Dysplasia in Gastrointestinal Tract: Practical Pearls and Issues

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Low Grade Dysplasia of GI Tract

- Lack surface maturation
- Nuclear elongation, crowding, pseudostratification and hyperchromasia
- No loss of nuclear polarity
  - No features of high grade dysplasia
  - No glandular crowding
- No significant inflammation
- Clear transition to adjacent mucosa
High Grade Dysplasia of GI Tract

- Lack surface maturation
- Enlarged hyperchromatic nuclei
  - Dark nuclei with clumped chromatin, inconspicuous nuclei
  - Prominent, irregular nuclei with dark chromatin and irregular nucleoli
- Loss of nuclear polarity
- Mitoses, often atypical
- Cribiforming, micropapillary formation
- Luminal necrosis
- No significant inflammation
High Grade Dysplasia of GI Tract

R/O intramucosal carcinoma
- Complex, expansive, cribiform architecture
- Dilated dysplastic glands with necrosis
- Neutrophils in dysplastic glands
- Back-to-back gland
- Budding
- Small, irregular clusters
- Desmoplastic stroma
Reactive and Regenerative Changes of Glandular Mucosa

- Accelerated response to mucosal injury, inflammation, erosion or ulceration
- Often very atypical and mimic high grade dysplasia
- Large vesicular nuclei with macronucleoli
- Mitoses
Is p53 IHC useful?

P53 can be helpful but has limitations

– Nuclear accumulation in non-dysplastic epithelium (10%), LGD (40%), HGD (85%), adenocarcinoma (100%)
– Nuclear staining on regenerative epithelium
  • Lower intensity than dysplastic epithelium
Is p53 IHC useful?

P53 can be helpful but has limitations

– “null pattern” – complete loss of nuclear staining = biallelic loss of TP53 gene
Is p53 IHC useful?

- P53 IHC should be interpreted with caution.
- P53 IHC should not be interpreted as positive for (high grade) dysplasia without supportive cytologic or histologic features.
Contamination & Artifacts

• Contamination:
  – Duodenal mucosa to “esophagus/GEJ” biopsy
  – Adenomatous lesion to normal mucosa

• Artifacts:
  – Tissue edges
  – Fragmentation
  – Tangential cut
  – Cauterization

• Unfamiliar staining characteristics:
  – Consultation/second opinion slides
Esophagus

- Dysplasia vs regenerative changes of squamous mucosa
- Dysplasia in Barrett esophagus
  - Indefinite for dysplasia
  - Variants of dysplasia
  - Role of immunohistochemical stains
  - Treatment
    - Endoscopic mucosal resection
    - Mucosal ablation
# Dysplastic vs Regenerative Squamous Mucosa

<table>
<thead>
<tr>
<th>Dysplastic SM</th>
<th>Regenerative SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No maturation</td>
<td>Surface maturation</td>
</tr>
<tr>
<td>Basophilia (LGD – basal layer, HGD – full thickness)</td>
<td>Basophilic basal layer</td>
</tr>
<tr>
<td>Disorganized proliferation</td>
<td>Vertical elongation of papillae “pseudoepitheliomatous hyperplasia”</td>
</tr>
<tr>
<td>Abnormal mitoses and scattered dyskeratotic cells</td>
<td>Basal mitoses</td>
</tr>
<tr>
<td>Pleomorphic, hyperchromatic nuclei with high N/C ratio</td>
<td>Monomorphic nucleoli with low N/C ratio</td>
</tr>
</tbody>
</table>
Barrett Esophagus

- Increasing esophageal adenocarcinoma incidence
- Reflux is a strong risk for adenocarcinoma
  - Large number of upper GI tract endoscopy
  - Barrett esophagus
- Risk factors for Barrett esophagus
  - Reflux >5 years, age >50 years, male, tobacco use, central obesity, Caucasian race
# Barrett Dysplasia Assessment

<table>
<thead>
<tr>
<th>Components</th>
<th>Non-dysplastic BE</th>
<th>Dysplastic BE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface maturation</td>
<td>Proliferating, hyperchromatic, stratified nuclei - more at basal layers of glands</td>
<td>Proliferating, hyperchromatic nuclei at basal and surface layers of glands</td>
</tr>
<tr>
<td>Gland architecture</td>
<td>Round with little budding, surrounded by abundant lamina propria</td>
<td>Crowding, budding of glands. Cribiform glands, cystic dilation, necrotic luminal debris</td>
</tr>
<tr>
<td>Cytologic features</td>
<td>Nuclear enlargement and atypia in basal layers and in mucosa adjacent to squamous epithelium</td>
<td>Hyperchromatic, loss of nuclear polarity</td>
</tr>
<tr>
<td>Inflammation &amp; erosion/ulcer</td>
<td>Proliferating, hyperchromatic nuclei at inflamed area or adjacent to erosion/ulceration</td>
<td>Hyperchromatic, atypia at and off the inflamed area</td>
</tr>
</tbody>
</table>
BE Negative for Dysplasia

- Surface maturation
- Normal architecture
- Hyperchromatic basal layer
- Nuclear polarity
BE Indefinite for Dysplasia

• Cytologic changes suggestive of dysplasia but with surface maturation
  – Hyperchromasia
  – Irregular nuclear membrane
  – Increased mitoses at basal layer
  – No loss of nuclear polarity

• “Garbage can” – unable to reach definitive diagnosis of dysplasia
  – Inflammation
  – Artifacts
BE Low Grade Dysplasia

- Lack surface maturation
- Glandular crowding
- No loss of nuclear polarity
  - No features of high grade dysplasia
- Minimal inflammation
- Some mimic tubular adenoma
  - “polypoid low grade dysplasia arising in Barrett esophagus”
BE High Grade Dysplasia

- Lack surface maturation
- Enlarged hyperchromatic nuclei
  - Dark nuclei with clumped chromatin, inconspicuous nuclei
  - Prominent, irregular nuclei with dark chromatin and irregular nucleoli
- Mitoses
- R/O invasive or intramucosal carcinoma
  - Cribiform architecture
  - Dilated dysplastic glands with necrosis
  - Ulceration
  - Neutrophils in dysplastic glands
  - Pagetoid spread into overlying squamous epithelium
Intramucosal Carcinoma

- Effacement of lamina propria
  - Single cells or small clusters
  - Desmoplasia
- Syncytial growth pattern
- Crowding & back-to-back glands
- Expansive glands
- Buddings & horizontal growths
Variants of Dysplasia

Basal crypt dysplasia
- Surface maturation
- Pleomorphic, large, hyperchromatic and irregular nuclei
- Increased N/C ratio
- Mucin depletion
- No clear surveillance guidelines – follow up according to LGD is suggested
- High interobserver variability
  - Low grade vs indefinite for dysplasia
Variants of Dysplasia

Gastric foveolar type dysplasia
- Lacks intestinal-type differentiation
- Abundant apical mucin
- Low or high grade dysplasia

Pyloric/cardia type dysplasia
- Lacks intestinal-type differentiation
- Densely packed small glands
Treatment

• Endoscopic mucosal resection:
  – Localized mucosal lesion
  – Challenges:
    • Cautery artifact
    • Lateral mucosal margin
    • Depth of invasion

• Radiofrequency ablation
  – Multifocal or extensive mucosal lesion
  – Challenges:
    • Buried metaplasia and dysplasia
## BE follow up

<table>
<thead>
<tr>
<th>Dysplasia grade</th>
<th>Follow up</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>3-5 years</td>
<td></td>
</tr>
<tr>
<td>Indefinite</td>
<td>12 months</td>
<td>Repeat 3-6 months after acid suppression treatment</td>
</tr>
<tr>
<td>Low grade</td>
<td>Every 6 months in the first year, then annually</td>
<td>Expert confirmation</td>
</tr>
<tr>
<td>High grade or intramucosal ca</td>
<td>Every 3 months in the first year, every 6 months in the second year, then annually</td>
<td>Expert confirmation</td>
</tr>
</tbody>
</table>

ACG 2015
Stomach

- Polypoid dysplasia = adenoma, low or high grade dysplasia
  - Intestinal type
  - Gastric foveolar type
- Flat dysplasia = dysplasia, low or high grade (similar to grading of BE)
Stomach

• Dysplasia in stomach polyps
  – Fundic gland polyp
  – Hyperplastic polyp
  – Pyloric gland adenoma

• Regeneration
# Hyperplastic, Hamartomatous and Juvenile Polyps

<table>
<thead>
<tr>
<th>Polyp type</th>
<th>Etiology</th>
<th>Features</th>
<th>Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperplastic (&quot;inflammatory&quot;)</td>
<td>Unknown (?mucosal injury)</td>
<td>Hyperplastic, elongated and dilated epithelium with inflammatory and edematous stroma</td>
<td>Rare (2-5%), occur in larger polyp</td>
</tr>
<tr>
<td>Peuz-Jeghers</td>
<td>Germ line mutation - LKB1/STK11</td>
<td>Hyperplastic, branching and dilated foveolar epithelium with smooth muscle stroma</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Juvenile</td>
<td>Germ line mutation – SMAD4/BM PR1A</td>
<td>Hyperplastic, elongated and dilated epithelium with inflammatory and edematous stroma</td>
<td>Rare (4-5%)</td>
</tr>
</tbody>
</table>

- Histologic classification can be difficult in small polyps
- Similar features in other parts of GI tract
Fundic Gland Polyp

- Sporadic and familial polyposis associated
- Sporadic polyp - do not progress to malignant polyp
  - Rare reported cases of adenocarcinoma arising in FAP-associated FGP
- Dysplasia is rare
  - FAP, MUTYH-associated polyposis (MAP), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)
Pyloric Gland Adenoma

- Closely packed pyloric type glands with cuboidal to low columnar epithelium
  - IHC: MUC6 +
- May contain low grade and high grade dysplasia
- Associated with atrophic gastritis
- Occur in stomach, gallbladder, duodenum and pancreatic duct
Regenerative Gastric Foveolar Epithelium

• Surface maturation
• Basophilic appearance
• Tortuous gastric pits with mitoses
• Large vesicular nuclei with macro nucleoli
• Often associated with reactive/chemical gastropathy or ulceration
Small Intestine

- Small intestinal dysplasia/neoplasm is rare, except in FAP, Lynch syndrome, or hamartomatous polyposis
  - Duodenal adenoma
  - Ampullary adenoma
- Direct extension or metastatic carcinoma
- Reactive and regenerative changes
Colon

- Polyps
  - Adenomas
  - Serrated polyps
- IBD-related dysplasia
- Reactive and regenerative changes
Adenomas

- Uncommon changes
  - Clear cell change
  - Squamous morules
- Pseudoinvasion
  - Prolapse in sigmoid or rectum
- High grade dysplasia
  - Cribiform
  - Loss of nuclear polarity
- High grade dysplasia/intramucosal carcinoma
  - Colonic mucosa lacks lymphatic channels
Serrated Polyps

- Hyperplastic polyps
- Traditional serrated adenoma
- Sessile serrated adenoma/polyp
- Sessile serrated adenoma with cytologic dysplasia

<table>
<thead>
<tr>
<th>Polyp type</th>
<th>Size</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP</td>
<td>&lt;1cm</td>
<td>10 years</td>
</tr>
<tr>
<td>SSA</td>
<td>&lt;1cm</td>
<td>Complete polypectomy, 5 years</td>
</tr>
<tr>
<td>SSA</td>
<td>≥1cm</td>
<td>Complete excision, 3 years</td>
</tr>
<tr>
<td>SSA with dysplasia</td>
<td></td>
<td>Complete excision, 3 years</td>
</tr>
<tr>
<td>TSA</td>
<td></td>
<td>3 years</td>
</tr>
<tr>
<td>Serrated polyposis</td>
<td></td>
<td>Annual</td>
</tr>
</tbody>
</table>

US Multi Society Task Force on Colorectal Cancer 2012
Serrated Polyps Issues

- “Large left sided HP”
  - >1cm, look for features of SSA (crypt dilation, lack of neuroendocrine cells)
- “Left sided SSA”
  - If small (<5mm), consider reactive changes in HP
- Last resort - consider using the term “serrated polyp with features of SSA” or “serrated polyp, not further classified”
Colitis-associated Dysplasia

- Low grade dysplasia
  - Dysplasia involving surface without loss of nuclear polarity
- High grade dysplasia
  - Dysplasia involving surface with loss of nuclear polarity
- Indefinite for dysplasia
  - Active inflammation
  - No definitive low grade dysplasia
Regenerative Colorectal Mucosa

- Atypical regenerative epithelium adjacent to or in eroded benign polypoid lesions, mucosal prolapse, inflammatory bowel disease
- Surface maturation
- Basophilic deep crypts
- Low nuclear-cytoplasmic ratio
- Comparison with biopsies from other segments often helpful – baseline features
Other Dysplasia in IBD

- IBD patients can develop sporadic adenomas and serrated polyps
  - Endoscopic findings of “polyp”
  - No dysplasia in surrounding mucosa
  - Managed as sporadic polyps

- Atypical serrated lesion
  - “Indefinite for dysplasia” for close follow up
  - Serrated colitis-associated dysplasia

- Incomplete maturation
  - “Indefinite for dysplasia” for close follow up