Clinical, Pathologic, and Molecular-Genetic Aspects of Colorectal Polyps

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KEYWORDS

• Colonic polyps • Colorectal neoplasms • Pathology • Surgical • Molecular genetics • Review

KEY POINTS

- Polyps are the most common colorectal neoplasms and are precursors of cancer.
- Polyps can be clinically divided into sporadic and syndromic and can be associated with inflammatory bowel disease.
- Pathologically polyps fall in one of the following categories: adenomatous, serrated, juvenile/retention, and Peutz-Jeghers.
- The combination of clinical, pathologic, and molecular-genetic abnormalities allows separating these lesions into discrete groups with predictable risk of progression to colorectal cancer.

In this article, the authors review the histologic classification of polyps, the different clinical scenarios in which polyps may be encountered, and the molecular genetic advances that allow segregating polyps into specific clinical-pathologic-molecular-genetic groups with inherent risks to progression to colorectal cancer (CRC).

The term polyp is often loosely applied to any discrete lesion of the colonic mucosa (raised, flat, depressed, pediculated, sessile). Histologically, however, only epithelial mucosal lesions are considered true polyps. Four histologic categories of epithelial polyps are recognized: (1) Adenomatous, (2) serrated, (3) juvenile/retention, and (4) Peutz-Jeghers. Clinically, they occur in 3 main scenarios: (1) Sporadic, (2) syndromic, and (3) associated with inflammatory bowel disease (IBD). The combination of the specific histologic category with the clinical scenario gives rise to many different clinicopathologic diagnostic categories, each with a different risk of progression to CRC.[1]

Most polyps (~90%) are sporadic, occur in individuals older than 50 years of age, and are more common in men. Less than 10% of polyps occur in the context of

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inherited or acquired genetic mutations, affect children or young individuals, are associated with markedly increased risk of developing CRC, and/or occur in large numbers. Less than 1% of CRC arises from polyps in the context of IBD.[1]

Whether sporadic, syndromic, or IBD associated, it is accepted that most CRC arises from polyps with adenomatous change/dysplasia through a years-long multistep process designated the "adenoma-carcinoma sequence." This model provides a rationale for implementing screening, surveillance, and eradication strategies tailored for specific clinicopathologic scenarios developed by public health organizations and/or professional gastroenterological or multidisciplinary societies.[2,3]

In syndromic polyps, the lifetime risk for progression is inherent to the underlying genetic abnormality, being almost universal for familial adenomatous (FAP) and mutY DNA glycosylase (MUTYH)-associated polyposis (MAP), moderate (40%–70%) for Lynch (LS), juvenile polyposis (JPS), and Peutz-Jeghers (PJS) syndromes, and much lower (<15%) for Cowden syndrome.[1]

In IBD-associated polyps/lesions, the risk of progression is directly proportional to the extent, duration, and severity of the disease. In general, lesions that are endoscopically characteristic of sporadic polyps are treated as such, whereas unusual-appearing mass-forming lesions are frequently associated with CRC and are usually treated by endoscopic mucosal resection or more extensive surgery.[1–3]

In the much more common sporadic polyps, the risk of dysplasia and progression is much lower (<5%) and influenced by age, gender, ethnicity, environmental factors, size, location, and number of polyps.[2]

Environmental Factors

Obesity, smoking, and meat and alcohol consumption have been proven to induce a direct mutational effect on the DNA or nonmutational (epigenetic) modifications of the genome.[4,5] Protective factors, such as dietary fiber, consumption of fruits and vegetables, and chemoprevention using calcium and nonsteroidal anti-inflammatory drugs among others, have also been established.[6]

Location

Although any type of polyp can occur at any location, in aggregate, specific morphologies and/or molecular-genetic signatures are much more common on the right or the left colon; for example, sessile serrated lesions and microsatellite (MS) unstable lesions are more likely to occur and to progress on the right colon, whereas adenomatous, MS stable lesions without epigenetic abnormalities are more common and more likely to occur and progress in the rectosigmoid. Different patterns of epigenetic modifications have also been documented for right- and left-sided adenomas.[7] These regional differences in the molecular profile of neoplasms of the right and left colon most likely reflect embryologically determined regional molecular heterogeneity of the stem cells at these sites that lead to site-specific genetic and epigenetic susceptibilities.[8] For this reason, it is relevant to submit lesions resected at different sites in different containers to the pathology laboratory.

Size

Diminutive polyps (<5 mm) have been shown to have no risk of malignant transformation. Small polyps (<1 cm) may harbor areas of high-grade dysplasia in less than 1% of cases but almost never invasive carcinoma.[9] Essentially all carcinomas arise in lesions greater than 1 cm, and the risk increases with increasing polyp size and is overall estimated to be less than 5%. Polyps $\geq$2 cm have also been shown to be a risk factor for metachronous CRC.[10] For lesions resected piecemeal, pathologists rely on the

endoscopic measure; for lesions resected in toto, pathologists rely on the gross description.

Number of Polyps

Provided an optimal examination is performed, the number of polyps identified at a screening colonoscopy is an indirect measure of the deleterious environmental effects on the genome of colonic stem cells of a particular individual. Statistically significant differences in the risk for metachronous malignancy have been shown in patients with 1 to 5, 6 to 9, and $\geq$10 polyps at screening colonoscopy.[3] When endoscopists submit many polyps in the same container, including polyps that have been resected piecemeal and others that were not, pathologists may only be able to confirm the presence or absence of adenomatous change, high-grade dysplasia, or different types of polyps.

ADENOMATOUS POLYPS

Epidemiology

Adenomatous polyps are the most common type, comprising ~70% of epithelial polyps. Their frequency increases with age, and in the United States, there is an overall prevalence of ~35% (male: 40%; female: 29%) at age 60 in autopsy studies and is associated with an ~4% lifetime risk of CRC.[10,11]

Pathology

Microscopically, there are 3 variants: tubular (TA), tubulovillous (TVA), and villous adenomas (VA). All show evidence of markedly increased proliferative activity manifested by increased density of glands, increased number of cells within glands, and increased mitotic and apoptotic activity, a phenomenon described as "adenomatous change" and equivalent to low-grade dysplasia (**Fig. 1**). When proliferation markers, such as Ki-67, are applied, there is a displacement and expansion of the proliferative compartment from its normal location at the base of the gland, to the neck and surface areas. With increasing polyp size, the proliferative compartment may expand further to comprise the entire gland.[12]

TAs are the most common type; most are less than 1 cm and have a smooth surface. As the lesions increase in size greater than 1 cm, fingerlike projections become apparent or predominant, and the lesions are classified as TVA if the villous component is greater than 25% or VA if greater than 75%.[1] In larger lesions, foci of increased cytologic atypia characterized by increased nuclear to cytoplasmic ratios, rounded nuclei with prominent nucleoli and loss of polarity, and architectural complexity characterized by cribriform architecture may begin to appear and are considered evidence of progression to "high-grade dysplasia." If glands with high-grade dysplasia invade through the muscularis mucosa, the lesion is classified as invasive adenocarcinoma. **Fig. 2** shows a flow chart with criteria used for the histologic classification of adenomatous polyps. Advanced adenomas are adenomatous polyps associated with increased risk of local recurrence and progression when resected piecemeal or incompletely excised and are defined as any polyp greater than 1 cm, and/or with a villous component, and/or with high-grade dysplasia. These polyps are also considered markers of increased risk of metachronous CRC or familial CRC.[3,13]

Molecular Genetic Aspects of Sporadic Adenomatous Polyps

The underlying cause of polyps is spontaneous sporadic mutations in colonic stem cells. The rate of mutation is affected by age, gender, the biome, and exposure to

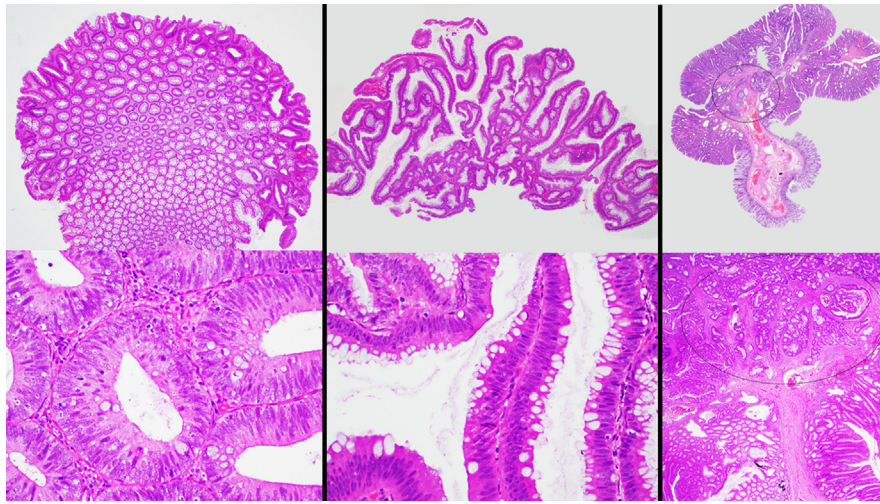

Fig. 1. Adenomatous polyps. The left panel shows a TA. At low magnification (*top*, hematoxylin-eosin [H&E], ×20), the surface appears smooth and dark, because of displacement of the proliferative compartment from the bottom of the crypts to the surface of the polyp. At high magnification (*bottom*, H&E, ×600), the nuclear pseudostratification, high nuclear density, and increased mitotic/apoptotic activity characteristic of adenomatous change are apparent. The middle panel shows a VA. The low power (*top*, H&E, ×20) shows thin tentacular projections that contrast with the appearance of the TA on the left. At high magnification (*bottom*, H&E, ×400), thin fibrovascular cores lined by adenomatous epithelium are seen. The right panel shows a malignant polyp. At very low magnification captured with a digital slide scanner (*top*, H&E, ×0.25), a large pediculated TA has a subset of glands invading the upper third of the stalk (*circle*). The base of the polyp is widely free of lesion. At low magnification (*bottom*, H&E, ×20), the invading glands show cribriform architecture and are surrounded by desmoplastic stroma (*circle*).

endogenous and exogenous carcinogens and protective agents in the feces and/or the blood. Epigenetic modifications of colonic stem cells are affected by the individual's environment and habits. The mutational effect of all these factors is time-dependent, and therefore, prevalence of polyps increases with age. Most small (<1 cm) sporadic adenomas are diploid and do not show chromosomal instability (CIN) or any molecular feature associated with progression. Molecular abnormalities in small TA are rare (≤5%) and include low-level CpG island methylator phenotype (CIMP), APC, and KRAS mutations.[14,15]

Advanced adenomas, by contrast, share the molecular abnormalities identified in CRC, which can be divided into 3 groups: (1) CIN pathway, (2) MS instability pathway, (3) CIMP.

Chromosomal instability pathway

These lesions show a progressive accumulation of mutations that induce a "mutator phenotype" and result in complex numerical and structural cytogenetic abnormalities that manifest morphologically as worsening dysplasia. A common early event is inactivating mutation of APC followed by activating mutations of KRAS or BRAF and additional mutations or losses of SMAD4, PIK3CA, TP53, and numerous other genes, of which less than 15 are considered critical for progression to invasive

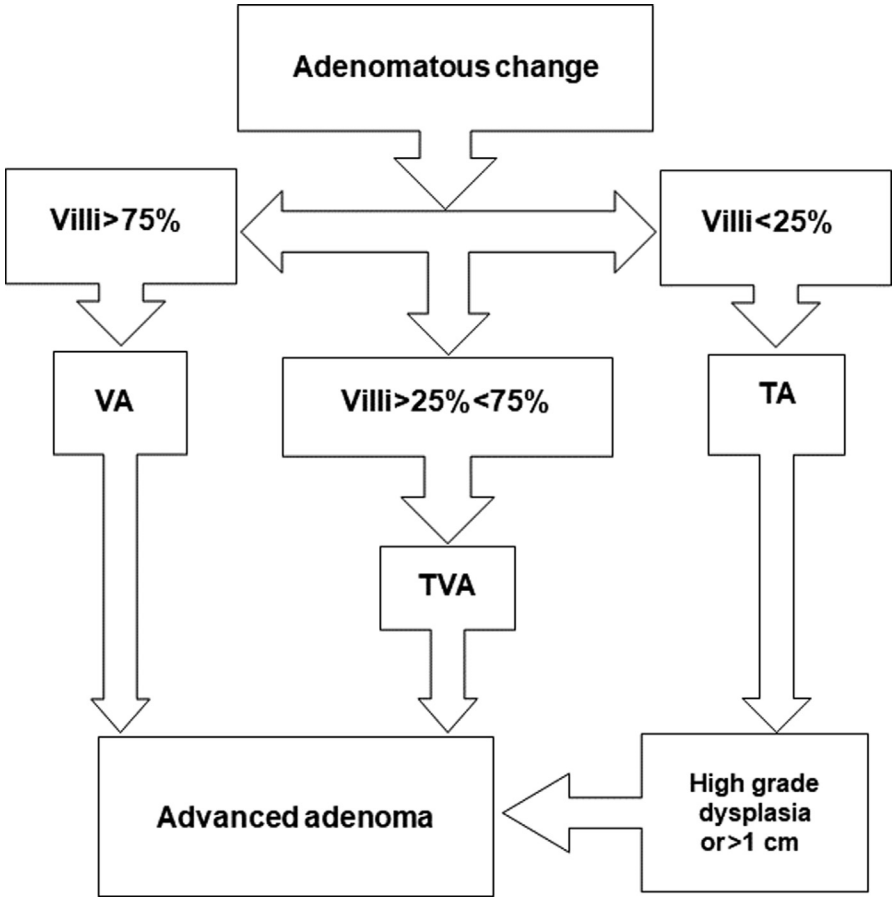

Fig. 2. Histologic classification of adenomatous polyps. The flow chart depicts the criteria used for the classification of adenomatous polyps based on the percentage of villous component. Advanced adenoma includes polyps with significant villous components or size >1 cm, or presence of high-grade dysplasia.

adenocarcinoma.[16] Although testing for many of the targetable recurrent mutations of the CIN pathway is currently standard for CRC, it is not usually done for adenomatous lesions.

Microsatellite instability pathway

These lesions result owing to acquired mutations in the DNA mismatch repair (MMR) system. The MMR proteins (MLH1, MSH2, MSH6, and PMS2) are needed to correct replication errors that occur in error-prone repetitive sequences of the DNA called microsatellites (MS). In the absence of MMR, these errors accumulate producing a microsatellite instability-high (MSI-H) phenotype. Sporadic MSI-H is detected in approximately 3% to 20% of all CRCs,[17,18] and it is usually due to silencing of the MLH1 gene through methylation of its promoter in the context of environmentally driven global hypermethylation.[18] In contrast to the CIN pathway, most sporadic MSI-H lesions are diploid, but given the tumorigenesis mechanism, they contain a high mutational

burden, a fact that has gained much relevance because metastatic lesions arising from these tumors can be targeted with immune checkpoint inhibitors.

CpG island methylator phenotype

The promoter regions of many genes contain cytosine-guanine (CG) dinucleotide-rich areas, defined as greater than 50% CG content per 200 base-pairs, which are susceptible to epigenomic silencing through methylation. Silencing of genes through methylation is much more common than through mutations. CIMP+ is responsible for most sporadic MSI-H lesions, but greater than 50% of CIMP+ lesions are MS stable. In those cases, CIMP+ is involved in silencing multiple tumor-suppressor genes and microRNAs. This abnormal methylation seems to occur due to an abnormal activation of an established epigenetic system that normally has a role in marking embryonic genes for repression and is mediated by *H3 trimethylated on Lys27* (*H3K27me3*) and the *Enhancer of zeste homolog 2* (*EZH2*)-containing polycomb complex.[19] Activation of this system can be indirectly induced by *BRAF* or *KRAS* mutations.[20,21]

Molecular Genetic Aspects of Syndromic Adenomatous Polyps

Adenomatous polyps are characteristic lesions of syndromes, including FAP, attenuated FAP (AFAP), FAP variants: Gardner and $Turcot_{subset}$, LS, LS variants: Muir-Torre and $Turcot_{subset}$, MAP, and polymerase proofreading-associated polyposis (PPAP).

All these syndromes are autosomal dominant, except for MAP, which is recessive.[1]

FAP and variants (AFAP, Gardner, Turcot) are characterized by germline mutations of the *APC* tumor-suppressor gene. The mutated protein loses its microtubule-binding sites, which are needed for its function as a regulator of cytoskeletal proteins that participate in contact inhibition of proliferation, and for interaction with proteins of the mitotic spindle. Loss of these functions leads to expansion of the mutant clone and CIN, respectively.[22,23]

MAP clinically resembles AFAP. Rarely, it may present as serrated polyposis syndrome (SPS) or with mixed adenomatous and serrated polyps. The underlying abnormality is biallelic germline mutations in the *MUTYH* gene, which codifies an enzyme involved in the repair of DNA damage induced by oxidative stress. Loss of function leads to the accumulation of mutations in several genes and high mutational burden, like the MMR pathway, making these lesions susceptible to be targeted with immune checkpoint inhibitors.[24] *APC* and *KRAS* are particularly susceptible to oxidative damage[25]; for this reason, MAP-associated polyps and CRC may show features of either the CIN pathway, the MSI pathway, or both.

LS and variants (Muir-Torre, $Turcot_{subset}$) are characterized by a germline mutation in one of the 4 MMR genes encoding the proteins that form the heterodimers *MSH2*/*MSH6* and *MLH1*/*PMS2*. The loss of expression of these proteins is usually demonstrated by immunohistochemistry (IHC). Loss of 1 protein of the heterodimer usually leads to loss of expression of its partner. Rarely, *MSH2* is silenced through methylation owing to a deletion of *EPCAM*/*TACSTD1*.[26] The *MSH6* gene contains a MS and its expression can be lost because of a MSI-H phenotype induced by *MLH1* or *PMS2* mutation, resulting in an MLH1/PMS2/MSH6 triple loss of expression by IHC. Very rarely, germline mutations in the 4 MMR genes occur and result in a cancer predisposition syndrome called "constitutional MMR deficiency syndrome (CMMRD)." It is associated with a high risk of developing different types of malignancies that include lymphomas, gliomas, and CRC and that usually manifest before age 18 years. Patients with CMMRD show clinical features of neurofibromatosis type I associated with a polyposis syndrome.[27] The MSI status is determined through conventional polymerase

chain reaction amplification/gel electrophoresis of 5 standardized MS loci known as the Bethesda panel.[28] MSI-H is defined as alteration in ≥2 of the 5 loci or greater than 40% of loci in larger panels. Common additional mutations in LS include mutations in the β-catenin or APC genes, but in contrast to sporadic MSI-H lesions, it is not associated with BRAF mutations.

PPAP is a relatively new addition to the list of polyposis syndromes and is characterized by germline mutations in the proofreading domains of POLE or POLD1, two DNA polymerases. Defects in DNA polymerase proofreading can lead to propagation of mistakes or mutations to daughter cells during cellular replication resulting in a mutator phenotype. Unlike LS, PPAP is MS stable with progression to CRC occurring via the CIN pathway.[29] The lifetime risk of progression of PPAP is high, at 36%.[30]

SERRATED POLYPS

Epidemiology

Serrated polyps are the second most common type comprising ~30% of epithelial polyps.[31] Although initially regarded as benign, it is now clear that these lesions also have a potential for progressing to carcinoma, albeit with lesser frequency than adenomatous polyps.

Pathology

Microscopically there are 3 variants: hyperplastic (HP), sessile serrated polyp/lesion (SSL), and traditional serrated adenoma (TSA). Although HP and SSL are very common, TSA is rare. **Fig. 3** shows a flow chart with the criteria for the histologic classification of serrated polyps. Serrated polyps are almost always sessile, and the superficial portion shows a characteristic saw-toothed architecture when the glands are sectioned longitudinally or appear star-shaped when sectioned transversally (**Fig. 4**). All serrated polyps have an aberrant immunophenotype with expression of the gastric-type mucin MUC5AC. In HP and SSL, the proliferative compartment remains at the base, and there is no adenomatous change/dysplasia. Their abnormal growth is due to inhibition of apoptosis, which causes an abnormal migration/maturation pattern of epithelial cells along the crypt.[32] Two types of HP are recognized, microvesicular and goblet cell rich. The former is more common and characterized by preponderance of variably vacuolated non–goblet cells and only scattered goblet cells; the latter shows preponderance of goblet cells and less prominent serrations and may be underrecognized.[33] Although the proliferative compartment in HP is well defined, in SSL it may be asymmetric and may expand beyond the base. HP are usually ≤5 mm, whereas SSL are typically larger than 5 mm and are more common on the right colon. Histologically, SSL differ from HP because the crypts appear dilated and complex at the base adjacent to the muscularis mucosa. In cases with ambiguous morphology between HP and SSL, most pathologists use site and size as additional parameters for classification: ambiguous right-sided lesions greater than 5 mm are usually defaulted to SSL; lesions less than 5 mm are usually defaulted to HP; and for the remaining lesions, variability in their classification is to be expected. Large SSL may show foci of conventional dysplasia and are classified as SSL with dysplasia. Right-sided SSL larger than 1 cm or with foci of dysplasia have an increased risk of progressing to CRC if incompletely excised and have been shown to be a risk factor for metachronous CRC; for these reasons, they are considered equivalent to "advanced adenoma" for surveillance purposes.[33] Carcinomas arising from SSL are designated "serrated pathway carcinomas."

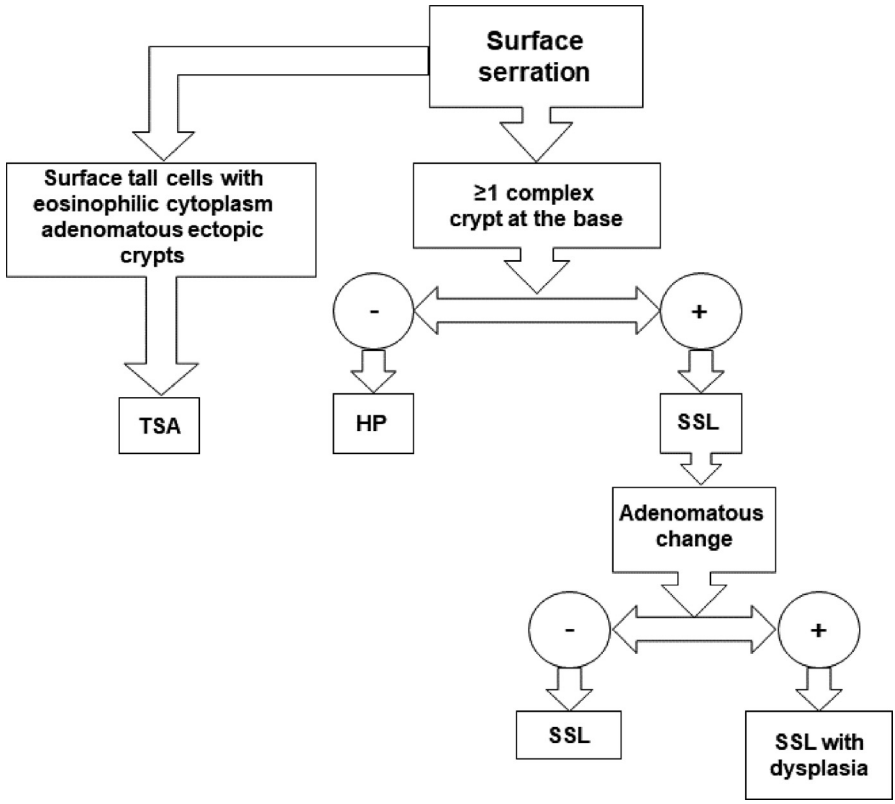

Fig. 3. Histologic classification of serrated polyps. HP and SSL differ by the complexity of the crypt bases, which reflect differences in the regulation of their proliferative compartments located at the base of the crypts. In HP, crypt bases are narrow and simple; in SSL, at least one, but usually many crypt-bases show branching and/or cystic dilatation indicative of greater dysregulation. TSA show superficial serrations like HP and SSL, but their surface cells are distinctively tall and pink, and the proliferative compartment is located in ectopic crypts along the villi and away from the muscularis mucosa.

In contrast to HP and SSL, TSA always shows adenomatous change. It occurs more frequently on the left colon of elderly individuals.[34] The superficial portion resembles small intestinal villi with slitlike serrations, scattered goblet cells, and surface epithelium with abundant eosinophilic cytoplasm. Ectopic crypt formation defined as the presence of crypt bases along the villous projections and away from the muscularis mucosa is characteristic. Ki-67 immunostain facilitates the recognition of the ectopic crypts and shows that the proliferative compartment is limited to these.[35] A subset of TSA arises from HP or SSL, and a residual precursor can often be recognized at the periphery of the polyp.[36] For surveillance purposes, they are considered equivalent to other adenomatous polyps; criteria for classifying them as advanced adenomas include size greater than 1 cm and/or presence of high-grade dysplasia.

Molecular Genetic Aspects of Sporadic Serrated Polyps

All serrated polyps have 3 molecular alterations in common: (1) Activation of mitogen-activated protein kinase-extracellular signal-regulated kinases (MAPK/ERK pathway),

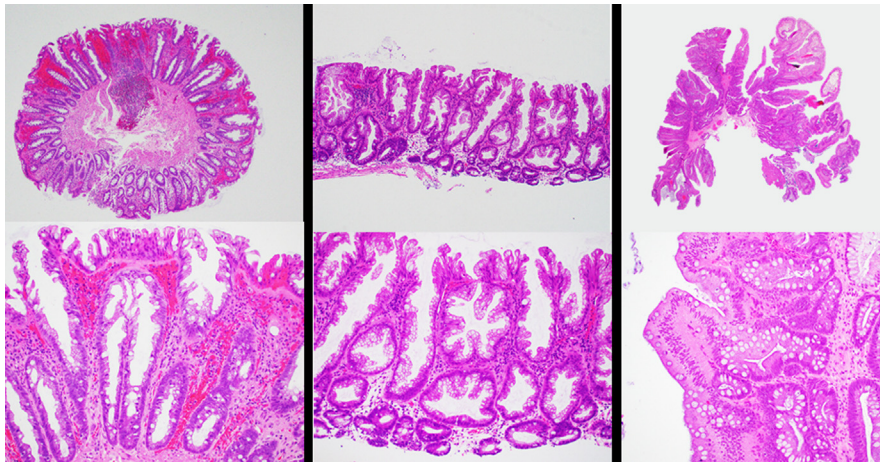

Fig. 4. Serrated polyps. The left panel shows an HP. At low magnification (*top*, H&E, ×20), the upper two-thirds of the gland appear lighter and display serrations. The deep portion of the crypts with the proliferative compartment appears darker. At intermediate magnification (*bottom*, H&E, ×200), the proliferative compartment lacks complex branching, and the glands are perpendicular to the muscularis mucosa (MM). The middle panel shows a sessile serrated lesion. At low power (*top*, H&E, ×20) the serrations are more prominent than the HP on the left. At intermediate magnification (*bottom*, H&E, ×200), the deep portions of the crypts appear complex and assume an orientation parallel to the MM. The right panel shows a TSA. At very low magnification captured with a digital slide scanner (*top*, H&E, ×0.5), a characteristic filiform architecture is apparent. At intermediate magnification (*bottom*, H&E, ×200), the surface epithelium consists of tall cells with abundant pink cytoplasm next to variably complex adenomatous ectopic crypts that hallmark the displacement of the proliferative compartment within the villi and away from its normal location next to the MM.

(2) inhibition of apoptosis, (3) epigenomic silencing of many tumor-suppressor genes through methylation.[37] Most HP, SSL, and TSA show mutually exclusive mutations of *BRAF* or *KRAS*, associated with a CIMP+ phenotype. *BRAF* mutations are more common on the right side and usually lead to CIMP+ and *MLH1* methylation, whereas *KRAS* mutations are more common on the left and have an overall low risk of progression to CRC. In general, *MLH1* methylation is responsible for the increased frequency of right-sided MSI-H CRC in tumors arising through the serrated pathway. TSA are more common in the left colon and therefore usually show *KRAS* mutations, associated with methylation of *the DNA repair gene O-6-methylguanine-DNA methyltransferase.*[37]

Molecular Genetic Aspects of Syndromic Serrated Polyps (SPS)

SPS is clinically defined as : (1) ≥5 serrated polyps proximal to the sigmoid with ≥2 of these being ≥1 cm, (2) any number of SSL proximal to the sigmoid in an individual with a first-degree relative with SPS, (3) greater than 20 SSL throughout the colon.[1] Two clinical variants are recognized: type 1: includes few proximal SSLs and has an increased risk of CRC; and type 2: includes only HPs and is not associated with CRC. Most affected patients are adults with a median age of 66 years. Genetic testing of reported cases have shown heterogenous results with most patients being negative for germline mutations,[38] except for rare familial cases in which germline mutations in *RING-type E3 ubiquitin ligase* (*RNF43*), an inhibitor of the *Wnt* pathway, have been found.[39] A subset of patients with MAP meets the criteria for SPS, but they should be considered MAP, and not an overlap syndrome.[40] CRC arising in the context of SPS usually show the typical molecular

signature of serrated pathway: BRAF+/CIMP+/MSI-H. Whether sporadic or syndromic, the lifetime risk of CRC in SPS type 1 is high, at 29%.[41]

JUVENILE/RETENTION POLYPS

Epidemiology

Juvenile/retention polyps are the most common polyps in children, but one-third occur in adults.[42] Most present as rectal bleeding in patients younger than 10 years. In 50% of children, more than 1 polyp is present on colonoscopy; however, concern for a polyposis syndrome is not warranted if there is no family history and fewer than 5 polyps are present.[42]

Pathology

These polyps are usually pedunculated and less than 3 cm. Upon sectioning, mucus-filled cystic spaces are grossly apparent, and for this reason, they are also called "retention" polyps. Microscopically, they consist of cystically dilated glands with reactive changes, separated by edematous, variably inflamed stroma (**Fig. 5**). Ulceration and granulation tissue formation are common on the surface. Polyps with a single stalk but multiple heads may occur in syndromic cases.[1]

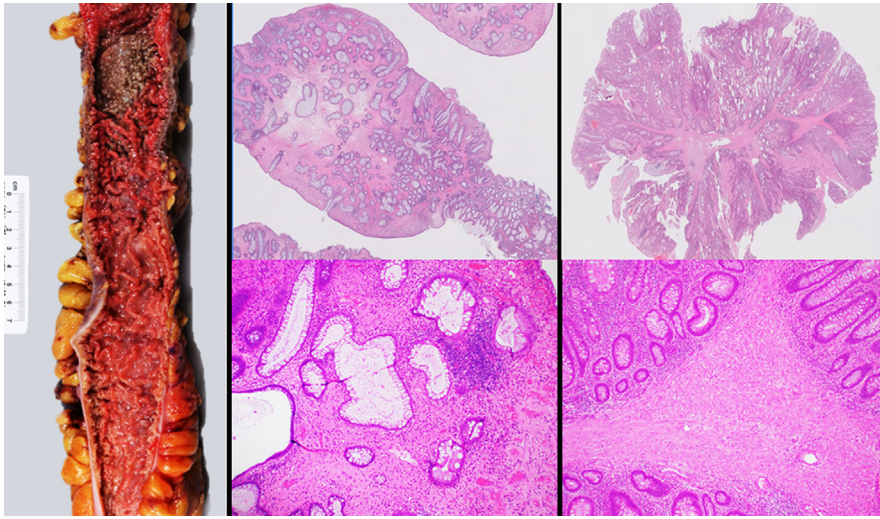

Fig. 5. Polyposis syndromes. The left panel shows a prophylactic colectomy specimen from a patient with FAP polyposis with innumerable small polyps. Histologically, these polyps would be adenomatous. The middle panel shows a juvenile/retention polyp from a young patient with JPS. At very low magnification captured with a digital slide scanner (*top*, H&E, ×0.5), the polyp appears pediculated, shows abundant edematous fibrous stroma and variably dilated hypermucinous glands. At intermediate magnification (*bottom*, H&E, ×200), cystic glands with distended goblet cells alternate with glands with regenerative changes and decreased mucin. The fibrous stroma contains increased inflammatory cells and lymphoid aggregates. The right panel shows a colonic Peutz-Jeghers polyp. At very low magnification captured with a digital slide scanner (*top*, H&E, ×0.25), the characteristic arborizing bundles of smooth muscle can be observed. At intermediate magnification (*bottom*, H&E, ×200), thick bundles of skeletal muscle compartmentalize the mucosa that shows mild hyperplastic changes and rectified gland contours characteristic of mucosal prolapse.

Table 1
Clinical-pathologic-molecular-genetic classification of polyps and their risk of progression to colorectal cancer

Clinical Presentation	Type of Polyp	Molecular Genetics	Risk of CRC	Extracolonic Neoplasms
Sporadic	Adenomatous	CIN pathway MSI pathway CIMP-high	Minimal if <1 cm; annual risk of progression if >1 cm or high-grade dysplasia: <5%	None
Familial adenomatous polyposis AFAP Gardner syndrome Turcot syndrome		Germline APC mutation, dominant	Lifetime risk: 70%–100%	Desmoid, osteomas, epidermoid cysts, fibromas, lipomas, gliomas
Lynch syndrome Muir-Torre syndrome Turcot syndrome		Germline mutation of MMR genes, dominant	Lifetime risk: 40%–70%	Endometrium, ovary, breast, prostate
Polymerase proofreading-associated polyposis		Germline mutation of POLE or POLD1, dominant	Lifetime risk: 36%	Endometrial, ovarian, brain, upper gastrointestinal tract
MUTYH-associated polyposis		Germline mutation MUTYH, recessive	Lifetime risk: 40%–70%	Gastrointestinal tract, thyroid
Sporadic	Serrated	MAPK/ERK pathway, BRAF or KRAS mutations leading to CIMP-high and MLH1 methylation	Hyperplastic polyp: none SSL/TSA: minimal if <1 cm; annual risk of progression if >1 cm or with dysplasia: <5%	None
Serrated polyposis syndrome		BRAF mutation, CIMP-high, MSI-high. Not inherited in most cases, rare familial cases associated with RNF43 mutations	Lifetime risk: 29%	None
Sporadic	Juvenile	KRAS mutation	None	None
Juvenile polyposis syndrome		Germline mutations of SMAD4 or BMPR1A, dominant	Lifetime risk: 21%–68%	SMAD4: stomach
Cowden syndrome Bannayan-Riley-Ruvalcaba syndrome		Germline mutation PTEN, dominant	Lifetime risk: <15%	Breast, thyroid, renal, uterine
Sporadic	Peutz-Jeghers	Somatic mutation STK11	None	None
Peutz-Jeghers syndrome		Germline mutation STK11, dominant	Lifetime risk: 39%	Breast

Molecular Genetic Aspects of Sporadic Juvenile Polyps

KRAS mutations and absence of APC mutations have been found in sporadic juvenile polyps.[43]

Molecular Genetic Aspects of Syndromic Juvenile Polyps

Juvenile polyps are associated with JPS, Cowden (CS), and its variant Bannayan-Riley-Ruvalcaba (BRRS) syndromes.[1]

The molecular features underlying JPS include germline abnormalities in the *SMAD4* and *BMPR1A* genes in ~60% of the cases and various genes in the remaining cases. The genes involved in JPS are part of the transforming growth factor-beta pathway, which regulates the transcription of genes involved in cell growth and division. Mutations of *SMAD4* are also associated with hereditary hemorrhagic telangiectasia (HHT) syndrome, and these patients present with JPS/HHT overlap syndrome.[44] Both genes predispose patients to CRC, and SMAD4 also predisposes to gastric cancer.

The underlying abnormality in CS and BRRS is germline mutations of the *PTEN* tumor-suppressor gene. Given the broad spectrum of clinical manifestations of patients with *PTEN* mutations, the term PTEN hamartoma tumor syndrome (PHTS) has been gaining traction to encompass any clinical syndrome with proven *PTEN* abnormalities. *PTEN* is the most important negative regulator of the PI3K signaling pathway, which exerts its actions through the AKT/mTOR axis. It has a plethora of effects that include negative regulatory effect of growth factor–mediated cell proliferation and survival, *ERK1/cyclin D1*–mediated transcription, translation and chromosomal stability, angiogenesis, stem cell self-renewal, and maintenance of tumor microenvironment.[45] Somatic mutations of PTEN also occur in ~6% of sporadic CRC and is more common in tumors arising through the serrated pathway.[46] PTEN-mutated neoplasms are potentially targetable with EGFR and MAPK-inhibitor therapies.

Characteristic extraintestinal manifestations of PHTS include glycogenic acanthosis of the esophagus, trichilemmomas, and mucocutaneous papillomas. Germline mutations of PTEN are more commonly associated with breast, thyroid, renal, and endometrial carcinomas than CRC.

PEUTZ-JEGHERS POLYPS

Epidemiology

Peutz-Jeghers polyps are more common in the small bowel than in the colon, and 40% to 72% are associated with a polyposis syndrome.[47]

Pathology

The most conspicuous finding in these polyps is the presence of ramifying bundles of smooth muscle fibers emanating from the muscularis mucosa. The glandular component is less distinctive and shows features of mucosal prolapse with mucous hypersecretion, regenerative changes, and angulated/rectified gland borders (see **Fig. 5**). Although PJS is associated with an increased risk of CRC, dysplasia is exceedingly rare in PJ polyps. The risk of extraintestinal neoplasms is high, especially breast cancer in female patients.[1]

Molecular Genetic Aspects of Peutz-Jeghers Polyps

The underlying molecular abnormalities are mutations in the LKB1/STK11 gene, somatic mutations in sporadic cases, and germline mutations in syndromic cases. STK11 is a tumor suppressor that exerts negative regulation over the mTOR pathway; inactivating mutations lead to overactivation of this pathway involved in cell

metabolism, growth, and proliferation. The use of mTOR inhibitors for chemoprevention of polyps/tumors in PJS has been limited by drug toxicities.[48]

SUMMARY

For a long time, it has been known that all disease processes are affected in varying proportions by genetic and environmental factors. The increasing use of molecular-genetic technologies in clinical studies is finally allowing us to decipher the intricate interplay of these factors in sporadic and syndromic polyps, and to predict more accurately their risk of progressing to CRC. As these sophisticated technologies become progressively integrated in the routine workup of pathology specimens, a clinical-pathologic-molecular-genetic classification of polyps is emerging (**Table 1**), which is being used to refine existing surveillance and eradication strategies for patients and their relatives, getting us closer to the long-held dream of personalized medicine.

CLINICS CARE POINTS

- Most polyps (~90%) are sporadic, occur in individuals greater than 50 years of age, are more common in men, and have a low risk (<5%) of progressing to colorectal cancer.
- Polyps in children or young adults are uncommon, may be associated with inherited or acquired genetic mutations, and are associated with markedly increased risk of developing colorectal cancer. Pertinent genetic testing should be considered.
- Diminutive polyps (<5 mm) have no risk of malignant transformation. Small polyps (<1 cm) may harbor areas of high-grade dysplasia in less than 1% of cases but almost never invasive carcinoma. Essentially all carcinomas arise in lesions greater than 1 cm, and the risk increases with increasing polyp size.
- The number of polyps identified at a screening colonoscopy is an indirect measure of the mutation rate of colonic stem cells. Statistically significant differences in the risk of synchronous or metachronous malignancy have been shown in patients with 1 to 5, 6 to 9, and $\geq$10 polyps.
- Advanced adenomas are defined as any polyp greater than 1 cm, and/or with a villous component, and/or with high-grade dysplasia. These polyps are associated with increased risk of local recurrence and progression when resected piecemeal or incompletely excised, and with metachronous or familial colorectal cancer.
- Right-sided sessile serrated lesions larger than 1 cm or with foci of dysplasia are considered equivalent to "advanced adenoma" for surveillance purposes.
- In 50% of children, greater than 1 juvenile polyp is present on colonoscopy; concern for a polyposis syndrome is not warranted if there is no family history and fewer than 5 polyps are present.
- Peutz-Jeghers polyps are associated with a polyposis syndrome in up to 72% of the cases. The risk of breast cancer in female patients with Peutz-Jeghers syndrome is much higher than the risk of colorectal cancer.

CONFLICT OF INTEREST DISCLOSURE

The authors do not have conflict of interest to declare.

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