can be used in screening of patients at risk for gastric cancer.

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