Pathology perspective of colonic polyposis syndromes

When are too many polyps too many?

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Pathology Lead, Colon Screening Program
Polyposis syndromes in the CSP?

<table>
<thead>
<tr>
<th># Adenomas (group)</th>
<th>Observations (n)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25014</td>
<td>46.62</td>
</tr>
<tr>
<td>2</td>
<td>12589</td>
<td>23.47</td>
</tr>
<tr>
<td>3</td>
<td>6571</td>
<td>12.25</td>
</tr>
<tr>
<td>4</td>
<td>3575</td>
<td>6.66</td>
</tr>
<tr>
<td>5</td>
<td>2135</td>
<td>3.98</td>
</tr>
<tr>
<td>6</td>
<td>1274</td>
<td>2.37</td>
</tr>
<tr>
<td>7</td>
<td>799</td>
<td>1.49</td>
</tr>
<tr>
<td>8</td>
<td>561</td>
<td>1.05</td>
</tr>
<tr>
<td>9</td>
<td>352</td>
<td>0.66</td>
</tr>
<tr>
<td>10</td>
<td>203</td>
<td>0.38</td>
</tr>
<tr>
<td>11</td>
<td>158</td>
<td>0.29</td>
</tr>
<tr>
<td>12</td>
<td>98</td>
<td>0.18</td>
</tr>
<tr>
<td>13</td>
<td>73</td>
<td>0.14</td>
</tr>
<tr>
<td>14</td>
<td>65</td>
<td>0.12</td>
</tr>
<tr>
<td>15</td>
<td>36</td>
<td>0.07</td>
</tr>
<tr>
<td>16</td>
<td>24</td>
<td>0.04</td>
</tr>
<tr>
<td>17</td>
<td>29</td>
<td>0.05</td>
</tr>
<tr>
<td>18</td>
<td>15</td>
<td>0.03</td>
</tr>
<tr>
<td>19</td>
<td>12</td>
<td>0.02</td>
</tr>
<tr>
<td>20</td>
<td>16</td>
<td>0.03</td>
</tr>
<tr>
<td>20+</td>
<td>51</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Polyposis Syndromes

Inherited risk for colorectal cancer is associated with a number of polyposis syndromes (genes), some of which are well-defined and others are less common. Identification of an unusual number of polyps and/or unusual polyps should prompt consideration of Hereditary Cancer Program referral for polyposis assessment.

Polyposis syndromes/genes include: Familial Adenomatous Polyposis/Attenuated Familial Adenomatous Polyposis (APC), Juvenile Polyposis (SMAD4, BMP15), MutYH-Associated Polyposis (MutYH), Polymerase Proofreading-associated syndrome (POLE/POLD1), Serrated Polyposis syndrome (formerly Hyperplastic Polyposis), and Mixed Polyposis. Peutz-Jeghers syndrome (STK11) and Cowden syndrome (PTEN) are also associated with specific types of polyps.

Polyposis Referral Criteria

Pathology reports, related operative reports and consult letters must be provided with a request for assessment.

Referral of children is appropriate for some polyposis syndromes because it may inform their medical management.

Referral for polyposis assessment should be considered for any person with:

- personal history of:
  - 10 or more adenomatous polyps, OR
  - 2 or more hamartomatous polyps, OR
  - 5 or more serrated polyps proximal to the sigmoid colon (serrated polyps include: hyperplastic polyps, sessile serrated adenomas/polyps, traditional serrated adenomas) OR
  - multiple polyp of different types (adenomatous, hamartomatous, serrated, hyperplastic)
- family history of:
  - a confirmed mutation in a polyposis gene – refer for carrier testing
  - 1 or more close relatives with polyposis (as defined above)
Overdiagnosis in Colorectal Cancer Screening: Time to Acknowledge a Blind Spot

Overdiagnosis is a major harm of any cancer screening test, including breast, prostate, and colorectal cancer screening, and it is an increasing concern. Overdiagnosis may lead to overtreatment, unnecessary medical procedures, and emotional distress for patients.

Three Harms of Overdiagnosis

1. The labelling of individuals as diseased, causing psychosocial harm such as anxiety, or economic consequences related to health care costs or insurance premiums.

2. Additional ineffective or unnecessary medical consequences of the diagnosis, such as intensive surveillance and follow-up (with the risk of more overdiagnosis and exposure to side effects).

3. Overtreatment of the cancer or precancerous condition itself, with all its short-term and long-term risks related to burden, side effects, and complications.

Tests and screening must be evaluated for efficacy, ensuring that any mortality or morbidity is outweighed by the benefits of screening. This includes evaluating the need for more frequent screening in certain populations and considering the potential harms of overdiagnosis.
Polyposis syndromes with predominately adenomas
- Familial adenomatous polyposis
- Attenuated familial adenomatous polyposis
- MUTYH-associated polyposis
- Polymerase proofreading associated polyposis syndrome
- Lynch syndrome (rarely)

Polyposis syndromes with both adenomas and serrated polyps
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Spectrum of polyps in MAP

<table>
<thead>
<tr>
<th>MAP patients (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis in years, mean (SD)</td>
</tr>
<tr>
<td>Total cases of colorectal cancer(^b), n (%)</td>
</tr>
<tr>
<td>New cases of colorectal cancer(^b), n (%)</td>
</tr>
<tr>
<td>Personal history of any neoplasm, n (%)</td>
</tr>
<tr>
<td>Familial history of colorectal cancer or colonic polyps, n (%)</td>
</tr>
<tr>
<td>Polyp number, median (25–75 interquartile range)</td>
</tr>
<tr>
<td>% Polyps &gt;1 cm, median (25–75 interquartile range)</td>
</tr>
<tr>
<td>% Proximal polyps, mean (SD)</td>
</tr>
</tbody>
</table>

Presence of serrated polyps, n (%) 11 (40.75%)

- Type (%)
  - SSA
  - HP 11
- Location (%)
  - Proximal colon 89
  - Distal colon

Dysplasia in polyps (%)
- HGD adenomas 7.4
- Serrated polyps 0

KRAS Gly12Cys mutation (%) 84.6

BRAF V600E mutation (%)
- Adenomas 0
- Serrated polyps 0

SSP from patient with MAP
Classic polyposis (≥100 adenomas, 1457 pts)
- 58% had an APC germline mutation
- 6.5% had biallelic MUTYH germline mutations

Attenuated polyposis (20-99 adenomas, 3253 pts)
- 10% had an APC germline mutation
- 7% had biallelic MUTYH germline mutations

10 to 19 adenomas (970 patients)
- 5% had an APC germline mutation
- 4% had biallelic MUTYH germline mutations

Earlier age at adenoma diagnosis and positive family history associated with increased likelihood of APC and/or MUTYH mutations
Pathologists’ view of lower GI polyposis

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• 4% of patients with familial colorectal cancer X mutations have POLE or POLD1 germline mutations

• 7% of patients with polyposis lacking germline APC or MUTYH mutations have POLE or POLD1 germline mutations

• Sporadic colorectal carcinoma with mutations in POLE have also been reported (~4% of CRC)

Lynch syndrome

• Accounts for 1 of every 35 patients with colorectal carcinoma
• Germline mutations or alterations in DNA mismatch repair (MMR) genes:
  – *MLH1* (~35-40%)
  – *MSH2* (~40%)
  – *MSH6* (~10-15%)
  – *PMS2* (~5-10%)
• Deletions in *EPCAM/TACSTD1* (~2%)
  • Result epigenetic silencing of the *MSH2* gene by hypermethylation and loss of MSH2 and MSH6 expression
Lynch syndrome

<table>
<thead>
<tr>
<th>No. of adenomas</th>
<th>Patients with a germline mutation</th>
<th>Patients with a VUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>2-5</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td>6-9</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>≥10</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>70</td>
<td>13</td>
</tr>
<tr>
<td>Amsterdam I/II compliant families</td>
<td>59</td>
<td>11</td>
</tr>
</tbody>
</table>

- 11/83 had ≥ 10 adenomas (13%)
- Maximum synchronous polyps = 22
- Maximum metachronous polyps = 24

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### Polyp landscape in SPS


#### TABLE 1. Characteristics of 100 Patients With Serrated Polyposis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment sites</td>
<td></td>
</tr>
<tr>
<td>Australia</td>
<td>40/100</td>
</tr>
<tr>
<td>New Zealand</td>
<td>28/100</td>
</tr>
<tr>
<td>USA</td>
<td>26/100</td>
</tr>
<tr>
<td>Canada</td>
<td>6/100</td>
</tr>
<tr>
<td>Sex</td>
<td>58% female</td>
</tr>
<tr>
<td>Age of diagnosis (y)</td>
<td>Mean 47.7; SD 14.3; median 50; range 17-69</td>
</tr>
<tr>
<td>WHO criteria 2010</td>
<td></td>
</tr>
<tr>
<td>Criterion 1</td>
<td>12/100</td>
</tr>
<tr>
<td>Criterion 3</td>
<td>72/100</td>
</tr>
<tr>
<td>Criterion 1 and 3</td>
<td>16/100</td>
</tr>
<tr>
<td>Total polyp count</td>
<td>Mean 45.1; SD 32.6; median 30; range 6-150</td>
</tr>
<tr>
<td>Polyp distribution</td>
<td></td>
</tr>
<tr>
<td>Pancolic</td>
<td>75/84 (89%)</td>
</tr>
<tr>
<td>Mostly proximal</td>
<td>6/84 (7%)</td>
</tr>
<tr>
<td>Mostly distal</td>
<td>3/84 (4%)</td>
</tr>
<tr>
<td>CRC present</td>
<td>39/93 (42%)</td>
</tr>
<tr>
<td>Conventional adenoma present</td>
<td>64/80 (80%)</td>
</tr>
</tbody>
</table>

### TABLE 2. Histologic Types of 406 Polyps Reviewed in Patients With Serrated Polyposis

<table>
<thead>
<tr>
<th>Polyp</th>
<th>N</th>
<th>Location in Proximal Colon, n (%)</th>
<th>Size (mm), Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional adenoma—total</td>
<td>69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular adenoma, low-grade dysplasia</td>
<td>54</td>
<td>27/38 (71%)</td>
<td>3.8 ± 3.3</td>
</tr>
<tr>
<td>Tubular adenoma, high-grade dysplasia</td>
<td>1</td>
<td>0/1 (0%)</td>
<td>10</td>
</tr>
<tr>
<td>Tubulovillous adenoma, low-grade dysplasia</td>
<td>11</td>
<td>1/4 (25%)</td>
<td>9.8 ± 5.4</td>
</tr>
<tr>
<td>Tubulovillous adenoma, high-grade dysplasia</td>
<td>3</td>
<td>1/3 (33%)</td>
<td>9.7 ± 3.9</td>
</tr>
<tr>
<td>Serrated polyps—total</td>
<td>337</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microvesicular HP</td>
<td>156</td>
<td>47/132 (36%)</td>
<td>3.2 ± 1.8</td>
</tr>
<tr>
<td>Goblet cell HP</td>
<td>25</td>
<td>7/22 (32%)</td>
<td>3 ± 1.6</td>
</tr>
<tr>
<td>SSA/P</td>
<td>110</td>
<td>55/86 (64%)</td>
<td>4.9 ± 2.6</td>
</tr>
<tr>
<td>SSA/P, low-grade dysplasia</td>
<td>22</td>
<td>11/20 (55%)</td>
<td>5.4 ± 2.6</td>
</tr>
<tr>
<td>SSA/P, high-grade dysplasia</td>
<td>6</td>
<td>4/5 (80%)</td>
<td>5.7 ± 2.9</td>
</tr>
<tr>
<td>TSA</td>
<td>18</td>
<td>12/17 (70%)</td>
<td>8.1 ± 5.4</td>
</tr>
</tbody>
</table>
Polyposis syndromes with predominately adenomas
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Hamartomatous polyps/polyposis

• Terms that are have been used for hamartomatous polyps
  – Peutz-Jeghers polyp (most specific term: rarely used in the colon)
  – Juvenile polyp
  – Inflammatory polyp

• Individually Juvenile polyps are identical to sporadic inflammatory polyps
  – When there are multiple “inflammatory polyps” raising possibility of polyposis I simply say simply say “hamartomatous/inflammatory polyps” instead of juvenile polyp as these type of polyps can be seen in many polyposis syndromes

• Both Juvenile/inflammatory polyps and PJ-polyps can be confused with mucosal prolapse polyps

\textit{PTEN} Hamartoma Tumor Syndrome

• Has been referred to as Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS)
• Autosomal dominant
• \textit{PTEN} (10q22-23) tumor suppressor gene
  — Regulates cell cycle, apoptosis, and angiogenesis
*PTEN* Hamartoma Tumor Syndrome

- 1 in 200,000 individuals
- Mutation in *PTEN* gene
- Increased cancer risk
- Intestinal polyposis
  - Upper and lower GI tract

Polyp types in PHTS

- Mixture of polyp types
- Pan GI polyps (colon predominance)
- ~40% had >50 colon polyps
- Hamartomatous polyps were present in all cases

<table>
<thead>
<tr>
<th>Characteristic Features of specific hamartomatous polyp types</th>
<th>PTHS</th>
<th>Peutz-Jeghers syndrome</th>
<th>Juvenile polyposis</th>
<th>Sporadic hamartomatous polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Usually colon</td>
<td>Small or large bowel</td>
<td>Usually colon</td>
<td>Almost always colon</td>
</tr>
<tr>
<td><strong>Mean size</strong></td>
<td>Small (mean, 0.4 cm)</td>
<td>Small (mean, 0.5 cm)</td>
<td>Large (mean, 1.1 cm)</td>
<td>Medium (mean, 0.7 cm)</td>
</tr>
<tr>
<td><strong>Architecture</strong></td>
<td>Sessile</td>
<td>Exophytic</td>
<td>Exophytic</td>
<td>Exophytic</td>
</tr>
<tr>
<td><strong>Erosion</strong></td>
<td>Almost never</td>
<td>Almost never</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Lamina propria</strong></td>
<td>Expanded, fibrotic</td>
<td>Expanded, edematous and fibrotic</td>
<td>Expanded, strikingly edematous and fibrotic</td>
<td>Expanded, fibrotic</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>Mild chronic</td>
<td>Marked chronic active</td>
<td>Marked chronic active with granulation tissue</td>
<td>Marked chronic active with granulation tissue</td>
</tr>
<tr>
<td>Cystic glands</td>
<td>Least occurrence</td>
<td>Common</td>
<td>Almost always</td>
<td>Almost always</td>
</tr>
<tr>
<td>Thick mucin</td>
<td>No</td>
<td>Common</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Smooth muscle proliferation</td>
<td>Mild</td>
<td>Highest level</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Lymphoid follicles</td>
<td>Common</td>
<td>No</td>
<td>Occasionally</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Ganglion cells</td>
<td>Rare</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Nerve fibers</td>
<td>Rare</td>
<td>No</td>
<td>No</td>
<td>Very rare</td>
</tr>
<tr>
<td>Mucosal fat</td>
<td>Rare</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Cronkhite-Canada syndrome

- **SPORADIC polyposis syndrome**
  - 50-80 years of age
  - Males > Females
- Polyps involve stomach, small bowel, and colorectum
- Polyps described as hamartomas BUT
  - Strikingly edematous lamina propria
  - Cystically dilated epithelial structures
  - May have abundant accompanying inflammation
    - Mucosal eosinophilia, withered crypts, apoptosis
- Atrophy and edema in non-polyp mucosa

Dermatologic manifestations

- Alopecia
- Nail dystrophy (thinning, splitting, shedding)
- Skin hyperpigmentation

Variety of other clinical features

- Cataracts
- Thrombosis
- Heart failure
- Psychiatric disorders

Generally poor survival (50% at 5 years)

- May be able to induce remission with immunosuppression
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