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Recent Discoveries in the Genetics of Familial Colorectal Cancer and Polyposis

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Overgrowth of cells & tissues that are native to the anatomic location (Greek = mistake/defect)
HAMARTOMATOUS POLYPEPOSES

INTRODUCTION

1. RARE

2. OUR CENTRE HAS AN INTEREST IN FAMILIAL CRC, HOWEVER THERE ARE ONLY A SMALL NUMBER OF THESE FAMILIES IN THE CLINICS

3. SPAN THE PAEDIATRIC & ADULT RANGE

4. THESE POLYPS CAN POSE DIAGNOSTIC DIFFICULTY. INTER-OBSERVER REPRODUCIBILITY IS NOT PERFECT

5. THERE IS A DIFFERENTIAL DIAGNOSIS WITH OTHER SYNDROMIC POLYPS & WITH SPORADIC POLYPS

6. AN OVERLAP OF POLYPS OCCURS BETWEEN SYNDROMES (PTEN, JPS)
What would you do next? 

Differential Diagnosis

- Adenocarcinoma
- Epithelial Misplacement in a PJ Polyp

Investigations

- IHC
- Literature Review
- Second/expert opinion
Dual pan cytokeratin/D2-40 IHC
p53 = wild type pattern
Epithelial Misplacement in Peutz-Jeghers Polyps
A Diagnostic Pitfall

TABLE 1. Epithelial misplacement in all 40 Peutz-Jeghers patients

<table>
<thead>
<tr>
<th>Site</th>
<th>Polyps examined</th>
<th>No. polyps</th>
<th>SM(^a) only</th>
<th>MP(^b) only</th>
<th>Serosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>88</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Duodenum</td>
<td>36</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Jejunum and ileum</td>
<td>202</td>
<td>29</td>
<td>11</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>163</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Totals</td>
<td>491</td>
<td>30</td>
<td>11</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

\(^a\) submucosa.
\(^b\) muscularis propria.

**Bottom line:**
Misplacement only seen in small intestinal polyps with a prevalence rate of 10%

**FIG. 1.** Epithelial misplacement in a jejunal polyp, 11.2 cm in diameter, in a 17-year-old male patient with Peutz-Jeghers syndrome. There is a mucinous cyst in the serosa (arrow), with retraction of the intestinal wall into the base of the polyp.

**FIG. 2.** A jejunal polyp from an 18-year-old female patient with Peutz-Jeghers syndrome. Epithelial misplacement is present in all layers of the bowel wall. A villous configuration is easily discerned. Inset: Macroscopic appearance of the polyp. It measures 1.6 cm in diameter.
I do not think any pathologist could entirely rule out that this represents very well differentiated mucinous adenocarcinoma. In making this diagnosis one is making a dual diagnosis of epithelial misplacement & cancer which in this instance lacks logic.

ON THE BALANCE OF PROBABILITIES, I THINK THIS IS ALL EPITHELIAL MISPLACEMENT
Outcome

- Patient alive & well, September 2019 (16 months)

Whole exome sequencing is being performed to compare this lesion with another uncomplicated PJ polyp in the same patient. Analysis is ‘ongoing’.
Peutz-Jeghers Syndrome

OVER EEN ZEER MERKWAARDIGE, GECOMBI-NEERDE FAMILIAIRE POLYPOSIS VAN DE SLIJMVLIEZEN VAN DEN TRACTUS INTESTINALIS MET DIE VAN DE NEUSKEELHOLTE EN GEPAAARD MET EIGENAARDIGE PIGMENTATIES VAN HUID- EN SLIJMVLIEZEN.

DOOR

J. L. A. PEUTZ,
1e geneesheer van het ziekenhuis.


Peutz-Jeghers syndrome (PJS)

- Autosomal dominant inheritance (complete penetrance) 1: 80,000
- Polyps can occur throughout GI, but small intestine is main site of predilection
- Gene STK11/ LKB1 (p53-mediated apoptosis) encoding a serine/threonine kinase on chromosome 19p13.3 (cancer risk does not vary by type of mutation)
- 40% lifetime risk CRC after the age of 50.
- 95% risk of developing malignancy by age 65.
  - Carcinomas of pancreas (36%), stomach (29%), small intestine (13%),
  - Breast (54%), ovary (21%), endometrium (9%)
  - Lung cancer (15%).
Clinical presentation

- Surgical emergency
- Childhood intussusception
- Obstruction
- Bleeding PR
- Volvulus

- Non-specific abdominal pain
Peutz-Jeghers polyps
Peutz-Jeghers polyps
Frond-like pattern – arborization with smooth muscle
Cystic gland dilatation +/- into deep layers
Can show dysplasia but rare
DDX

- Juvenile Polyposis
- Hereditary Mixed Polyposis

Surveillance regimes are intensive.
Main aim: reduce intussusception in childhood & remove polyp.
GUT INFLAMMATION

LKB1 deficiency in T cells promotes the development of gastrointestinal polyposis


TUMORIGENESIS

Inflamed T cells and stroma drive gut tumors

Loss of a tumor suppressor in T cells and stromal cells drives gastrointestinal polyp growth

Pablo E. Hollstein and Reuben J. Shaw
Juvenile Polyposis

- A familial cancer syndrome with autosomal dominant trait
- The average onset is 18 years.
- Approximately half of cases arise in patients with no family history (de novo)
- Germline mutations involve the TGF-β signal transduction pathway
  - SMAD-4 gene on 18q21.1 (40%)
  - BMPR1A on 10q22.3 (40%)
Juvenile Polyposis

- Affects 1:100,000
- 5 - 200 colorectal polyps
- Congenital anomalies in 15% (macrocephaly & dystonia)
- Significant risk of CRC
  - From around 20y and increases in the 4th decade of life
  - Lifetime risk of CRC is up to 68% by age 60
  - Gastric cancer 15–21%
  - Small intestinal carcinoma 10%
- Two groups
  - JPS (pure)
  - JPS + other features
    - Hereditary haemorrhagic telangiectasia (HHT) or congenital conditions
Juvenile Polyposis

Diagnostic criteria:

3-5 juvenile polyps in colorectum

or

juvenile polyps throughout GI tract

or

juvenile polyp(s) + family history
Typical polyps of juvenile polyposis

POLYP SITES

GASTRIC ONLY = 36%

GASTRIC & INTESTINE = 27%

COLORECTUM ONLY 36%

CANCERS FOLLOW POLYP DISTRIBUTION
Juvenile Polyposis Genetics
(mutation found in 50%)

- **SMAD4**: 40% of families
  - recurrent ‘hotspot’ mutation, 1372–1375delACAG, accounts for about half of SMAD4 cases
  - 20% of individuals with a SMAD4 mutation develop JPS/Hereditary Haemorrhagic Telangiectasia (HHT)

- **BMPR1A**: 40% of families

- **NO EXTRAINTESTINAL CANCER RISK**
Juvenile Polyposis

CLINICAL PRESENTATION

INFANTS
GI BLEEDING,
INTUSSUSCEPTION,
RECTAL PROLAPSE,
PROTEIN-LOSING ENTEROPATHY,
15% CONGENITAL BIRTH DEFECT

ADULTS
GI BLEEDING,

ENDOSCOPY: SMOOTH, SPHERICAL,
‘RED HEAD’ ON A STALK 5-50mm

PATHOLOGY: MUCIN-FILLED CYSTIC DILATATION OF EPITHELIAL TUBULES IN AN INFLAMED LAMINA PROPRIA. ABSENCE OF SMOOTH MUSCLE PROLIFERATION
Juvenile Polyposis
DIFFERENTIAL DIAGNOSIS

- OTHER INFLAMMATORY POLYPS
  - IBD-ASSOCIATED

- PROLAPSE-ASSOCIATED POLYP
  - INFLAMMATORY CAP POLYP
  - INFLAMMATORY CLOACOGENIC POLYP
  - SOLITARY RECTAL ULCER SYNDROME
  - DIVERTICULAR-ASSOCIATED POLYPS

- CRONKITE-CANADA SYNDROME

- INFLAMMATORY MYOGLANDULAR POLYP (AJSP 1992;16; 772).
Juvenile Polyposis
SINGLE VS MULTIPLE CONUNDRUM

- Relatively common (1% children/adolescents)

- ISOLATED – NO MALIGNANT POTENTIAL

- Almost exclusively distal colon & rectum

- Small bowel Juvenile Polyp = likely Syndrome

- MORE FROND-LIKE, LESS STROMA, FEWER DILATED GLANDS, & MORE PROLIFERATION THAN SYNROMIC POLYPS (not reproducible)
Clinical History & Pathology

- 67 year old male (now)
- Multiple colorectal polyps over a 26 year period with a total of 19 adenomas & 5 juvenile polyps

Working diagnosis = Attenuated FAP until juvenile polyp appeared
Hereditary mixed polyposis syndrome due to a **BMPRIA** mutation

**Mixed Juvenile & adenomatous polyposis**

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**Figure 1** Diagram showing the important elements of the BMP signalling pathway which is closely related to the TGF-β pathway, an important pathway in the inhibition of cell growth. Both pathways share a common signalling element, SMAD4. Germline mutations of SMAD4 and BMPRIA genes have been associated with JPS and HMPS.
Figure 2  Family pedigree and relationship of *BMPR1A* gene mutation.
Hereditary Mixed Polyposis Syndrome: HMPS

Adenoma with serrated features

Mixed hyperplastic – adenomatous polyp

Mixed juvenile-hyperplastic-adenoma

Courtesy: Dr Ian Frayling & Prof. Ian Tomlinson


Clinical History

- 38 year old female
- Episodes of rectal bleeding
- Polyposis, colorectal (15 -20 polyps, 0.5 – 1cm)
PATHOLOGY

Mucosal ganglioneuroma and leiomyoma x2
PTEN (PHOSPHATASE & TENSIN HOMOLOG) HAMARTOMA TUMOUR SYNDROME (PHTS)

- Autosomal dominant (1/200,000 underestimate)

  Incorporates /replaces Cowden syndrome (CS)
  Bannayan-Riley-Ruvalcaba (BRR) syndrome,
  Adult Lhermitte-Duclos syndrome
  Autism spectrum disorders associated with macrocephaly

- Majority of clinical data is on CS (only 35% with clinical criteria have PTEN mutation)
Consensus diagnostic criteria for CS were initially established in 1996 by an international research consortium. This was prior to identification of the CS gene and the criteria were based upon early clinical experience published in the literature, with their inherent ascertainment biases [14]. The single largest patient series in any of these reports comprised 21 patients [15]. It was not until 2013 that an evidence-based review led to a significant revision of the diagnostic criteria (summarized in Table 1), which were then adopted by the U.S. National Comprehensive Cancer Network [16,17].

Table 1. Revised PTEN hamartoma tumor syndrome (PHTS) diagnostic criteria.

<table>
<thead>
<tr>
<th>Revised PTEN Hamartoma Tumor Syndrome (PHTS) Clinical Diagnostic Criteria [16,17]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Operational Diagnosis in an Individual (either of the following):</strong></td>
</tr>
<tr>
<td>(1) Three or more major criteria, but one must include macrocephaly, Lhermitte–Duclos disease, or gastrointestinal hamartomas; OR</td>
</tr>
<tr>
<td>(2) Two major and three minor criteria;</td>
</tr>
<tr>
<td><strong>Operational Diagnosis in a Family where One Individual Meets Revised PHTS Clinical Diagnostic Criteria or Has a PTEN Mutation:</strong></td>
</tr>
<tr>
<td>(1) Any two major criteria with or without minor criteria; OR</td>
</tr>
<tr>
<td>(2) One major and two minor criteria; OR</td>
</tr>
<tr>
<td>(3) Three minor criteria</td>
</tr>
<tr>
<td><strong>Major Criteria</strong></td>
</tr>
<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>Endometrial cancer (epithelial)</td>
</tr>
<tr>
<td>Thyroid cancer (follicular)</td>
</tr>
<tr>
<td>Gastrointestinal hamartomas (including ganglioneuromas, but excluding hyperplastic polyps) (≥3)</td>
</tr>
<tr>
<td>Lhermitte–Duclos disease (LDD), adult</td>
</tr>
<tr>
<td>Macrocephaly (≥97 percentile)</td>
</tr>
<tr>
<td>Macular pigmentation of the glans penis</td>
</tr>
<tr>
<td>Multiple mucocutaneous lesions (any of the following):</td>
</tr>
<tr>
<td>Multiple trichilemmomas (≥3), at least one biopsy proven</td>
</tr>
<tr>
<td>Acr al keratoses (≥3) palmoplantar keratotic pits and/or acral hyperkeratotic papules</td>
</tr>
<tr>
<td>Mucocutaneous neuromas (≥3)</td>
</tr>
<tr>
<td>Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy-proven OR dermatologist-diagnosed</td>
</tr>
<tr>
<td><strong>Minor Criteria</strong></td>
</tr>
<tr>
<td>Autism spectrum disorder</td>
</tr>
<tr>
<td>Colon cancer</td>
</tr>
<tr>
<td>Esophageal glycogenic acanthosis (≥3)</td>
</tr>
<tr>
<td>Lipomas (≥3)</td>
</tr>
<tr>
<td>Mental retardation (i.e., Intelligence Quotient (IQ) ≤ 75)</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Testicular lipomatosis</td>
</tr>
<tr>
<td>Thyroid cancer (papillary or follicular variant of papillary)</td>
</tr>
<tr>
<td>Thyroid structural lesions (e.g., adenoma, multinodular goiter)</td>
</tr>
<tr>
<td>Vascular anomalies (including multiple intracranial developmental venous anomalies)</td>
</tr>
</tbody>
</table>
CLINICAL SYNDROME

- Multiple hamartomas of skin (trichilemmomas), GIT & soft tissues (angiomas, fibromas, lipomas)
- Benign thyroid disease
- Macrocephaly
- Dysplastic gangliocytoma of cerebellum
- Learning difficulties

- GI polyps: characteristic

- Cancer risk high for breast, follicular thyroid, endometrium, renal carcinomas

- The risk for colorectal cancer is ‘only’ 9% but occurs at a younger age.
  - Colonoscopy 2-yearly from 40 years

Trichilemmomas

Acral keratoses

Papillomatosis of the gums

Lingual papillomatosis

Courtesy: Prof. Frédéric Caux, Hôpital Avicenne, Bobigny
PTEN/ Cowden Syndrome

- Large bowel Ganglioneuroma (characteristic)

Additional Polyps in PTEN

- Leiomyoma
- Juvenile polyp
- Hyperplastic polyp
- Adenoma
- Lymphoid polyps
## PTEN Syndrome GI POLYPS SPECIFIC FEATURES

### Table 3: Characteristic features of specific hamartomatous polyp types

<table>
<thead>
<tr>
<th>Feature</th>
<th>CS</th>
<th>PJS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Usually colon</td>
<td>Small or large</td>
</tr>
<tr>
<td>Mean size</td>
<td>Small (mean, 0.4 cm)</td>
<td>Small (mean, 0.3 cm)</td>
</tr>
<tr>
<td>Architecture</td>
<td>Sessile</td>
<td>Exophytic</td>
</tr>
<tr>
<td>Erosion</td>
<td>Almost never</td>
<td>Almost never</td>
</tr>
<tr>
<td>Lamina propria</td>
<td>Expanded, fibrotic</td>
<td>Expanded, edematous and fibrotic</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Mild chronic</td>
<td>Marked chronic</td>
</tr>
<tr>
<td>Cystic glands</td>
<td>Least occurrence</td>
<td>Common</td>
</tr>
<tr>
<td>Thick mucin</td>
<td>No</td>
<td>Common</td>
</tr>
<tr>
<td>Smooth muscle proliferation</td>
<td>Mild</td>
<td>Highest level</td>
</tr>
<tr>
<td>Lymphoid follicles</td>
<td>Common</td>
<td>No</td>
</tr>
<tr>
<td>Ganglion cells</td>
<td>Rare</td>
<td>No</td>
</tr>
<tr>
<td>Nerve fibers</td>
<td>Rare</td>
<td>No</td>
</tr>
<tr>
<td>Mucosal fat</td>
<td>Rare</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: CS, Cowden syndrome; PJS, Peutz-Jeghers syndrome; JuvPS, juvenile polyposis syndrome.

\[n = 375 \text{ polyps}\]

\[\text{CS} = 15 \text{ pts}\]

\[\text{PJP} = 13 \text{ pts}\]

\[\text{JPS} = 12 \text{ pts}\]

\[\text{Sporadic} = 32 \text{ pts}\]
1. Increased susceptibility to infection
2. Increased frequency of auto-immune disease
3. Increased cancer risk: may be partly due to an immune tolerant tumour microenvironment
TAKE HOME MESSAGES

• **POLYPECTOMY** (vs BIOPSY) ADVISED FOR DEFINITE DIAGNOSIS

• **PJP**: BEWARE EPITHELIAL MISPLACEMENT

• **PJP & PTEN HAMARTOMA SYNDROME**: HIGH RISK OF EXTRAINTESTINAL CANCER

• **JUVENILE POLYPOSIS**: MAIN RISK IS GI CANCERS. REMEMBER HHT

• **CORRELATE POLYP HISTOLOGY WITH CLINICAL & ENDOSCOPIC FINDINGS AT ALL TIMES**
TAKE HOME MESSAGES

• EMBRACE THE ROLE OF THE PATHOLOGIST IN THE DIAGNOSIS OF HEREDITARY CANCER

• GERMLINE TESTING IS BECOMING MORE SENSITIVE & SPECIFIC FOR PRECISE SYNDROMIC DIAGNOSIS

• CLINICAL CRITERIA REMAIN VALID IN MANY CASES

• NEW THERAPEUTIC OPTIONS MAY APPEAR IN THE FUTURE


How to Screen for Hereditary Cancers in General Pathology Practice

Brandon S. Sheffield, MD; Veronica Hirsch-Reinshagen, MD; Kasmintan A. Schrader, MBBS, PhD, FRCPC
ACKNOWLEDGEMENT

- Centre for Colorectal Disease, SVUH, Dublin
- Medical & Lab staff, SVUH
- Dr Ian Frayling, Cardiff
- Prof Neil Shepherd, Cheltenham, UK
### Peutz-Jeghers Syndrome

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk ratio (95% CI)</th>
<th>Frequency (%)</th>
<th>Mean age (y)</th>
<th>Age range (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oesophagus</td>
<td>57 (2.5-557)</td>
<td>0.5</td>
<td>67</td>
<td>-</td>
</tr>
<tr>
<td>Stomach</td>
<td>213 (96-368)</td>
<td>29</td>
<td>30</td>
<td>10-61</td>
</tr>
<tr>
<td>Small bowel</td>
<td>520 (220-1306)</td>
<td>13</td>
<td>42</td>
<td>21-84</td>
</tr>
<tr>
<td>Colon</td>
<td>84 (47-137)</td>
<td>39</td>
<td>46</td>
<td>27-71</td>
</tr>
<tr>
<td>Pancreas</td>
<td>132 (44-261)</td>
<td>36</td>
<td>41</td>
<td>16-60</td>
</tr>
<tr>
<td>Lung</td>
<td>17 (5.4-39)</td>
<td>15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Testis</td>
<td>4.5 (0.12-25)</td>
<td>9</td>
<td>8.6</td>
<td>3-20</td>
</tr>
<tr>
<td>Breast</td>
<td>15.2 (7.6-27)</td>
<td>54</td>
<td>37</td>
<td>9-48</td>
</tr>
<tr>
<td>Uterus</td>
<td>16 (1.9-56)</td>
<td>9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ovary</td>
<td>27 (7.3-68)</td>
<td>21</td>
<td>28</td>
<td>4-57</td>
</tr>
<tr>
<td>Cervix</td>
<td>1.5 (0.31-4.4)</td>
<td>10</td>
<td>34</td>
<td>23-54</td>
</tr>
</tbody>
</table>