Barrett’s Esophagus

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Two Main Problems in Barrett’s Pathology

• Over diagnosis of Barrett’s esophagus

• Over diagnosis of high-grade dysplasia
Barrett’s Esophagus

Definition: 2-Fold

- Endoscopically visible columnar epithelium in esophagus that on biopsy has:
  - Metaplastic columnar epithelium, defined by goblet cells

ACG Practice guidelines. Am J Gastroenterol 2008;103:788
Barrett’s Esophagus
Questions in the Histologic Dx of Barrett’s Esophagus

• Is it Barrett’s or normal columnar epithelium in the esophagus?

• Are all goblet-like cells metaplastic?

• Does Alcian blue positivity = metaplasia?

• How much metaplastic epithelium is needed to diagnose Barrett’s?
Columnar Epithelium in the Esophagus May Be Normal

- The S-C junction (Z-line) may be irregular with “tongues” of columnar epithelium in the esophagus, or

- The entire S-C junction may lie within the esophagus
Normal Esophagus
Any Columnar vs. Goblet Barrett’s??

300,000,000 Americans

100,000,000 GERD

with columnar mucosa

4,000,000 Barrett’s with goblets

16,000 annual Barrett’s CA
Esophageal Adenocarcinoma

Should we screen

100,000,000 “any columnar/gastric” Barrett’s?

OR

4,000,000 with goblet-cell Barrett’s?

Noto bene: Even using the goblet Barrett’s definition, screening is ineffective!
Questions in the Histologic DX of Barrett’s Esophagus

• Is it Barrett’s or normal columnar epithelium in the esophagus?

• How much metaplastic epithelium is needed to diagnose Barrett’s?
TURNAROUND IN THE STOMACH

FORCEP STRADDLING SQUAMO-COLUMNAR JUNCTION
Significance of Few Metaplastic Glands Unknown

- Prevalence as high as 30%
- No good evidence of cancer predisposition
- Avoid Barrett’s diagnosis, instead use: “Focal Intestinal Metaplasia”

(personal opinion)
How Much Metaplastic Epithelium is Needed to Diagnose Barrett’s?

• No one knows! But,

• If only rare glands – I diagnose intestinal metaplasia

• Intestinal glands replacing biopsy -- consider diagnosing Barrett’s
Case

- **History**: 72-yr-old man with long-standing reflux & Barrett’s esophagus
- **Endosc**: 8 cm Barrett’s segment; no mass lesions
- **Bxs**: 4 quadrant every 2 cm to rule out dysplasia
Barrett’s Esophagagus with Dysplasia
Neoplastic Progression in Barrett’s Esophagus

Chronic Reflux

GERD

Metaplasia

Dysplasia

Adenocarcinoma
Dysplasia

Definition

Neoplastic epithelium confined within the basement membrane of the gland within which it arose
Grading System for Dysplasia

• Negative
• Indefinite
• Positive
  • Low-grade
  • High-grade

IBD/DMSG Hum Pathol 1983 Pathol 1983;14:831
Barrett’s Dysplasia

• Two types
  • Intestinal (85%)
  • Gastric Foveolar (15%)
Barrett’s Intestinal-type Dysplasia
Intramucosal Adenocarcinoma

- Single cell lamina propria invasion
- Sheets of malignant cells
- Abortive angulated glands
- Never ending gland pattern
Invasive Adenocarcinoma

• Unequivocal desmoplasia

• Indicates at least submucosal invasion
Barrett’s
Gastric Foveolar-type Dysplasia
Gastric-Type Barrett’s Dysplasia

- **Very** different criteria from intestinal-type dysplasia
- Non-stratified, basal nuclei precludes loss of nuclear polarity criterion

Gastric-Type Barrett’s Dysplasia

- *Gastric-type* LGD & HGD distinguished by
  - nuclear size cut off of 3-4X small lymph
  - increased but mild pleomorphism
  - prominent nucleoli
  - eosinophilic to oncocytic cytoplasm
  - crowded, irregular gland architecture

Gastric-Type Barrett’s Dysplasia

Natural history poorly defined

- 49 patients in present composite literature
- F:M = 2.7:1
- Decade older than intestinal-type dysplasia (73 vs 63 yrs mean age)
- More often high-grade (70%)
- Neoplastic progression in 64% over 8 years of follow-up

DDX GERD vs. Foveolar Dysplasia

<table>
<thead>
<tr>
<th></th>
<th>GERD</th>
<th>FOV</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nuclear stratif</strong></td>
<td>0</td>
<td>80%</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td><strong>Top-heavy atypia</strong></td>
<td>0</td>
<td>80%</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td><strong>Full thick atypia</strong></td>
<td>80%</td>
<td>0</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td><strong>Villiform</strong></td>
<td>6%</td>
<td>53%</td>
<td>0.00006</td>
</tr>
<tr>
<td><strong>Crowded glands</strong></td>
<td>78%</td>
<td>0</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td><strong>Nucleoli</strong></td>
<td>79%</td>
<td>33%</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Pleomorph–mild</strong></td>
<td>35%</td>
<td>10%</td>
<td>0.09</td>
</tr>
</tbody>
</table>

- 3,698 EGD bxs from 461 Barrett’s patients
- 80 bxs foveolar gastric-type dysplasia (13 LGD, 30 HGD)
- 60 severe GERD

Reactive Cardia/GERD
Villiform Architecture &
“Top-Heavy” Atypia
Reactive Cardia/GERD: Stratified Surface Nuclei
Gastric-type Dysplasia: Full-thickness Atypia
Gastric-type Dysplasia: Non-stratified Nuclei
Dysplasia: Problems

- Sampling
- Distinction from reactive change
- Observer variation
- Squamous overgrowth
- Natural history incompletely understood
Distribution of Dysplasia

- Metaplasia ("specialized")
- High grade Dysplasia
- Indefinite for Dysplasia/Low grade Dysplasia
- Cancer
Biopsy Protocol

![Diagram showing the esophagus and stomach with color-coded regions: Squamous, Gastric, Metaplastic. The diagram indicates a distance of 2 cm between the LES and the stomach.](image-url)
Dysplasia: Problems

- Sampling
- Distinction from reactive change
Dysplasia: Problems

- Sampling
- Distinction from reactive change
- Observer variation
Spectrum of Dysplasia

- Negative
- Indefinite
- Low Grade
- High Grade
## Interobserver Agreement: Dysplasia in Barrett’s Esophagus

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Kappa Statistic</th>
<th>Agreement</th>
</tr>
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<tbody>
<tr>
<td>HGD/CA</td>
<td>0.65</td>
<td>Substantial</td>
</tr>
<tr>
<td>LGD</td>
<td>0.32</td>
<td>Fair</td>
</tr>
<tr>
<td>Indefinite</td>
<td>0.15</td>
<td>Poor</td>
</tr>
<tr>
<td>Negative</td>
<td>0.58</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*From: Montgomery E, et al. *Hum Pathol* 32:368-78; 2001*
Two Main Problems In Barrett’s Pathology

• Over diagnosis of Barrett’s esophagus
• Over diagnosis of high-grade dysplasia
Inaccuracy in the Diagnosis of Barrett’s with HGD

- PDT multi-center trial for Barrett’s HGD
  - 485 patients with “HGD” screened
    - Review original slides
    - Repeat protocol study endoscopy 4 quad q2cm
  - 248 with confirmed HGD (51%)
  - 193 patients downgraded (40%)

Sangle N, Bronner MP: Mod Pathol, In press 2015
### 193 Downgraded Patients

<table>
<thead>
<tr>
<th>Reinterpretations</th>
<th>No.</th>
<th>Percent</th>
</tr>
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<tbody>
<tr>
<td>Gastric only</td>
<td>18</td>
<td>9%</td>
</tr>
<tr>
<td>Barrett’s negative</td>
<td>35</td>
<td>18%</td>
</tr>
<tr>
<td>Barrett’s indefinite</td>
<td>61</td>
<td>32%</td>
</tr>
<tr>
<td>Barrett’s LGD</td>
<td>79</td>
<td>41%</td>
</tr>
</tbody>
</table>

Sangle N and Bronner MP: Mod Pathol, In press 2015
Diagnostic Pitfalls: HGD in Barrett’s Esophagus

• NOT atypia limited to basal glands
• NOT reactive gastric cardiac-type mucosa
• NOT inflammatory reactive change
• Sampling error
NOT Baseline Glandular Atypia
NOT Reactive Gastric Mucosa
NOT Inflammatory Atypia
Over Diagnosis of HGD in BE

• Under utilization of loss of nuclear polarity as most objective criterion
• Morphologic spectrum without precise definable boundaries
• Accuracy is experience and volume dependent
Loss of Nuclear Polarity to Distinguish Low and High-Grade Dysplasia
ACG GUIDELINES

High-grade dysplasia in Barrett’s esophagus should be confirmed by an expert GI pathologist

High Grade Dysplasia

Management Options

Surveillance

Ablation (e.g. PDT)

Surgery
Can we tell BAD from WORSE?

HGD <-> IMC <-> SMC

# Interobserver Variability: At Least High-grade Dysplasia

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Kappa</th>
<th>P-value</th>
<th>95% CI</th>
<th>Interp</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>0.30</td>
<td>&lt;0.001</td>
<td>0.28-0.32</td>
<td>Poor</td>
</tr>
<tr>
<td>HGD</td>
<td>0.47</td>
<td>&lt;0.001</td>
<td>0.44-0.51</td>
<td>Mod</td>
</tr>
<tr>
<td>HGD-MAD</td>
<td>0.21</td>
<td>&lt;0.001</td>
<td>0.18-0.25</td>
<td>Poor</td>
</tr>
<tr>
<td>IMC</td>
<td>0.30</td>
<td>&lt;0.001</td>
<td>0.26-0.33</td>
<td>Poor</td>
</tr>
<tr>
<td>SMC</td>
<td>0.17</td>
<td>&lt;0.001</td>
<td>0.14-0.21</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Can we tell BAD from WORSE?

- NO! Not on Biopsies!
- Management based on distinction between HGD, IMC & SMC in *biopsies* is questionable
- What about EMR?
### Bx vs. EMR Histology

<table>
<thead>
<tr>
<th>Study</th>
<th># of Pt</th>
<th>Up-stage by EMR</th>
<th>Down-stage by EMR</th>
<th>Total EMR Altered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larghi, 2005</td>
<td>48</td>
<td>13%</td>
<td>2%</td>
<td>15%</td>
</tr>
<tr>
<td>Hull, 2006</td>
<td>41</td>
<td>34%</td>
<td>5%</td>
<td>39%</td>
</tr>
<tr>
<td>Chennat, 2009</td>
<td>49</td>
<td>14%</td>
<td>31%</td>
<td>45%</td>
</tr>
<tr>
<td>Moss, 2010</td>
<td>75</td>
<td>20%</td>
<td>28%</td>
<td>48%</td>
</tr>
</tbody>
</table>

**Note:** EMR results altered the bx diagnosis 15-48% of the time
T1a Esophageal CA

- Intramucosal carcinoma
  - Invades into
    - lamina propria
    - muscularis mucosae
  - Low metastatic rate 1-2%
T1b Esophageal CA

- Submucosal carcinoma
- Subdivided into thirds (no reliable significance)
- High metastatic rate
  - ~30%
EMR for T1a (HGD/IMC)

<table>
<thead>
<tr>
<th>Study</th>
<th># Pt’s</th>
<th>Avg F/U</th>
<th>Compl Resp</th>
<th>Recur/Metachr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ell, 2000</td>
<td>35</td>
<td>12 mo</td>
<td>97%</td>
<td>14%</td>
</tr>
<tr>
<td>May, 2002</td>
<td>70</td>
<td>34 mo</td>
<td>98%</td>
<td>30%</td>
</tr>
<tr>
<td>Pech, 2008</td>
<td>279</td>
<td>64 mo</td>
<td>97%</td>
<td>22%</td>
</tr>
<tr>
<td>Chennat, 2009</td>
<td>32</td>
<td>23 mo</td>
<td>97%</td>
<td>3%</td>
</tr>
<tr>
<td>CBE-EMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moss, 2010</td>
<td>75</td>
<td>31 mo</td>
<td>94%</td>
<td>11%</td>
</tr>
</tbody>
</table>
Duplicated Muscularis Mucosae in Barrett’s

Duplicated Muscularis Mucosae

- Easy to overcall split MM space as submucosal invasion (T1b)
- EMR & EUS also overstage
- >60% of IMC cases overstaged

Mandal, et.al. *AJSP* 2009;33:620
Split MM CA’s are T1a

<table>
<thead>
<tr>
<th>Invasion Depth</th>
<th>Nodal Mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosa &amp; Dupl MM</td>
<td>1/69 (1.4%)</td>
</tr>
<tr>
<td>Submucosa</td>
<td>10/30 (33.3%)</td>
</tr>
</tbody>
</table>
BE Dysplasia Summary-1

- Grading of dysplasia: intestinal & gastric foveolar types
- Problems with dysplasia
  - Sampling
  - Observer variation
  - Natural history: prevalent vs. incident
BE Dysplasia Summary-2

- Over diagnosis of HGD
  - Baseline atypia of metaplasia
  - Reactive cardia
  - Inflammatory change
  - Loss of nuclear polarity
- HGD management options broadening
BE Dysplasia Summary-3

• HGD management options broadening
• Continued surveillance: incident HGD
• Ablation
• CBE-EMR
  • Duplicated muscularis mucosae: beware of overstaging T1a to T1b