Evaluating gastric polyps and understanding genetic risks for gastric cancer

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Disclosures

CPP Pharma (clinical trial)
SLA Pharma (advisor)

Neither relevant to this talk
Stomach Polyps and Cancer Risk

Scope:
- Usual gastric polyps
- Familial syndromes, including HDGC
- Little or nothing about NET, GIST
Fundic Gland Polyps
Fundic Gland Polyps

Size: small (1-5 mm)

Number: usually multiple

Appearance: sessile, shiny and translucent

Background mucosa: typically normal
Fundic Gland Polyps and PPI Use

Jalving: Alim Pharm & Ther ’06; 24:1341
Figure 2. Haematoxylin and eosin-stained tissue sections of fundic gland polyps (FGPs). (a) FGP from a patient who had never used proton pump inhibitors (PPIs) showing a few small cysts (arrow), original magnification – 40×. (b) FGP from a patient with more than 1 year of PPI use showing a large number of cysts (arrow), original magnification – 40×. (c) FGP from a patient with more than 1 year of PPI use showing parietal cell hyperplasia and parietal cell protrusions (arrow), original magnification – 100×. (d) FGP from a patient with more than 1 year of PPI use showing parietal cell hyperplasia and parietal cell protrusions (arrow), original magnification – 400×.
Hyperplastic Polyps
Hyperplastic Polyps

Location: more common in the antrum

Size: generally less than 20 mm

Number: solitary (66%)/multiple (33%)

Appearance: sessile or pedunculated.
- Small lesions: smooth surface.
- Larger lesions: superficial erosion

Background mucosa: inflammation, atrophic/chronic gastritis and intestinal metaplasia with H. pylori infection common. Thus, inflammatory and hyperplastic polyps constituted a spectrum—-inflammatory where infiltrate predominates, and “hyperplastic” when foveolar glandular proliferation predominates.

Shaib, Rugge, Graham & Genta: CGH ’13; 11:1374
Castro: Best Pract & Res Clin Gast ’17; 31:381
Hyperplastic Polyps

Excellent overview and synthesis of endoscopy and pathology

Shaib, Rugge, Graham & Genta: CGH ’13; 11:1374
Hyperplastic Polyps

Shaib, Rugge, Graham & Genta: CGH ’13; 11:1374
Hyperplastic Polyps

Figure 3. (A) Hyperplastic polyp with focus of high-grade dysplasia. (B) Multiple sections from this 3-cm hyperplastic polyp revealed an area with dysplastic epithelial cells forming complex glandular structures. These represent high-grade dysplasia or possibly a focus of intramucosal carcinoma.
Hyperplastic Polyps

Shaib et al would consider all polyps in inflammatory-hyperplastic spectrum as “hyperplastic”

They would remove all >1cm and would in such cases sample surrounding mucosa (severity of gastritis and/or atrophy, which are generally present)

Shaib, Rugge, Graham & Genta: CGH ’13; 11:1374
Hyperplastic Polyps

Sampling of adjacent mucosa:

Establishes OLGA: “Operative Link for Gastritis Assessment”, though no consensus as to surveillance, if any, when IM found

Shaib, Rugge, Graham & Genta: CGH ’13; 11:1374
Gastric Adenoma

Shaib, Rugge, Graham & Genta: CGH '13; 11:1374
Gastric Adenoma

Location: Predominantly in antrum

Size: variable

Number: solitary (>80%)

Appearance: sessile or flat with velvety lobulated surface

Background mucosa: chronic atrophic gastritis

with intestinal metaplasia is common---essentially the same settings in which hyperplastic polyps occur

Shaib, Rugge, Graham & Genta: CGH ’13; 11:1374
Castro: Best Pract & Res Clin Gast ’17; 31:381
FAP
Fundic Gland Polyps
Presence and extent of FGPs in FAP poorly predictive of duodenal involvement
Presence and extent of duodenal adenomas in FAP poorly predictive of FGPs
Stomach evaluation

- FGPs nearly universal
- Sample FGPs occasionally
- Expect focal surface foveolar dysplasia
- Cancer from FGPs rare but may be increasing
- Uncertain risk/benefit from removing FGP >1cm--I don’t unless progressive dysplasia
- Polyps in antrum rare, much more likely adenoma
I cannot stress enough the importance of familiarity with and intensive review of pathology with a good GI pathologist!!
• No St Ca at CCF 1979-2006
• 10/767 with St ca since ‘06
• Despite surveillance, polypectomy
Rarely, dysplasia in FGPs can progress to invasive cancer. The number of polyps and confluence makes endoscopic management virtually impossible.
Adenoca in confluent FGPs
47 yo woman CRC X2 w >1000 adenomas in 2009
Gastric Adenoca and Proximal Polyposis of Stomach (GAPPS)

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome

D L Worthley,1 K D Phillips,2 N Wayte,3 K A Schrader,4 S Healey,5 P Kaurah,4 A Shulkes,6 F Grimpen,7 A Clouston,7 D Moore,8 D Cullen,9 D Ormonde,9 D Moundley,10 X Wen,11 N Lindor,12 F Carneiro,11 D G Huntsman,4 G Chenevix-Trench,5 G K Suthers2,13

• Dominant pattern in 3 families, youngest ca @ 33
• No colon polyps
• No APC mutation (but see next)

Worthley: Gut ’12; 61:774
Gastric Adenoca and Proximal Polyposis of Stomach (GAPPS)

3 point mutations in APC promoter 1b in each of 6 families

Li: A J Hum Genet ’16; 98:830
Peutz-Jeghers Syndrome

• Mutations in tumor suppressor STK 11 gene on chromosome 19p13
• Hyperpigmented macules, GI hamartomas (may onset w intussusception in teens)
• Increased risk of GI, breast, thyroid lung, pancreatic, uterine Ov/testicular ca
• Lifelong endoscopic & pancreas surveillance
  – ? Role of capsule endoscopy surveillance
Peutz Jeghers: Stomach
Peutz Jeghers: Stomach
Hyperplastic polyp
High grade dysplasia with cribriforming of glands
Focus of intramucosal adenocarcinoma/ invasion into lamina propria in a background of hyperplastic polyp
Juvenile Polyposis Syndrome

- Clinical diagnosis (Jass criteria); intestinal hamartomas
- Mutations in 40 – 60% of patients (BMPR1A, SMAD4)
- Modestly increased risk of colorectal and gastric cancer (SMAD4)
- Anemia >> gastrectomy in some (SMAD4)
- Lifelong endoscopic (annual / ? two years colonoscopy +/- EGD)
- HHT in SMAD4
Juvenile Polyposis
So far, emphasis upon polyps and their risk of cancer, and upon familial/genetic susceptibility to such polyps, but what about susceptibility to stomach cancer in the absence of polyps???
Diffuse Gastric Cancer

- “linitis plastica”
- Typically lacking identifiable lesion
- Poor prognosis
- Early diagnosis rare
- Familial reports date back decades
Hereditary Diffuse Gastric Cancer (HDGC)
Diffuse Gastric Carcinoma

Original E-Cadherin Linkage Discovery

• New Zealand Maori family identified in 1964 with > 25 cases of stomach ca
• “Candidate gene” approach (CDH1 suspected as it is often somatically mutated in DGC)
• Max lod score 5.04 at D162752
• Sequence analysis: G>T transversion exon 7 in 2 affected, 4 obligate carriers
• Mutation in CDH1 found in 2 other families
• Breast cancer (lobular) association in another

Guilford: Nature ’98; 392:402
Guilford: Hum Mut ’99; 14:249
Hereditary Diffuse Gastric Cancer (HDGC)

- Due to high risk of diffuse gastric cancer in CDH1 carriers, prophylactic total gastrectomy only effective treatment at present
- Presurgical EGD typically done with multiple (eg >50) biopsies
- No known surface epithelial clues
- No known role for EUS, other imaging
HDGC testing criteria

1. Two or more documented cases of gastric cancer at any age in first-degree or second-degree relatives, with at least 1 confirmed diffuse gastric cancer

2. Personal history of diffuse gastric cancer before the age of 40 years

3. Personal or family history (first-degree or second-degree relatives) of diffuse gastric cancer and lobular breast cancer, 1 diagnosed before the age of 50 years

Van der Post: J Med Genet ’15; 52:361
Yield of CDH-1 mutation testing:

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Families tested, n</th>
<th>Mutations</th>
<th>Mutation detection rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meeting HDGC criteria 2010&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 gastric cancer cases, 1 DGC &lt; 50 y</td>
<td>53</td>
<td>8</td>
<td>15.1</td>
</tr>
<tr>
<td>≥3 DGC at any age</td>
<td>10</td>
<td>5</td>
<td>50.0</td>
</tr>
<tr>
<td>1 DGC &lt; 40 y</td>
<td>41</td>
<td>2</td>
<td>4.9</td>
</tr>
<tr>
<td>Personal or family history of DGC and LBC, 1 &lt; 50 y</td>
<td>14</td>
<td>1</td>
<td>7.1</td>
</tr>
<tr>
<td>Not meeting HDGC criteria 2010&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DGC and/or LBC, not meeting HDGC criteria&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38</td>
<td>1</td>
<td>2.6</td>
</tr>
<tr>
<td>Combined DGC, IGC, and/or MGC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>31</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>(Familial) IGC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>67</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Personal and/or family history of LBC&lt;sup&gt;c&lt;/sup&gt;</td>
<td>22</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Other</td>
<td>78</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Incomplete clinicopathologic data for HDGC criteria 2010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index with DGC or LBC, incomplete pathology data of relatives</td>
<td>77</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Index without gastric or breast cancer (FDR), family meets HDGC criteria</td>
<td>25</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Index without gastric or breast cancer (FDR), incomplete pathology data of relatives</td>
<td>43</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Total: 499 families, 18 mutations, 3.6% mutation detection rate.

FDR, first-degree relative.
<sup>a</sup>Index patients with a diagnosis of DGC or LBC and obligate carriers were included in this group.
<sup>b</sup>Index patients with a diagnosis of gastric cancer (DGC, IGC, or MGC) were included in this group.
<sup>c</sup>Index patients with a diagnosis of LBC were included in this group.

van der Post: Gastro ‘15; 149:897
Welcome to the GeneTests Web site, a publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers, available at no cost to all interested persons. Use of this Web site assumes acceptance of the terms of use.

At This Site

- **GeneReviews**
  Online publication of expert-authored disease reviews
- **Laboratory Directory**
  International directory of genetic testing laboratories
- **Clinic Directory**
  International directory of genetics and prenatal diagnosis clinics
- **Educational Materials**
  - Illustrated glossary
  - About genetic services
  - PowerPoint® slide presentations
A breast cancer panel

- Breast 44
- Stomach 58
- Colon 70's
- Colon 80
- Stomach 58
- Breast 50s
- Intraductal breast cancer ER/PR +, age 53
- Stomach 60

ER/PR +, age 53

Breast 50s

Breast 44

Intraductal breast cancer ER/PR +, age 53

Stomach 60

Stomach 58

Colon 70's

Colon 80
A breast cancer panel:

**CDH1 mutation detected**

Intraductal breast cancer
ER/PR +, age 53
Healthy 30 year-old Anglo woman
Adopted—no knowledge of biological parents
Curious about heritage, undergoes “23 and me” consumer testing: is 50% Ashkenazi Jewish
Undertakes some online research, consults gynecologist about BRCA risk
Undergoes “expanded” BRCA panel
Healthy 30 year-old Anglo woman
Adopted—no knowledge of biological parents
Curious about heritage, undergoes “23 and me” consumer testing: is 50% Ashkenazi Jewish
Undertakes some online research, consults gynecologist about BRCA risk
Undergoes “expanded” BRCA panel
Found to have CDH1 variant of uncertain significance
Figure 2. Cumulative Risk of Gastric and Breast Cancer for CDH1 Mutation Carriers by Sex

Hansford: JAMA Onc ’15; 1:23
Management

Charlton: Gut '04; 53:814
Clinical Features of HNPCC

- Early but variable age at CRC diagnosis (~45 years)
- Tumor site in proximal colon predominates
- Extracolonic cancers: endometrium, ovary, **stomach**, urinary tract, small bowel, bile ducts, sebaceous skin tumors
- Characteristic pathology: poorly differentiated, mucinous, Tumor-infiltrating lymphocytes, MSI
### Stomach Cancer Risk in HNPCC

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>10 years</th>
<th></th>
<th>20 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk, %</td>
<td>(95% CI)</td>
<td>Risk, %</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Both sexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney etc.*</td>
<td>1.90</td>
<td>(0.87 to 3.17)</td>
<td>5.15</td>
<td>(2.86 to 7.68)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>1.61</td>
<td>(0.65 to 2.75)</td>
<td>3.15</td>
<td>(1.37 to 5.20)</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.92</td>
<td>(0.28 to 1.73)</td>
<td>4.00</td>
<td>(1.92 to 6.41)</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.66</td>
<td>(0.13 to 1.40)</td>
<td>1.15</td>
<td>(0.19 to 2.48)</td>
</tr>
<tr>
<td>Hepatobiliary tract†</td>
<td>0.83</td>
<td>(0.16 to 1.69)</td>
<td>1.42</td>
<td>(0.42 to 2.73)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>2.74</td>
<td>(0.86 to 4.77)</td>
<td>5.90</td>
<td>(2.69 to 9.76)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrium</td>
<td>12.12</td>
<td>(7.66 to 17.11)</td>
<td>23.99</td>
<td>(16.79 to 32.84)</td>
</tr>
<tr>
<td>Breast</td>
<td>1.94</td>
<td>(0.58 to 3.83)</td>
<td>11.38</td>
<td>(0.63 to 16.69)</td>
</tr>
<tr>
<td>Ovary</td>
<td>0.94</td>
<td>(0.00 to 2.11)</td>
<td>0.94</td>
<td>(0.00 to 2.11)</td>
</tr>
</tbody>
</table>
## Table: Cumulative incidence by age (% (95% CI))

<table>
<thead>
<tr>
<th>Age</th>
<th>path_M LH1</th>
<th>path_MS H2</th>
<th>path_MS H6</th>
<th>path_P MS2</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>0.3 (0.0 to 0.9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>50</td>
<td>0.8 (0.0 to 1.7)</td>
<td>0.5 (0.0 to 1.4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>60</td>
<td>2.4 (0.7 to 4.0)</td>
<td>1.6 (0.0 to 3.4)</td>
<td>1.4 (0.0 to 4.2)</td>
<td>0</td>
</tr>
<tr>
<td>70</td>
<td>6.3 (3.0 to 9.7)</td>
<td>4.1 (0.8 to 7.5)</td>
<td>1.4 (0.0 to 4.2)</td>
<td>0</td>
</tr>
<tr>
<td>75</td>
<td>7.1 (3.5 to 10.8)</td>
<td>7.7 (1.9 to 13.6)</td>
<td>5.3 (0.0 to 13.1)</td>
<td>0</td>
</tr>
</tbody>
</table>
# Multisociety GI Recommendations

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Recommendation</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td>Every 1-2 y beginning at age 20-25 y or 2-5 y younger than youngest age at diagnosis of CRC in family if diagnosis before age 25 y Considerations: Start at age 30 y in MSH6 and 35 in PMS2 families Annual colonoscopy in MMR mutation carriers</td>
<td>Strong recommendation: Level of evidence (III): well-designed and conducted cohort or case-controlled studies from more than 1 group with cancer GRADE rating: moderate</td>
</tr>
<tr>
<td>Pelvic examination with endometrial sampling</td>
<td>Annually beginning at age 30-35 y</td>
<td>Offer to patient: Level of evidence (V): expert consensus GRADE rating: low</td>
</tr>
<tr>
<td>Transvaginal ultrasound</td>
<td>Annually beginning at age 30-35 y</td>
<td>Offer to patient: Level of evidence (V): expert consensus GRADE rating: low</td>
</tr>
<tr>
<td>EGD with biopsy of the gastric antrum</td>
<td>Beginning at age 30-35 y and subsequent surveillance every 2-3 y can be considered based on patient risk factors</td>
<td>Offer to patient: Level of evidence (V): expert consensus GRADE rating: low</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Annually beginning at age 30-35 y</td>
<td>Consideration: Level of evidence (V): expert consensus GRADE rating: low</td>
</tr>
</tbody>
</table>

EGD, esophagogastroduodenoscopy; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation.
NCCN--Gastric and small bowel cancer:
• No clear evidence supports screening for gastric, duodenal, and small bowel cancer for LS; selected individuals or families or those of Asian descent may consider EGD with extended duodenoscopy every 3-5 y beginning at age 30-35y. (Proposed: Consider test and treat H Pylori)
Where are we now?
The Gastric Cancer Panel analyzes genes that are associated with an increased lifetime risk of developing stomach cancer. These genes were selected based on the available evidence to date to provide broadest hereditary gastric cancer test. Many of these genes are also associated with an increased risk of other cancer types.
Stomach Cancer Susceptibility “Panels”

<table>
<thead>
<tr>
<th>Primary panel (18 genes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
</tr>
<tr>
<td>KIT</td>
</tr>
<tr>
<td>NF1</td>
</tr>
<tr>
<td>SDHB</td>
</tr>
<tr>
<td>STK11</td>
</tr>
</tbody>
</table>
Where are we going?

From shot-gunning

To test everyone for everything?