The Role of the Surgical Pathologist in the Diagnosis of Rare Polyposis Syndromes

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Hereditary gastrointestinal polyposis syndromes comprise a diverse group of phenotypically distinct entities with clinical, pathological and genetic features. Lynch syndrome and familial adenomatous polyposis (FAP) are the two most common syndromes and account for up to 5% of all colorectal carcinomas. Hamartomatous polyposis syndromes are dominantly inherited, less common and more difficult to diagnose. However, proper identification of affected individuals is important as there is an increased risk of gastrointestinal and extra-gastrointestinal cancers (Table 1). Family history is often lacking and the diagnosis of these syndromes is essentially a clinical process, confirmed by genetic testing. Surgical pathologists can play a major role in the identification of gastrointestinal polyps with features suggestive of a hereditary gastrointestinal syndrome.

1. Lynch Syndrome

Lynch syndrome (LS) is an autosomal dominant condition, defined by the identification of a pathogenic germline mutation in one of the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 or PMS2 or in the EPCAM gene leading to constitutional epigenetic silencing of the nearby MSH2 gene. The Amsterdam I criteria were developed in 1991 to define hereditary non-polyposis CRC (HNPCC), a term coined to separate familial predisposition to CRC from the other known polyposis syndromes at that time (FAP and hamartomatous polyposis syndromes) [1]. However, not all HNPCC individuals are diagnosed with LS and not all LS individuals fulfil the clinical criteria for HNPCC. Up to 50% of HNPCC individuals do actually not have LS [2]. The other half comprises patients with an MSI CRC but no germline alteration in an MMR gene (Lynch-like syndrome) and patients with MSS CRC, referred to as familial colorectal cancer type X (FCCTX) [3].

The diagnosis of LS is a multistep process in which pathologists play an instrumental role. Tumours arising in LS patients demonstrate high levels of microsatellite instability (MSI) secondary to altered DNA MMR mechanisms in tumour cells. Immunohistochemistry for DNA MMR proteins is widely used to identify MMR deficiency in CRC as a first screening test for LS [4]. There have been several alternative recommendations for MMR-deficiency testing in CRC using different cut-offs for age at diagnosis. However, several groups recommend that all newly diagnosed CRC should be tested for MMR-deficiency regardless of age at diagnosis or family history given that a proportion of LS CRC occur at old age. This so-called ‘universal screening’ has virtually complete sensitivity [5]. The pattern of MMR protein loss of expression in tumour cells is indicative of the most likely underlying genetic alteration and guide geneticists for gene screening strategies. However, the majority of MSI CRC caused by MLH1 loss of expression are not related to LS but occur sporadically secondary to the acquired methylation of the promoter of the MLH1 gene. While LS-associated CRC arise from conventional adenoma usually in
young patients, sporadic MLH1-deficient CRC arise from sessile serrated adenoma, harbouring BRAF mutation, and more frequently in older women. BRAF mutation testing is commonly performed to stratify patients with MLH1-deficient CRC into sporadic (mutation present) or possibly related to LS (mutation absent). From various studies pooled together, 59% of patients with an apparently non-sporadic CRC do not seem to have a mutation in a DNA MMR gene [6]. These Lynch-like patients and their family members are difficult to manage. Some may represent LS with a hidden mutation that cannot be detected with the current methods while others may not be LS (MMR deficiency secondary to bi-allelic somatic alterations).

Testing polyps for MMR deficiency is often requested by clinicians but rarely shows abnormal expression of MMR proteins. Up to 95% of conventional adenomas in known LS patients demonstrate loss of the appropriate MMR protein, in particular if high grade dysplasia or a villous component is present [7]. If age only (<40 years) or history of a relative with CRC (without meeting AC-1 criteria) is used, the probability to find abnormal expression of MMR protein in an adenoma is very low, making such testing questionable [8]. Moreover, it is useless to perform MMR protein testing in serrated polyps (sessile serrated adenoma and hyperplastic polyp) to screen for LS; it may even lead to the wrong interpretation of MLH1 loss in advanced serrated adenoma suspicious for LS while it is the common pathway for sporadic MSI CRC caused by MLH1 methylation.

2. Adenomatous polyposis syndromes

FAP is an autosomal dominant syndrome characterized by the development of hundreds to thousands of conventional adenomas throughout the large bowel and the inevitable transformation to CRC, justifying total colectomy early in adulthood [9]. Neoplasms in the stomach and the small intestine also commonly occur. The diagnosis of FAP is essentially clinical, known at time of colonoscopy or surgery; the role of the pathologist is usually to confirm that the polyps are conventional adenomas and to exclude a carcinoma. Caused by a mutation in APC, FAP can be diagnosed in 30-50% of patients with no familial history of colorectal carcinoma or polyps, usually secondary to a de novo mutation. The location of the mutation in the APC gene correlates with the phenotype, including attenuated forms of polyposis (<100 polyps) and variants of FAP. Gardner syndrome includes fibromatosis (desmoid tumor), epidermoid cysts and osteoma; Turcot syndrome includes brain tumors (medulloblastoma).

MUTYH-associated polyposis (MAP) should be considered when there is no ‘vertical’ history of CRC as this is a recessive condition [10]. Bi-allelic carriers often present with multiple conventional adenomas (but not as many as FAP patients) and also with serrated polyps. The phenotype of MAP overlaps with the phenotype of attenuated FAP (<100 polyps) and of serrated polyposis syndrome [11]. Gene testing for APC and MUTYH is usually done together; however in a significant proportion of cases no mutation is identified in any of these genes. Recently polymerase proofreading-associated polyposis has been described as an autosomal condition caused by a mutation in POLE or POLD1 [12]. Mutation carriers have a phenotype between Lynch syndrome and attenuated FAP; colorectal cancers are usually without MSI. Another new gene has been found implicated in a recessive inherited polyposis
syndrome resembling MAP: NTHLI also involved in DNA base excision repair function [13].

3. Hamartomatous polyposis syndromes

3.1. Juvenile polyposis syndrome

Juvenile polyposis syndrome (JPS) is an autosomal dominant condition and the most common of the 3 main hamartomatous polyposis syndromes (prevalence 1:16,000 to 1:100,000). JPS individuals are predisposed to develop hamartomatous polyps in the large bowel, the stomach and less commonly in the small bowel. Most affected individuals develop polyps before age 20 years; however the diagnosis can be made much later in life in late adulthood (‘juvenile’ refers to the type of polyp and not the age of onset of polyp or age of diagnosis). The phenotype can vary between affected families and between affected members within a family, from a few polyps to >100 polyps.

The clinical diagnosis of JPS is made if any of these findings is present:

- ≥5 juvenile polyps of the large bowel
- Multiple juvenile polyps of the upper and lower GI tract
- Any number of juvenile polyps with family history of JPS

Up to 45% of individuals with a clinical diagnosis of JPS have a pathogenic mutation: SMAD4 in 20% and BMPR1A in 20-25%, two genes from the TGFβ signalling pathway [14]. In 25% of probands, no family history of polyps is found (de novo mutation).

Juvenile polyps are large pedunculated or small sessile hamartomas composed of dilated crypts/glands often filled with mucin and neutrophils and expanded lamina propria by oedema and inflammatory cells. Smooth muscle is rarely present in the lamina propria. Surface erosions are frequent leading to bleeding and anaemia; other polyp complications include intussusception, obstruction and auto-amputation. It is worth noting that most juvenile polyps are sporadic (not part of JPS) and are found in up to 2% of the paediatric population.

A gastric phenotype (juvenile gastric polyposis) is more frequently found in SMAD4 mutation carriers than in BMPR1A mutation carriers. Some SMAD4 mutation carriers can present with a combined JPS / hereditary haemorrhagic telangiectasia syndrome. History of epistaxis and arteriovenous malformations are clues to the diagnosis.

The role of the pathologist is essential in establishing the diagnosis of juvenile polyps. In the large bowel, the diagnosis of JP is usually straightforward for large pedunculated polyps with typical histological features. However, small polyps can have the same morphology as non-specific inflammatory polyps and may be indistinguishable from pseudo-polyps in the context of inflammatory bowel disease or can be misdiagnosed as inflammatory serrated polyps. In the stomach, JPs are more difficult to diagnose and resemble hyperplastic polyps or other hamartomatous polyps (Peutz-Jeghers syndrome, Cowden syndrome) [15,16]. In florid gastric polyposis, hypertrophic gastropathy (Menetrier disease) is sometimes considered by
endoscopists. Small bowel JPs are rare and usually associated with JP in the large bowel and the stomach.

Affected JPS individuals are at increased risk of malignancy: 40% risk of colorectal cancer and 20% risk of gastric cancer [17,18]. Increased (undefined lifetime) risk of pancreatic cancer and of small bowel cancer has also been reported. Upper GI endoscopy and colonoscopy are recommended from age 15 years or at the time of initial presentation and every 1 to 3 years depending on polyp burden [19].

3.2. Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant condition characterized by the association of gastrointestinal hamartomas and mucocutaneous pigmentation. The phenotype is variable; affected individuals can present with isolated mucocutaneous pigmentation, with polyposis only or with both.

The clinical diagnosis of PJS [20] is made if any of these findings is present:

- ≥3 PJS-type hamartomatous polyps
- Any number of PJS-type polyps with a family history of PJS
- Characteristic mucocutaneous pigmentation with a family history of PJS
- Any number of PJS-type polyps with characteristic mucocutaneous pigmentation

A pathogenic germline mutation in STK11 is identified in up to 94% of individuals with the clinical diagnosis of PJS [21]. A family history of PJS is not found in 45% of probands, which may represent de novo mutations and possibly subtle unreported findings in other family members.

Peutz-Jeghers polyps are most frequently found in the small bowel (jejunum > ileum > duodenum) but can also occur in the stomach and the large bowel. Often PJS individuals present with multiple surgical procedures caused by complications of GI polyps: intussusception, obstruction, bleeding. Polyps in affected individuals can be pedunculated or sessile and have a typical lobulated architecture. They are composed of non-dysplastic epithelium and exhibit an arborizing pattern of growth with bundles of smooth muscle. The lamina propria is usually normal. Dysplasia can occur. PJS individuals are also at increased risk of adenoma throughout the GI tract.

The role of the pathologist is to establish or suggest the diagnosis of Peutz-Jeghers type polyp. In the small bowel, the diagnosis is usually straightforward for polyps with typical histology. In the large bowel, PJS polyps can resemble non-dysplastic polyps with prolapse changes. The context is essential to favour a hamartomatous polyp over a prolapse polyp (age, polyp location, number of polyps, and other pathology). In the stomach, PJS polyps may be indistinguishable from juvenile polyps or hyperplastic polyps. Table 2 below summarises differences between PJS polyps and JPS polyps.

Affect PJS individuals are at increased risk of multiple malignancies. The cumulative risk of all malignancies in PJS individuals from ages 15–64 years has been estimated to 93% [20]: breast cancer 54%, colorectal cancer 39%, pancreatic cancer 36%. Rare tumours with uncommon histology can occur: ovarian sex cord tumour with annular tubules, large cell calcifying Sertoli cell tumour, adenoma malignum of the uterine
3.3. *Cowden syndrome*

Cowden syndrome (CS) is part of the *PTEN* hamartoma tumour syndrome (PHTS) that also includes Bannayan-Riley-Ruvalcaba syndrome, *PTEN*-related Proteus syndrome, and Proteus-like syndrome. Like the other hamartomatous syndromes described above, CS is inherited in an autosomal dominant fashion with variable phenotype. The reported prevalence of CS is 1:200,000 but is likely to be underestimated. CS is characterized by multiple hamartomas associated with macrocephaly, benign skin lesions and a high risk of tumours of the thyroid, breast and endometrium.

The clinical diagnosis of CS is based on diagnostic criteria divided into 3 categories [22]:

- **Pathognomonic criteria:**
  - Adult Lhermitte-Duclos disease, defined as the presence of a cerebellar dysplastic gangliocytoma
  - Mucocutaneous lesions: Trichilemmomas, acral keratosis, papillomatous lesions

- **Major criteria**
  - Breast cancer
  - Epithelial thyroid cancer (non-medullary), especially follicular thyroid cancer
  - Macrocephaly
  - Endometrial carcinoma

- **Minor criteria:** Other thyroid lesions, intellectual disability, hamartomatous intestinal polyps, fibrocystic disease of the breast, lipomas, fibromas, genitourinary tumours and malformations, uterine fibroids

An online scoring system has been developed from the Cleveland Clinic [http://www.lerner.ccf.org/gmi/ccscore/](http://www.lerner.ccf.org/gmi/ccscore/)

A pathogenic germline mutation in *PTEN* is identified in up to 85% of individuals with a clinical diagnosis of CS.

Gastrointestinal manifestations of CS are subtle but can suggest the diagnosis if associated with other features of CS. Polyps in the large bowel are small and sessile and easily overlooked as benign unclassified mucosal bumps (BUMB). They often present as lesions with preserved crypt architecture, fibrous lamina propria that contains bland spindle cells arranged in concentric fashion around cross-cut crypts, some adipose tissue and lymphoid aggregates. Other colonic polyp types include ganglioneuroma, lipoma, and fibrolipoma. In the stomach, CS polyps do not have any specific features and often present as small hyperplastic polyps. Clues to suggest CS is the number of colonic polyps showing these subtle morphological changes, the association with glycogenic acanthoma in the oesophagus and previous history of CS-associated pathology. The skin lesions (acral keratosis, papillomas and trichilemmomas) are almost always present by age 30 years. If you are suspicious of
CS, ask your clinician (and expect a pause in the conversation) to measure the head circumference of the patient.

Affected CS individuals have very high risk of multiple tumors [23]. Reported lifetime risks are:

- 85% for breast cancer
- 35% for thyroid cancer
- 35% for renal cell cancer
- 28% for endometrial cancer
- 9% for colorectal cancer
- 6% for melanoma

Based on these risks, the surveillance and management of CS affected individuals is complex and includes colonoscopy and upper GI endoscopy, screening for lesions in the thyroid and the breast [19].

**Conclusions**

The diagnosis of hereditary gastrointestinal polyposis syndromes requires a multidisciplinary approach with good communication between pathologists, gastroenterologists, oncologists and geneticists. Surgical pathologists need to be aware of the broad phenotype of these syndromes, in particular extra-gastrointestinal manifestations (skin) and the types of tumors that affected individuals are at increased risk. In the appropriate clinical setting, pathologists can suggest the possibility of a rare syndrome and should comment on their suspicion in the pathology report while being aware of the non-specific histology of many of these polyps. Searching for clinical clues and combining findings from different pathology reports may lead to the right call and get the probands and family relatives the chance to benefit from the appropriate surveillance and clinical management.
References


Table 1. Summary of the main features of the 6 hereditary gastrointestinal syndromes discussed in this handout.

<table>
<thead>
<tr>
<th></th>
<th>Gene</th>
<th>Prevalence Inheritance</th>
<th>Risk of CRC</th>
<th>Other cancers / Conditions</th>
<th>GI Polyposis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lynch syndrome</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM</td>
<td>1/440</td>
<td>20-60%</td>
<td>Endometrium, hepato-pancreatobiliary tract, stomach, small intestine, urinary tract, brain, ovary, sebaceous</td>
<td>Low number of colonic adenomas</td>
</tr>
<tr>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
<td>1/40,000</td>
<td>100%</td>
<td>Small intestine, stomach, fibromatosis, hepatoblastoma, some brain and thyroid tumours, osteoma</td>
<td>Multiple (&gt;100) colonic adenomas, gastric FGP, SI adenomas</td>
</tr>
<tr>
<td>MUTYH-associated polyposis</td>
<td>MUTYH</td>
<td>1/20,000</td>
<td>70%</td>
<td>Bladder, ovarian, duodenum</td>
<td>Multiple colonic adenomas, some serrated polyps; gastric FGP and duodenal polyps</td>
</tr>
<tr>
<td>Juvenile polyposis syndrome</td>
<td>SMAD4, BMPR1A</td>
<td>1/100,000</td>
<td>40%</td>
<td>Stomach, small intestine / hereditary haemorrhagic telangiectasia</td>
<td>Hamartomatous polyps with inflamed lamina propria and cystic crypts</td>
</tr>
<tr>
<td>Peutz-Jeghers syndrome</td>
<td>STK11 (LKB1)</td>
<td>1/100,000</td>
<td>50%</td>
<td>Small intestine, stomach, pancreas, breast, ovarian, Sertoli cell, sex cord, cervix adenoma malignum / muco-cutaneous pigmentation</td>
<td>Hamartomatous polyps with arborizing smooth muscle</td>
</tr>
<tr>
<td>PTEN hamartoma (Cowden) syndrome</td>
<td>PTEN</td>
<td>1/200,000</td>
<td>9%</td>
<td>Breast, thyroid, kidney, endometrium / macrocephaly, trichilemmomas, and papillomatous papules</td>
<td>Lipoma, ganglieneuroma, lymphoid hyperplasia, juvenile-type gastric polyp</td>
</tr>
</tbody>
</table>
Table 2. Comparison between gastrointestinal polyps in Peutz-Jeghers syndrome and in juvenile polyposis syndrome

<table>
<thead>
<tr>
<th></th>
<th>Peutz-Jeghers syndrome</th>
<th>Juvenile polyposis syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predominant location</strong></td>
<td>Small bowel &gt; large bowel &gt; stomach</td>
<td>Large bowel &gt; stomach &gt; small bowel</td>
</tr>
<tr>
<td><strong>Small bowel polyp</strong></td>
<td>Typical appearance with lobulation and arborizing smooth muscle</td>
<td>Rarely found</td>
</tr>
<tr>
<td><strong>Large bowel polyp</strong></td>
<td>• Smooth surface, non-eroded</td>
<td>• Eroded</td>
</tr>
<tr>
<td></td>
<td>• Normal lamina propria</td>
<td>• Expanded inflamed lamina propria</td>
</tr>
<tr>
<td></td>
<td>• Smooth muscle proliferation</td>
<td>• Rare smooth muscle</td>
</tr>
<tr>
<td></td>
<td>• Lobulation with distorted crypts</td>
<td>• Cystic glands with mucin and neutrophils</td>
</tr>
<tr>
<td><strong>Gastric polyp</strong></td>
<td>Hyperplastic / inflammatory polyp</td>
<td>Hyperplastic / inflammatory polyp</td>
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