Pathology of Gastrointestinal Polyposis Disorders

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KEYWORDS

• Gastrointestinal polyposis • Adenomatous polyposis • Serrated polyposis
• Hamartomatous polyposis • Hereditary cancer

KEY POINTS

- Gastrointestinal polyposis syndromes can be classified based on the predominant histologic type of colorectal polyp and associated gene mutation.
- Most syndromes are associated with polyps in the upper gastrointestinal tract and an increased risk of colorectal cancer.
- Serrated polyposis syndrome is defined by arbitrary clinical criteria and is very rarely associated with a genetic defect.
- Hamartomatous polyposis syndromes are autosomal dominant disorders with an increased risk of cancer in the colon and other organs, and frequent extraintestinal manifestations.

INTRODUCTION

The study of gastrointestinal polyposis syndromes has been instrumental in unraveling the molecular pathways involved in colorectal cancer (CRC) pathogenesis.[1,2] Gastrointestinal polyposis syndromes are generally classified based on the histologic subtype of the colorectal polyps most frequently present in each of these syndromes (**Table 1**).

Familial adenomatous polyposis (FAP) is the prototypical polyposis syndrome. Several other polyposis syndromes with predominantly adenomatous polyps have been recently recognized (see **Table 1**). In addition, there are syndromes with predominantly hamartomatous polyps, serrated colorectal polyps, or a mixture of histologic polyp types. Several of these syndromes are also associated with upper gastrointestinal tract polyps, extraintestinal manifestations, and increased risks of cancer.

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Table 1
Gastrointestinal polyposis syndromes classified according to histologic subtype of colorectal polyps

Polyp Subtype	Mode of Inheritance	Gene(s)	Pathway
Adenomatous polyps			
FAP	Autosomal dominant	*APC*	WNT pathway
MAP	Autosomal recessive	*MUTYH*	DNA base excision repair
PPAP	Autosomal dominant	*POLE*, *POLD1*	DNA polymerase proofreading
NTHL1 tumor syndrome	Autosomal recessive	*NTHL1*	DNA base excision repair
Serrated polyps			
SPS	ND	*RNF43* (2%)	WNT pathway
Hamartomatous polyps			
PJS	Autosomal dominant	*STK11*	-
Juvenile polyposis syndrome	Autosomal dominant	*BMPR1A*, *SMAD4*	TGFβ pathway
PTEN hamartoma tumor syndrome/CS	Autosomal dominant	*PTEN*	PI3K pathway
CCS	NA	NA	

Abbreviations: NA, Not applicable (non-hereditary condition); ND, not determined.

In this review, the clinical genetic and histopathologic aspects of adenomatous polyposis, serrated polyposis, hamartomatous polyposis syndromes, Lynch syndrome (LS), and Cronkhite-Canada syndrome (CCS) are presented.

FAMILIAL ADENOMATOUS POLYPOSIS

Definition

FAP is an autosomal dominant inherited syndrome caused by germline (constitutional) mutations (pathogenic variants) in the *adenomatous polyposis coli* (*APC*) gene, resulting in the upregulation of the WNT signaling pathway. The estimated prevalence is 1 in 8000 to 10,000 affecting both sexes equally.[3]

Clinical Features

The phenotype of the classic form of FAP is the development of more than 100 colonic adenomatous polyps starting in teenage years. Attenuated FAP is characterized by fewer colorectal adenomatous polyps (10–100, average 30). In addition to colorectal adenomas and adenocarcinomas, most patients with FAP develop duodenal and gastric polyps and a variety of benign and malignant extraintestinal tract manifestations. Desmoid tumors, mainly in the small bowel mesentery, abdominal wall, or extremities, are the most frequent extraintestinal tract neoplasia, occurring in about 10% of patients and can cause severe morbidity and mortality.[4,5] Benign extraintestinal features include osteomas, dental abnormalities, and congenital hypertrophy of the retinal pigment epithelium.[3]

A rare subtype of FAP, called gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is characterized by carpeting fundic gland polyposis of the proximal stomach sparing the antrum, increased risk of gastric carcinoma and absence or a small number of duodenal and colorectal adenomas.[6,7]

Pathogenesis

A germline mutation in *APC* resulting in a truncated or absent APC protein is identified in most patients. In 20% to 30% of cases, no family history is found; these patients may have de novo variants in *APC* or a recessive polyposis syndrome.[8] Several associations between the location of the *APC* variant and the clinical manifestations have been reported (**Table 2**).[9,10] GAPPS is caused by a mutation in the YY1 binding site of the *APC* exon (promoter) 1B.

Pathologic Condition

Patients with classic FAP have hundreds to thousands of polyps carpeting the entire large bowel, with a predominance for the distal colon. In attenuated FAP, fewer polyps are present and show a proximal colon predominance. Size of polyps varies from barely visible macroscopically to very large polyps measuring several centimeters in diameter. Malignant transformation occurs essentially in larger polyps.

FAP-associated colorectal adenomas show similar tubular, tubulovillous, or villous histologic features that are indistinguishable from sporadic adenomas. Dysplasia can be restricted to a single or a few colonic crypts in otherwise normal mucosa, which is very suggestive of FAP. Invasive adenocarcinomas are also identical morphologically to sporadic colorectal adenocarcinomas.

Duodenal polyps occur in almost all patients with FAP and are conventional intestinal-type adenomas.

Gastric polyps are present in most patients with FAP. Most of these polyps are fundic gland polyps (FGPs), characterized by cystically dilated gastric glands. Although low-grade dysplasia is present in about a third of FGPs, progression to high-grade dysplasia or carcinoma is extremely rare.[11] Other histologic subtypes of gastric polyps are low-grade foveolar adenomas, with a low risk of neoplastic progression,[12] and pyloric gland adenomas (PGAs), which seem to have a higher risk of neoplastic progression (**Fig. 1**). Histologically, PGAs are composed of densely packed glands lined by cuboidal to low columnar epithelium resembling pyloric gland cells. These glands are positive, and the pyloric gland mucin MUC6 and the overlying foveolar epithelium are positive for foveolar mucin MUC5A and often show dysplasia.[13] Of note, the endoscopic assessment and histologic distinction among FGP with dysplasia, foveolar adenoma, and PGA can be difficult in case of extended polyposis carpeting the stomach.[14]

Table 2
Genotype phenotype associations in familial adenomatous polyposis

FAP Phenotype	Location of APC Mutation
Classic FAP	Central part of the gene (between codons 160 and 1393)
Profuse polyposis (>1000 polyps)	Mid-portion of the gene (between codons 1250 and 1464)
Attenuated FAP	Far proximal (5′) end, far distal (3′) end, or certain locations of exon 9 of the APC gene
Desmoid tumors	3′ end of codon 1444
Congenital hypertrophy of the retinal pigment epithelium	Between codons 463 and 1444
Multiplicity of extraintestinal lesions	Codons 1465, 1546, and 2621
GAPPS	Promoter 1B (YY1 binding site)

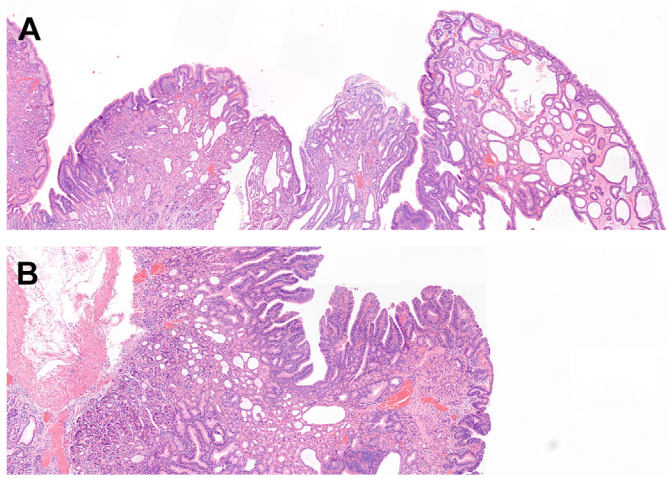

Fig. 1. (*A*) Gastric polyps in FAP showing adjacent FGP (left) and PGA (right) with low-grade foveolar type dysplasia. (*B*) This patient also had multiple foci of high-grade foveolar dysplasia overlying both FGPs (shown) and PGAs.

Risk of Malignancy

If prophylactic colectomy is not performed, virtually all patients with FAP develop CRC at a mean age of 45 years. Attenuated FAP patients have a slightly reduced risk and later onset of CRC (70%–80%) mean age at diagnosis of 56 years.[15,16]

The risk of duodenal adenocarcinoma is 5%.[17] Gastric adenocarcinomas are almost exclusively reported in the proximal stomach and associated with extensive carpeting fundic gland polyposis, a large size (>20 mm) of polyps and dysplasia.[18]

Although less frequent, FAP has also been associated with an increased risk of thyroid carcinoma, hepatobiliary tree tumors, childhood hepatoblastoma, adrenocortical adenomas and carcinomas, and brain tumors particularly medulloblastoma.

Treatment

Treatment strategies of patients with FAP are guided by the severity of polyposis and the clinical presentation. Screening colonoscopy starts early in childhood and followed by surveillance colonoscopy. The age of prophylactic colectomy depends on polyp burden and is followed by surveillance of the ileal pouch. Chemoprevention with nonsteroidal anti-inflammatory drugs may be used to prevent further polyp development. Management of duodenal adenomas in FAP is in most current guidelines guided by the (modified) Spigelman stage of duodenal adenomas, which grades the severity of duodenal polyposis.[19,20] The European FAP consortium recently proposed a novel flowchart for the management of duodenal and gastric adenomas, which will be prospectively evaluated.[21]

MUTYH-ASSOCIATED POLYPOSIS

Definition

MUTYH-associated polyposis (MAP) is an adenomatous polyposis caused by autosomal recessively inherited pathogenic variants in *MUTYH.*[22] The estimated prevalence is 1 in 2000.[23]

Clinical Features

MAP shares many clinical features with attenuated FAP. Most affected patients develop multiple adenomatous polyps throughout the large bowel (usually 10–100, rarely >100 polyps).[24] Duodenal adenomatous polyps are present in 20% of affected patients.[25]

Pathogenesis

MAP is caused by pathogenic variants in the DNA-base excision repair gene *MUTYH*.[22] The biallelic MUTYH loss prevents the removal of incorrectly incorporated adenine residues opposite 8-oxoguanine, resulting in C:G > A:T transversions. The c.34 G > T *KRAS* mutation is frequently observed in MAP-associated tumors.

Pathologic Condition

The colonic phenotype overlaps with that of attenuated FAP although some patients with MAP tend to develop multiple serrated polyps.[26] MAP-associated adenomas and adenocarcinomas do not have any distinctive histologic features.

Risk of Malignancy

The cumulative lifetime of CRC is 63% at the age of 60 years.[27] Other increased tumor risks include duodenal adenocarcinoma, sebaceous skin tumors, and ovarian and bladder cancers.[28] Heterozygous carriers of monoallelic *MUTYH* variants have a mild increased risk of CRC.[28]

Treatment

Patients with MAP are managed by colonoscopy with polypectomy starting at 25 to 30 years and every 1 or 2 years, or colectomy depending on polyp burden. Baseline upper gastrointestinal endoscopy is recommended at the age of 30 to 35 years with surveillance depending on initial findings.

POLYMERASE PROOFREADING–ASSOCIATED POLYPOSIS

Definition

Polymerase proofreading–associated polyposis (PPAP) is an autosomal dominant inherited syndrome caused by germline mutations in the exonuclease (proofreading) domains of *POLD1* and *POLE*.[29]

Clinical Features

Patients with PPAP present with an attenuated or oligoadenomatous colorectal polyposis and duodenal adenomas.[30,31] The phenotype overlaps with LS and attenuated adenomatous polyposis (*APC*/*MUTYH*).

Pathogenesis

POLE or *POLD1* mutations result in a defect in replication-associated polymerase proofreading, leading to an increased mutation rate in tumors.

Pathologic Condition

Adenomas and adenocarcinomas associated with PPAP are similar to sporadic tumors but are associated with a hypermutant phenotype.

Risk of Malignancy

Affected patients have a high risk of CRC (identified in 60%–64% of *POLE* and *POLD1* carriers) and probably an increased risk of brain tumors.[30,31] *POLD1* female carriers have an increased risk of endometrial and breast cancers.

Treatment

Hypermutant carcinomas associated with PPAP may be responsive to PD1/PDL1 inhibitors.[32] Colonoscopy is recommended every 1 to 2 years. Gastroduodenal endoscopy screening should start at the age of 20 to 25 years with follow-up every 3 years or more depending on the initial findings. Screening for endometrial cancer and breast cancer should also be considered.[30]

NTHL1 TUMOR SYNDROME

Definition

NTHL1 tumor syndrome (also called *NTHL1*-associated polyposis) is an autosomal recessive DNA base excision repair disorder caused by biallelic *NTHL1* pathogenic variants.[33]

Clinical Features

The phenotype of *NTHL1* tumor syndrome is not clearly defined and includes attenuated or oligoadenomatous colorectal polyposis originating in adulthood and duodenal polyps.[33,34]

Pathogenesis

The *NTHL1* gene encodes a base excision repair glycosylase. *NTHL1*-associated CRC are associated with frequent C > T mutations.

Pathologic Condition

Adenomas and adenocarcinomas are similar to sporadic tumors. Colorectal serrated polyps are frequently diagnosed.

Risk of Malignancy

Affected patients have a high risk of CRC. The cumulative lifetime risk of developing extracolonic cancer by age 60 years has been estimated at 35% to 78%. This includes endometrial cancer, breast cancer, urothelial cancer, brain tumors, hematologic malignancies, and various skin tumors.[33,34]

Treatment

The management of *NTHL1* tumor syndrome overlaps with LS and attenuated FAP. Breast cancer screening is recommended.

SERRATED POLYPOSIS SYNDROME

Definition

Serrated polyposis syndrome (SPS) is condition of largely unknown genetic cause, characterized by the development of multiple serrated polyps in the large bowel and an increased risk of CRC for affected individuals and their first-degree relatives.[35–37] The revised World Health Organization (WHO) clinical criteria are presented in **Box 1**.[38] The prevalence is up to 0.1% in primary screening colonoscopies.[39]

Box 1
Clinical diagnostic criteria for serrated polyposis syndrome.

Criterion 1	≥5 serrated lesions/polyps proximal to the rectum, all being ≥5 mm in size, with ≥2 being ≥10 mm in size
Criterion 2	>20 serrated lesions/polyps of any size but distributed throughout the large bowel, with ≥5 proximal to the rectum

The polyp count is cumulative over multiple colonoscopies. Any histologic subtype of serrated polyps is included in the final polyp count. The upper gastrointestinal tract is not affected

Clinical Features

Most patients are diagnosed at 50 to 60 years of age, with some patients diagnosed earlier in their 30s.[40–43] Men and women are equally affected. The phenotype is heterogeneous encompassing patients who barely meet the WHO criteria and those with multiple large polyps fulfilling both criteria. About 25% of patients fulfill only criterion 1, 45% only criterion 2, and the remaining 30% meet both criteria.[41,42]

Some well-characterized genetic syndromes may present with a phenotype overlapping with SPS. This has been documented for MAP, juvenile polyposis syndrome, and Cowden syndrome (CS).[26,44,45] However, serrated polyps are usually not the dominant polyp type and are associated with polyps that are more characteristic of each syndrome. Moreover, testing for germline mutation in *BMPR1A*, *SMAD4*, *PTEN*, *MUTYH*, and *GREM1* did not show any pathogenic variants in a large series of patients with SPS.[46]

Pathogenesis

Pathogenic germline variants in *RNF43* (*Ring Finger Protein 43*), a negative feedback regulator of the WNT signaling pathway, have been reported in less than 2% of affected individuals.[47,48]

Approximately 50% of CRC in patients with SPS have a *BRAF* mutation, less than 5% a *KRAS* mutation, and 40% are *MLH1*-deficient.[49,50] This molecular phenotype suggests that half of CRC develop from serrated polyps via the serrated neoplasia pathway and the other half presumably following the conventional adenoma–carcinoma pathway.

Pathologic Condition

All subtypes of serrated polyps can develop in the large bowel: hyperplastic polyps, sessile serrated lesion (SSL), SSL with dysplasia, and traditional serrated adenoma[51] (**Fig. 2**). Conventional adenomas are also commonly seen and may be associated with

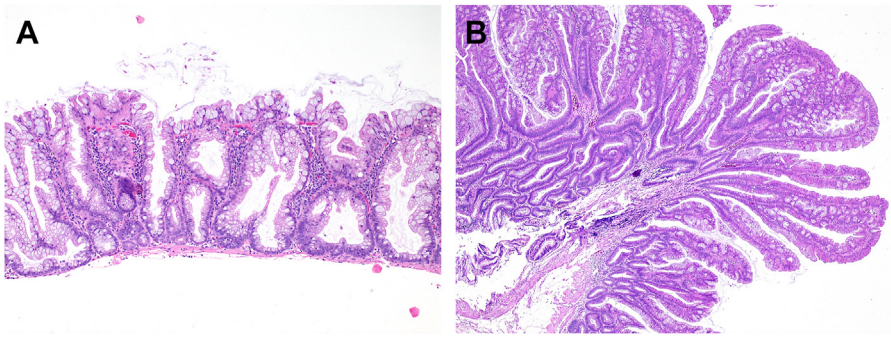

Fig. 2. (*A*) SSL showing abnormal colonic crypt architecture with dilated bases. (*B*) Traditional serrated adenoma with villous projections showing ectopic crypt formations and lined by cells with eosinophilic cytoplasm.

an increased risk of CRC.[50] SPS-associated serrated polyps are identical histologically and molecularly to those occurring outside SPS.[52,53] Most nondysplastic serrated polyps in SPS are in the proximal colon and show histologic features of SSL with atypical symmetric dilatation of the crypt bases.[54] The median cumulative polyp number is most commonly 30 to 40, with a range as wide as 6 to 240 polyps and frequent pancolonic distribution.[37]

Risk of Malignancy

Affected patients have a 15% to 30% risk of CRC.[41,42] Despite serrated polyps being predominant in the proximal colon, nearly 50% of CRC are in the rectosigmoid. Reported factors associated with CRC included the fulfillment of both WHO criteria, having more than 2 SSLs proximal to the splenic flexure, at least one SSLD, and at least one advanced conventional adenoma.

Treatment

The current guidelines recommend initial colonoscopic clearing of all relevant polyps (≥5 mm in size or any size and suspicious for dysplasia) followed by colonoscopy surveillance with 1 to 3 years intervals depending on findings from the last procedure.[55–57] Surgery may be required if colonoscopy control of polyps is not feasible. Surgical referral may be as low as 5% when patients with SPS are closely monitored with effective reduction of polyp burden by colonoscopy.[58]

In first-degree relatives, screening colonoscopy is recommended at the age of 40 years or starting 10 years younger than the age at diagnosis of the youngest affected relative. Follow-up colonoscopy should be performed every 5 years or more frequently depending on polyp burden.[59]

HAMARTOMATOUS POLYPOSIS SYNDROMES

Peutz-Jeghers Syndrome

Definition

Peutz-Jeghers Syndrome (PJS) is an autosomal dominant hereditary syndrome characterized by hamartomatous gastrointestinal polyps and pigmented cutaneous and mucosal membrane macules. The clinical diagnostic criteria of PJS are summarized in **Box 2**.

Clinical features

Patients with PJS often present in the first 2 decades of life with symptoms of abdominal pain, intestinal bleeding, anemia, or intussusception.[60] Although the histologically typical PJS polyps are the main hallmark of PJS, the characteristic mucocutaneous

Box 2
Peutz-Jeghers syndrome diagnostic criteria.

Criterion 1	≥3 histologically confirmed Peutz-Jeghers polyps
Criterion 2	Any number of Peutz-Jeghers polyps with a family history of PJS
Criterion 3	Characteristic, prominent* mucocutaneous pigmentation with a family history of PJS
Criterion 4	Any number of Peutz-Jeghers polyps and characteristic, prominent mucocutaneous pigmentation

*Some melanin pigmentation is also regularly seen in unaffected individuals, hence the emphasis on the prominence of the pigmentation. Moreover, the pigmentation in patients with PJS may disappear with time or can, in rare cases, be absent altogether

pigmentations sometimes allows diagnosis of otherwise asymptomatic individuals in affected families.

Pathogenesis

PJS is caused by constitutional pathogenic variants in *STK11* (*Serine Threonine Kinase 11*) gene, which can be found in more than 90% of patients fulfilling the clinical diagnostic criteria. Most variants are point mutations and small intragenic deletions. In some patients, larger deletions of one or more exons have been found.[61]

Pathologic Condition

Patients usually have 10 to 20 gastrointestinal hamartomatous polyps. Polyps are most frequently found in the small intestine (60%–90%), but also in the large bowel (50%–60%), stomach (15%–30%), and rarely in the gallbladder, respiratory, and urinary tract.[62]

Macroscopically, small intestinal and colonic Peutz-Jeghers polyps are usually pedunculated and have a smooth and lobulated surface (**Table 3**). The size varies from several millimeters to centimeters. Microscopically, polyps are characterized by arborizing strands of smooth muscle in the lamina propria (**Fig. 3**). The polyps are lined by nonneoplastic epithelium characteristic for the specific location.[63,64] The differential diagnosis includes other hamartomatous polyps, mucosal prolapse polyps, and hyperplastic polyps. Mucosal prolapse type polyps can closely mimic PJS polyps as both show smooth muscle displacement and proliferation in the lamina propria, which may be related to the role of mucosal prolapse in the pathogenesis of PJS polyps.[65]

Most gastric polyps are found in the antral region and are typically small and asymptomatic. Gastric PJS polyps feature foveolar hyperplasia with cystic change, muscular proliferation, lamina propria edema, and inflammation but the histology of gastric polyps is less distinctive than colonic or small intestinal polyps (see **Fig. 3**). By histology alone, it is often impossible to reliably differentiate gastric PJS polyps from gastric juvenile and hyperplastic polyps, although there may be subtle histologic differences.[66] The diagnosis of hamartomatous gastric polyps remains challenging and, without knowledge of the clinical history, a note about the differential diagnosis that includes other hamartomatous polyps and hyperplastic polyps, may be most appropriate.

Dysplasia is very rare, and it is has been suggested that PJS polyps are in fact an epiphenomenon to the cancer-prone condition instead of the obligate precursor lesions of cancer.[65]

Table 3
Histologic features of polyps in Peutz-Jeghers syndrome and in juvenile polyposis syndrome

	Peutz-Jeghers Syndrome	Juvenile Polyposis Syndrome
Predominant site	Small bowel (jejunum) > large bowel > stomach	Large bowel > stomach > small bowel
Small bowel polyp	Lobulation with arborizing smooth muscle	Rarely seen
Large bowel polyp	Smooth surface Normal lamina propria Smooth muscle proliferation Lobulation with distorted crypts	Red appearance, eroded Inflamed lamina propria Scant smooth muscle Cystic glands with mucin and neutrophils
Gastric polyp	Hyperplastic/inflammatory polyp	Hyperplastic/inflammatory polyp

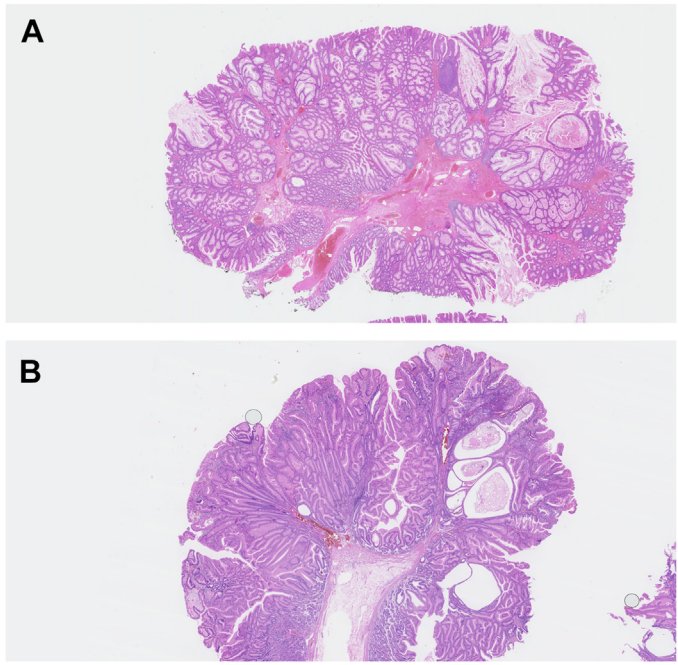

Fig. 3. (*A*) Colonic PJS polyp showing strands of smooth muscle in the lamina propria and nonneoplastic colonic epithelium with lobulated clusters of colonic crypts. (*B*) Gastric PJS polyp showing foveolar hyperplasia, some cystic dilatation, and increased inflammatory stroma.

Risk of malignancy

Patients with PJS have a high lifetime risk of a variety of gastrointestinal and extraintestinal malignancies and an overall lifetime risk of any cancer of 81% by the age of 70 years (Table 4).[60,67] The main extraintestinal tumors in PJS are breast and pancreatic adenocarcinoma and rare gonadal tumors of the ovary (sex-cord tumors with annular tubules) and testis (Sertoli cell tumors).

Table 4
Peutz-Jeghers syndrome cancer risks for specific site at 65 to 70 y of age[60,67]

Site	Cancer Risk (%)
Colorectum	39
Small intestine	13
Stomach	29
Pancreas	11–36
Breast	32–54
Uterus	9
Ovary	21
Cervix	10
Testes	9
Lung	7–17

Treatment

Management of patients with PJS including upper gastrointestinal endoscopy and colonoscopy should be performed every 2 to 3 years, starting from the late teens.[57] Small bowel visualization is recommended from age 8 to 10 years and repeated every 2 to 3 years. Other screening procedures related to cancer risk of the breast, female genital tract, testis, and pancreas can also be implemented.

JUVENILE POLYPOSIS SYNDROME

Definition

Juvenile polyposis syndrome (JPS) is an autosomal dominant syndrome defined by the presence of multiple colorectal juvenile polyps developing in the first and second decade of life. The clinical diagnosis criteria are presented in **Box 3**.[68,69]

Clinical Features

JPS can present as either colorectal or generalized juvenile polyposis, or as juvenile polyposis of infancy. Gastrointestinal bleeding, anemia, a prolapsed rectal polyp, passage of tissue through the anus, intussusception, and abdominal pain are frequent symptoms. Infant patients with JPS have extensive colorectal and gastric polyposis causing protein losing enteropathy, malabsorption, failure to thrive, and death at a young age. This rare form of JPS is caused by contiguous germline deletion of both the *BMPR1A* and *PTEN* gene.[70]

Pathogenesis

In 50% to 60% of the patients fulfilling these criteria a germline alteration in the TGB-β pathway genes *SMAD4* or *BMPR1A* gene is identified. Patients with *SMAD4* germline defects are more prone to develop gastric polyps, often in a profuse form, and can have hereditary hemorrhagic telangiectasia.[71,72] Immunohistochemistry for SMAD4 can be used as a surrogate marker for genetic *SMAD4* loss in juvenile polyps and as an adjunct in the molecular diagnosis of JPS.[73]

Although the pathogenesis and neoplastic progression of juvenile polyps is not completely understood, early studies suggested that mechanical mucosal erosion with superimposed inflammatory reaction may lead to the formation of juvenile polyps and stressed the inflammatory basis of these polyps.[74] Recent studies suggest that an exaggerated inflammatory response to mucosal injury due to the inherent transforming growth factor beta (TGFβ) pathway defect in patients with JPS may underlie polyp development and inflammation-driven colon cancer.[75]

Pathologic Condition

Patients with JPS primarily have colorectal polyps but many also have polyps in upper gastrointestinal tract. Gastric polyps are found in 60% to 85% of patients, duodenal polyps in 14% to 33%.[11]

Box 3
Juvenile polyposis syndrome diagnostic criteria.

Criterion 1	>3–5 juvenile polyps of the Colorectum
Criterion 2	Juvenile polyps throughout the gastrointestinal tract
Criterion 3	Any number of juvenile polyps with a family history of juvenile polyposis syndrome

Other syndromes involving hamartomatous gastrointestinal polyps should be ruled out clinically or by pathologic examination

Colorectal juvenile polyps are 5 to 50 mm in size, spherical and with a smooth surface due to erosion (see **Table 3**). Histologic features are an expanded stroma with edema, a mixed inflammatory infiltrate, and entrapped cystically dilated glands lined by nonneoplastic reactive epithelium (**Fig. 4**). Syndromic juvenile polyps are indistinguishable from sporadic juvenile polyps.[76] Approximately 50% of juvenile polyps show dysplasia but distinction between dysplasia and reactive atypia can be difficult. Inflammatory colorectal polyps form an important differential diagnosis of juvenile polyps.

Gastric juvenile polyps are characterized by abundant edematous stroma lined by hyperplastic and reactive foveolar epithelium[77] (see **Fig. 4**). An "epithelium-rich" variant with varied amount of stroma, tightly packed glands, and hyperplasia of surface epithelium can be seen. As with other hamartomatous polyps, gastric juvenile polyps are virtually indistinguishable from sporadic hyperplastic polyps without knowledge of the correct clinical context. High-grade dysplasia and gastric cancer can develop, particularly in *SMAD4* mutations carriers. The estimated risk of gastric adenocarcinoma is 10% to 30%.[78]

Risk of Malignancy

Affected patients have an increased risk of gastrointestinal cancer, mainly CRC. The risk of CRC is about 40% by the age of 80 years at a mean age of diagnosis of 44 years (range: 15–68 years).[79] Gastric cancer is mainly seen in *SMAD4* germline mutation carriers. The lifetime risk of gastric cancer is estimated between 10% and 30% and the median age of diagnosis is 58 years (range: 21–73 years).[57]

Treatment

Upper gastrointestinal endoscopy and colonoscopy are recommended starting at the age of 15 years or at the time of initial presentation. Depending on endoscopic findings, surveillance every 1 to 3 years should be performed.[57]

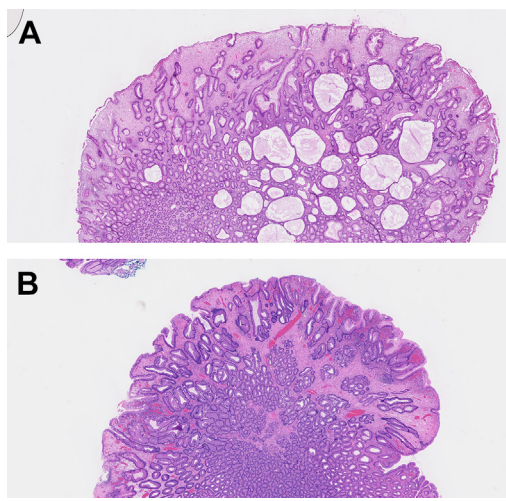

Fig. 4. (*A*) Typical colonic juvenile polyp characterized by eroded surface, expanded stroma with edema and inflammatory infiltrate and cystically dilated glands lined by nonneoplastic epithelium. (*B*) Gastric juvenile polyp showing abundant edematous stroma and hyperplastic and reactive foveolar epithelium.

PHOSPHATASE AND TENSIN HOMOLOG HAMARTOMA TUMOR SYNDROME/ COWDEN SYNDROME

Definition

CS is an autosomal dominant disorder, now part of the phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome that also includes Bannayan-Riley-Ruvalcaba syndrome, PTEN-related Proteus syndrome and Proteus-like syndrome.[80] The reported prevalence of CS is 1 in 200,000 people,[81] a likely underestimate.

Clinical Features

The main features of CS are macrocephaly and multiple benign hamartomatous lesions in various organs, including skin and gastrointestinal tract. Mucocutaneous lesions (trichilemmomas of the face, oral papillomas, and acral and plantar keratosis) are characteristic and nearly always present by the age of 20 years.[82] The National Comprehensive Cancer Network established consensus diagnostic criteria.[82]

Pathogenesis

A constitutional pathogenic variant in *PTEN* is identified in 80% of individuals with a clinical CS diagnosis CS.[80] *PTEN* is a tumor suppressor gene encoding for a phosphatase that regulates cell proliferation, cell migration, and apoptosis through inhibition of the Phosphoinositide 3-kinase/AKT pathway.[83]

Pathologic Condition

Colonic polyps in CS are small sessile lesions that are easily overlooked during colonoscopy.[83] A mixture of hamartomatous and nonhamartomatous benign colonic polyps are typical of CS. Hamartomatous polyps show mildly abnormal crypt architecture and fibrous lamina propria that may contain bland spindle cells with various amount of adipose tissue and lymphoid aggregates (**Fig. 5**). Other histologic types include ganglioneuroma, lipoma, fibrolipoma, and inflammatory pseudopolyps.[84] Conventional adenomas and serrated polyps are also frequently found.[84,85]

In the upper gastrointestinal tract, patients with CS often develop multiple glycogenic acanthosis lesions of the esophagus presenting endoscopically as small white plaques and histologically with hyperplasia of the squamous epithelium showing enlarged cells in the superficial layers caused by glycogen accumulation in the cytoplasm. In the stomach and the duodenum, CS polyps do not have any specific features and often present as small hyperplastic or inflammatory polyps such as in other hamartomatous syndromes.

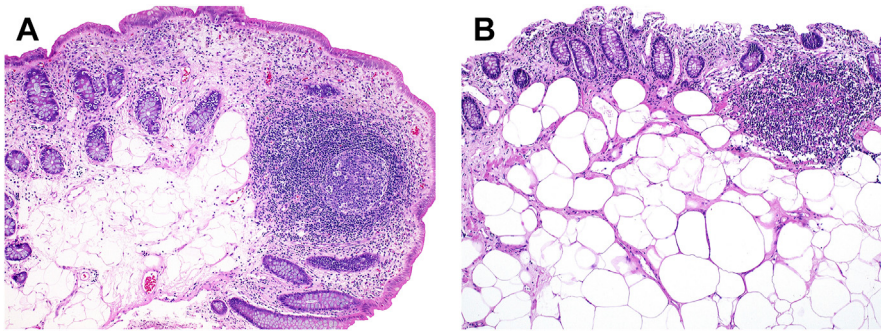

Fig. 5. (*A*) Colonic CS polyp with mixture of adipose tissue and lymphoid follicle. (*B*) Mucosal lipoma of the colon in CS.

Clues for suggesting the diagnosis are a high number of small colonic polyps with various histology identified through multiple colonoscopies and the association with glycogenic acanthosis of the esophagus. Previous history of other CS manifestations may further support the suspicion for the diagnosis and prompt genetic counseling.

Risk of Malignancy

The cumulative lifetime risk for any cancer is 89% by the age of 70 years (**Table 5**).[86] Affected women have an 81% risk of breast carcinoma with 50% penetrance by the age of 50 years.[87] Other cancer risks are 21% for thyroid carcinoma, 19% for endometrial carcinoma, and 15% for renal cell carcinoma. The risk of CRC is 9% to 16%. Benign lesions in the breast and thyroid are also common.

Treatment

The management of patients with CS includes screening for lesions in the breast, thyroid, the endometrium, and kidney.[57] Colonoscopy should start at the age of 35 years and repeated at 5 years interval or more frequently depending on symptoms and polyp findings.

LYNCH SYNDROME

Definition

LS is an autosomal dominant disorder caused by inherited pathogenic variants in one of the DNA mismatch repair (MMR) genes mutL homolog 1 (*MLH1*), mutL homolog 2 (*MLH2*), mutL homolog 6 (*MLH6*), and postmeiotic segregation increased, S. cerevisiae, 2 (*PMS2*) or by deletions in the 3' end of the epithelial cell adhesion molecule (*EPCAM*) gene leading to transcriptional silencing of *MSH2.*[88]

Clinical Features

LS is the most common genetic cause of CRC accounting for approximately 3% of all cases. Affected individuals also develop tumors of the endometrium, ovaries, small intestine, urinary tract, pancreas, hepatobiliary tract, stomach, brain, prostate, and breast.[89] Most individuals do not develop a large number of colorectal polyps.

Pathogenesis

MMR deficiency is the hallmark of LS-associated tumors. This deficiency occurs when the second allele of the same MMR gene that is constitutionally altered is hit by a somatic event. As a result, deficient MMR cells gain a growth advantage and are at risk of acquiring point mutation especially in short DNA repetitive sequences.

Table 5
Cowden syndrome lifetime cancer risks[87,99]

Site	Lifetime Risk (%)
Breast	25–85
Thyroid	35
Endometrium	19–28
Kidney (Renal cell)	34
Colon	9
Melanoma	6

Immunohistochemistry is used to identify MMR deficiency when the expression of one or more MMR protein(s) is lost in tumor cells. Polymerase chain reaction-based microsatellite instability analysis on tumor tissue is another and sometimes complementary approach to demonstrate MMR deficiency. This phenotype is not specific of LS. Approximately 15% of non-LS associated CRC are MMR deficient caused by somatic hypermethylation of the *MLH1* gene promoter. Most of these sporadic deficient MMR (dMMR) CRC develop from serrated polyps and are associated with a *BRAF* mutation, which can be used to help distinguishing sporadic dMMR CRC from LS-associated CRC. However, most LS-associated CRCs are thought to develop from conventional adenomas.

Pathologic Condition

LS-associated CRC has typical histologic features of MMR deficiency including poor differentiation, mucinous and signet-ring cell features, medullary growth pattern, tumor infiltrating lymphocytes, and Crohn like peritumoral reaction. These characteristics are also present in non-LS dMMR CRC caused by somatic *MLH1* methylation.

Conventional colorectal adenomas in LS can show loss of expression of the MMR protein(s) concordant to the gene that is constitutionally altered in 70% to 80% of cases. Adenomas with high-risk features (large size, with a villous component, with high-grade dysplasia) have the highest rate of dMMR.[90] Testing colorectal adenomas for MMR deficiency by immunohistochemistry may only be warranted if there is a strong family history of CRC suggestive of LS. It is not useful in young patients without a family component.[91] Moreover, a normal MMR protein expression in adenoma does not exclude LS.

Risk of Malignancy

Individuals with a pathogenic variant in *MLH1*, *MSH2*, or *MSH6* have a 20% to 60% cumulative risk of CRC to age 70 years depending on the MMR gene mutated and the sex of the carrier.[92] The risk is lower for *MSH6* carriers and even lower for *PMS2* carriers.

Treatment

Colonoscopy with the removal of all polyps is recommended every 1 to 2 years starting at age 20 to 25 years or 2 to 5 years before earliest CRC diagnosis in the family.

CRONKHITE-CANADA SYNDROME

Definition

CCS is an extremely rare, nonhereditary, protein-losing enteropathy resulting in ectodermal changes and is associated with diffuse gastrointestinal hamartomatous polyposis.

Clinical Features

The clinical presentation is highly variable. Most patients present with diarrhea, weight loss, vomiting, and dysgeusia.[93] In this context, ectodermal changes should raise the suspicion for CCS and include nail dystrophy, alopecia, and diffuse skin pigmentation.

Pathogenesis

The pathogenesis is unknown. However, most studies suggest an autoimmune cause.[94]

Pathologic Condition

Polyps are usually small, broad-based, measuring less than 20 mm and present in the stomach, the duodenum, and the large bowel.[95,96] Endoscopically, these polyps can be described as diffuse mucosal hyperplasia. The gastric mucosa shows an expanded, edematous lamina propria with a moderate mixed inflammatory infiltrate and prominent eosinophils. The architecture is abnormal with cystic dilatation of the glands and foveolar hyperplasia. In the duodenum, there is villus blunting, architectural changes with crypt dilatation, and withering in an inflamed lamina propria. Eosinophilic cryptitis and crypt abscesses are commonly found. The colonic mucosa shows nonspecific inflammatory and architectural changes, resembling inflammatory pseudopolyps.

The most helpful feature that distinguishes CCS from hereditary hamartomatous syndromes is that the mucosa between the polyps is also abnormal with prominent inflammatory changes.

Risk of Malignancy

The risk of malignancy is controversial. However, patients with CCS are at an increased risk of adenoma and adenocarcinoma in the large bowel and the stomach, possibly secondary to the diffuse chronic mucosal inflammation.[97]

Treatment

The prognosis is poor. Correction electrolyte abnormalities and nutritional deficiencies are essential and often associated with immunosuppression.[96]

SUMMARY

The diagnosis of gastrointestinal polyposis syndromes requires a multidisciplinary approach involving pathologists, gastroenterologists, and geneticists.[98] Most hereditary disorders of the gastrointestinal tract present with increased numbers of colorectal polyps of various histologic types and are associated increased risks of cancer. Early diagnosis of these disorders allows appropriate clinical surveillance for the patient and affected relatives.

DISCLOSURE

L.A.A. Brosens: None. C. Rosty: None.

DECLARATION OF INTERESTS

None to declare.

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