Update on pyloric gland adenomas
[of stomach, duodenum & gall bladder]

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Gastric pyloric gland adenoma: a multicentre clinicopathological study of 67 cases


Clinicopathologic features of duodenal pyloric gland adenoma – an analysis of 20 cases

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Pyloric Gland Adenoma (PGA) of the Gallbladder
A Unique and Distinct Tumor from PGAs of the Stomach, Duodenum, and Pancreas

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Pyloric Gland Adenoma [PGA]

- Neoplasms with pyloric gland differentiation.
- Risk for malignant transformation.
- Most frequently identified in the stomach.
- Also: gallbladder, duodenum, bile duct, & esophagus.
- In pancreas, the terms IPMNs of the gastric type, pyloric gland variant & IPMN w/ pyloric gland features have been coined.

Morphologic characteristics

- Tightly packed tubular glands.
- Cuboidal or columnar cells.
- Eosinophilic to amphophilic cytoplasm.
- Round to oval nuclei.
- Occasional prominent nucleoli.
Special stains & IHC

- PAS/AB shows granular cytoplasmic staining.
- No PAS+ mucin cap identified (vs foveolar epithelium)
- Positivity for apoprotein MUC6 and MUC5AC confirm gastric differentiation.
  - MUC6 is more specific since MUC5AC is expressed by both foveolar-type adenomas and PGAs.
- Focal intestinal differentiation with labeling by CDX2 and/or intestinal MUC2 staining.

## STOMACH

### Pyloric Gland Adenoma (<3% of all polyps)

Oberhuber G. Virchows Archiv; 2000; 437:581-90

<table>
<thead>
<tr>
<th>Tubulo-villous Pyloric gland adenoma</th>
<th>Tubular Pyloric gland adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.jpg" alt="Tubulo-villous Pyloric gland adenoma" /></td>
<td><img src="image2.jpg" alt="Tubular Pyloric gland adenoma" /></td>
</tr>
</tbody>
</table>
Classic immunophenotype of PGA

TFF2 is also diffusely expressed [MST1 and pepsinogen can be focally expressed]
What we know about PGA

• Older pts (mean age: 70 yrs)
• Females > males (3:1)
• Oxyntic mucosa
• Autoimmune gastritis +
• FAP; Lynch Sd.
• 53% with HGD (23 cases)
• Freqt. assoc. of gastric PGAs w/ CAs, ranging from 12% to 30%.
• Pyloric-phenotype (MUC6+)
• < 30% MUC5AC+

What is new about PGA

• Antrum (6%), pylorus (3%)
• 73% not associated with AIG
  • 36% in normal mucosa
• Parietal cells noted in all FAP associated PGAs
• 55% LGD [avg: 1.7 cm]; 37% HGD [avg: 3.4 cm]
  • TVA pattern more commonly associated w/ in HGD (52%) than LGD
• 51% co-expressed MUC5AC in an intermixed pattern
• 7% w/ recurrence at 1 year

Molecular Pathogenesis

- P53+ in 22.3% of cases [85.7% in intestinal-type adenomas]
  - Some w/ high-grade dysplasia.
- Frequent p53 expression in 82.1% of PGAs associated with CA vs 59.3% for those without associated CA.
- Infrequent loss of MMR expression: 4.3% (1/23) showing loss of both MLH1 & PMS2.

Molecular Pathogenesis

- 63% of PGAs show activating mutations of GNAS.
- **no** GNAS mutations in foveolar-type adenomas, intestinal type adenomas, or adenocarcinomas.
- KRAS mutations in 41% of cases
  - vs 9% of foveolar & intestinal-type adenomas
- 37% have dual-activating mutations in both GNAS and KRAS.

DDX: Polypoid foveolar type gastric dysplasia

MUC5: diffusely positive; MUC6: negative
Gastric Adenocarcinoma of Fundic Gland Type (Chief Cell Predominant Type): Proposal for a New Entity of Gastric Adenocarcinoma

Gastric Adenocarcinoma With Chief Cell Differentiation

A Proposal for Reclassification as Oxytic Gland Polyp/Adenoma

Chief cell-predominant gastric polyps: a series of 12 cases with literature review

Karen Chan,1 2 Ian S Brown,3 Trevor Kyle,4 Gregory Y Lauwers5 & Marian Priyanthi Kumarasinghe1 6
Relationship between PGAs & Oxyntic adenoma

• Frequent detection of parietal cells in PGAs (syndromic AFP)
• Expression of chief cell markers in some PGAs

Original Article
Gastric adenocarcinoma of the fundic gland type shares common genetic and phenotypic features with pyloric gland adenoma

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 3</th>
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<tbody>
<tr>
<td>Tumor</td>
<td>Tumor</td>
</tr>
<tr>
<td>ACA</td>
<td>ACA</td>
</tr>
<tr>
<td>C</td>
<td>K</td>
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<tr>
<td>G</td>
<td>G</td>
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<tr>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>100</td>
<td>90</td>
</tr>
<tr>
<td>Non-tumor</td>
<td>Non-Tumor</td>
</tr>
<tr>
<td>ACA</td>
<td>ACA</td>
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<td>C</td>
<td>G</td>
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<tr>
<td>C</td>
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<tr>
<td>90</td>
<td>100</td>
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GNAS mutation
Relationship between PGAs & Oxyntic adenoma
PGAs in DUODENUM
## Duodenal Pyloric Gland Adenoma [n=42]

<table>
<thead>
<tr>
<th></th>
<th>LGD (n=25)</th>
<th>HGD (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, (range)</strong></td>
<td>73.4 (54-85)</td>
<td>69.8 (51-77)</td>
</tr>
<tr>
<td><strong>Sex, male (%)</strong></td>
<td>13 (52)</td>
<td>9 (56.5)</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>D2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>D3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td><strong>Size, mm (range)</strong></td>
<td>9.5 (2-37)</td>
<td>19.6 (7-60)</td>
</tr>
</tbody>
</table>

*P:0.008*

Miller G et al. *in preparation*
<table>
<thead>
<tr>
<th></th>
<th>LGD (n=25)</th>
<th>HGD (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastric heterotopia (%)</strong></td>
<td>4 (16)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td><strong>Architecture</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubular (%)</td>
<td>17 (68)</td>
<td>7 (37.5)</td>
</tr>
<tr>
<td>Tubulovillous (%)</td>
<td>8 (32)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td><strong>MUC staining pattern</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyloric (%)</td>
<td>5 (21.7)</td>
<td>4 (28.6)</td>
</tr>
<tr>
<td>Mixed (%)</td>
<td>18 (78.3)</td>
<td>10 (71.4)</td>
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<tr>
<td><strong>Recurrence</strong></td>
<td>1</td>
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<tr>
<td><strong>Associated carcinoma</strong></td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

Miller G et al. *in preparation*
PGAs in GALL BLADDER

2/3 sessile
7% LGD \( [n=17] \) vs 29\% HGD/carcinomas \( [n=7] \)
Diffuse positivity for MUC6

- **Focal detection**
  - MUC2: 50% of cases
  - MUC5AC: 70.8% of cases
  - CDX2: 100% of cases

- **PAS staining:**
  - 11 (45.8%) mucin-rich type
  - 13 (54.2%) mucin-poor type.
CDX2 [+] in goblet cells, Paneth cells, squamous morules
squamoid morules in 25% cases [mucin-poor PGAs];
Molecular Pathogenesis

• CTNNB1 missense mutations in all cases (21/21)
  – but β catenin staining varies: 10% to 90%.
  – β -catenin signaling pathway plays an essential role in induction of transdifferentiation toward morule-formation
• KRAS missense mutation in one case (4.2%).
• No GNAS missense mutation detected.
UPDATE in PGAs

• **Gastric PGAs**
  – Not all associated with AIG
  – Low malignant potential
  – OGA and PGA: ? same spectrum w/ subtle changes?

• **GB – PGAs vs Gastric / Duod**
  • Can differentiate toward foveolar and intestinal phenotype.
  • Frequent CTNNB1 mutations.
    • Variable nuclear accumulation of β-catenin.
  • Infrequent or no KRAS or GNAS-mutations.