GERD and its complications

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Outline

1. GERD definition
2. Endoscopy indications
3. GERD complications
GERDisease: Montreal Definition
distinguishes GERD from episodic heartburn

“when reflux of stomach contents causes troublesome symptoms and/or complications.”

does not require endoscopy

……start treatment

Am J Gastroenterol. 2006;101:1900-1920
Q: When do we need to look...
Endoscopy indications?

Patient failed empiric treatment

a.  ? Wrong diagnosis
b.  ? complicated

Look for complications:

a. Barrett’s
b. Dysplasia
c. Cancer
Patients failed empiric treatment

Female...young (18)
Predominant symptom dysphagia
F18 with dysphagia – cardioEso junction.

Too many eosinophils barily15/HPF.
EOSINOPHILs
(GERD vs. Eosinophilic Esophagitis)

Eos found in proximal biopsies
Eos found in proximal biopsies
Eos Not at top except next to ulcer
Eos absent in proximal biopsies
Few Eos (if found)

Eos abscess
Reach superficial layer
numerous

Eosinophilic eosophagitis
GERD
F18 with dysphagia.
distal esophagus – too many eosinophils
(barely 15/HPF)

The differential:
  – GERD (perhaps next to an ulcer)
  – Eosinophilic esophagitis
We need 3 esophageal biopsies

In a differential of Eosinophilic esophagitis vs. GERD:

- 10 cm proximal
- 5 cm proximal
- Squamo-columnar junction
# Eosinophilic Esophagitis vs GERD

<table>
<thead>
<tr>
<th></th>
<th><strong>Eosinophilic Esophagitis</strong></th>
<th><strong>GERD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardio Esophageal junction</td>
<td>&gt; 15 Eosiophils + other features</td>
<td>+ &gt; 15 Eosiophils + other features</td>
</tr>
<tr>
<td>5 cm proximal</td>
<td>≥ 15 Eosiophils + other features</td>
<td>Negative</td>
</tr>
<tr>
<td>10 cm proximal</td>
<td>≥ 15 Eosiophils + other features</td>
<td>Negative</td>
</tr>
</tbody>
</table>
We know it is GERD

Is there more to it?

? complications
GERD complications

- Barrett’s
- Dysplasia
- Carcinoma
First question

?? is it Barrett’s
Squamo-columnar junction
Looking from inside

GEJ is where squamous epithelium stops and columnar starts
Gastro-esophageal junction

What is Barrett’s esophagus?

Original definition of Barrett’s Esophagus is replacement by Columnar Lined Esophagus (CLE) with or without goblets.
Intestinal metaplasia increases cancer risk

“Barrett’s” only for biopsies with intestinal
Patient has to have an endoscopic diagnosis of Barrett’s
Any Columnar Lined Esophagus (CLE) is Barrett’s
Is it Barrett’s?
Japan & Britain

No goblet cells or intestinal metaplasia required

Columnar lined Epithelium

Endoscopic abnormality
1. Definition of Barrett’s

1. Endoscopic abnormality
2. Histologic confirmation
   a) Requires the presence of intestinal metaplasia (US, Canada)
   b) Columnar lined epithelium without and without goblets (UK, Japan)
1. Do we need intestinal metaplasia?
2. How good is the endoscopic definition?
Barrett’s Definition

1. Do we need intestinal metaplasia?

2. How good is the endoscopic definition?
Odds of detecting intestinal metaplasia

<table>
<thead>
<tr>
<th>Factor</th>
<th>p-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of samples of tissue</td>
<td>&lt; 0.001</td>
<td>1.24</td>
<td>1.166 - 1.318</td>
</tr>
<tr>
<td>First segment length (cm)</td>
<td>&lt; 0.001</td>
<td>1.10</td>
<td>1.065 - 1.142</td>
</tr>
<tr>
<td>Gender (Male/Female)</td>
<td>0.031</td>
<td>1.24</td>
<td>1.020 - 1.518</td>
</tr>
<tr>
<td>Age at biopsy (years)</td>
<td>0.438</td>
<td>1.00</td>
<td>0.995 - 1.01</td>
</tr>
</tbody>
</table>

Scandinavian Journal of Gastroenterology, 2008; 43: 524530
Goblet cells may NOT be seen in Barrett’s

*Children* - esp first decade

*SSBE* - with repeat biopsies

*LSBE* - with numerous biopsies

Requiring goblets:
Assumes non – intestinal mucosa has no malignant potential. Is this true?

1. What goes on in the non-metaplastic component of BE?
2. Does dysplasia and carcinomas arise in non-metaplastic mucosa?
3. What are the implications?
What goes on in the non-metaplastic component of BE?
## Goblets versus no goblets

<table>
<thead>
<tr>
<th>Reference</th>
<th>Marker Description</th>
<th>Goblets</th>
<th>No Goblets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mod Pathol 2004;17:1282-1288</td>
<td>Cdx2 (intestinal differentiation)</td>
<td>100%</td>
<td>38%</td>
</tr>
<tr>
<td>Am J Gastro 2009;104(4):81</td>
<td>Chroosomal gains</td>
<td>1%</td>
<td>99%</td>
</tr>
<tr>
<td>Mol Path 2007;20:788-796</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: The table shows the percentage of goblets and no goblets for different markers.*
Chromosomal and DNA abnormalities in metaplastic and non-metaplastic compartments.
Conclusion: Non-goblet cells are not normal, and often share features with intestinalized epithelium
Does dysplasia and carcinomas arise in non-metaplastic mucosa?
Intestinal Metaplasia in Barrett’s Adenocarcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Mean tumor size cm</th>
<th>Intestinal metaplasia %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clark et al 1994</td>
<td>31</td>
<td>3.5</td>
<td>42</td>
</tr>
<tr>
<td>Cameron et al 1995</td>
<td>24</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>Van Sandick et al 2000</td>
<td>12</td>
<td>2.3</td>
<td>100</td>
</tr>
<tr>
<td>Ruol et al 2000</td>
<td>16</td>
<td>2</td>
<td>69</td>
</tr>
<tr>
<td>Cameron et al 2002</td>
<td>22</td>
<td>1.4</td>
<td>86</td>
</tr>
<tr>
<td>Tsuju et al 2004</td>
<td>54</td>
<td>&lt;4</td>
<td>38</td>
</tr>
<tr>
<td>Nunobe et al 2007</td>
<td>48</td>
<td>2</td>
<td>46</td>
</tr>
<tr>
<td>Takubo et al 2009</td>
<td>141</td>
<td>6.6</td>
<td>30</td>
</tr>
</tbody>
</table>

Dysplasia & Carcinoma in non-Goblet Barrett’s?

• Studied 141 small (minute) esophageal areas of dysplasia or adenocarcinomas resected by endoscopic mucososal resection

• The mucosa on each side of the tumors was examined for the type of epithelium.

Takubo & Vieth et al Hum Pathol 2009 ; 40 : 65 – 74
Mucosa around the early Barrett’s cancer < 2 cm

- 70% cardiac type only
- 22% intestinal only
- 8% both

*Takubo & Vieth et al* Hum Pathol 2009; 40: 65 – 74
1.5 mm in diameter area of “high-grade dysplasia” by the WHO criteria, is surrounded only by cardiac-type mucosa.
Kaiyo TAKUBO, MD
No goblets
Summary Takubo/Vieth study

- >70% of adenocarcinomas were located adjacent to cardiac/fundic-type, rather than intestinal-type, mucosa
- Intestinal metaplasia was not observed in over half (56.6%) of the cases.
U.K. Follow up study: CLE vs. intestinal metaplasia in GE J cancer

<table>
<thead>
<tr>
<th>Initial histology</th>
<th>Number (%) developing adenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columnar Lined</td>
<td>ma 3.1%</td>
</tr>
<tr>
<td>Columnar Intestinal Metaplasia</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

Scandinavian Journal of Gastroenterology, 2008; 43: 524530
Non intestinalized mucosa in BE

• Has numerous characteristics of intestinalized mucosa

• Have about 70% the risk of getting adenocarcinoma cf. intestinalized BE mucosa
What is the problem with the definition?

- Normal distal esophagus — may display short cephalad extent of columnar epithelium above the gastroesophageal junction
- ? Hiatal Hernia
Barrett’s Run:

Let the gastroenterologist decide on an issue a diagnosis of:

Columnar Lined epithelium (%)
Negative for intestinal metaplasia

Columnar Lined Epithelium (%)
Intestinal metaplasia present (   )
1. How good is the endoscopic definition?
endoscopic landmarks

Japan: lower limit of palisade vessels.

Western countries: upper end gastric longitudinal folds
Working Group Results
The Prague C&M Criteria

*Reliability coefficient for*
- Barrett’s any length 0.49
- **Barrett’s length < 1cm** 0.22
- Barrett’s length > 1cm 0.72

*Reliability coefficient for*
- Proximal margin of gastric folds 0.88
- Pinch at the distal esophagus 0.78
- Diaphragmatic hiatus 0.85
Barrett’s Epithelium – Statement 47

Barrett’s Run: gastroenterologist

• The presence and extent of reflux-related columnar metaplasia in the distal esophagus should be recorded as “endoscopic suspicion of Barrett’s epithelium”

• Formal diagnosis of “Barrett’s epithelium” requires histological confirmation

Let the pathologist decide

1. Definition of Barrett’s

1. Endoscopic abnormality
2. Histologic confirmation
   a) Requires the presence of intestinal metaplasia (US, Canada)
   b) Columnar lined epithelium without and without goblets (UK, Japan)
Is there dysplasia?
<table>
<thead>
<tr>
<th>Dysplasia</th>
<th>Proposed guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>After 2 negative, every 2–3 years</td>
</tr>
<tr>
<td>Indefinite and Low grade dysplasia</td>
<td>Every 3 - 6 months looking for HGD or worse, consider EMR</td>
</tr>
<tr>
<td>High grade dysplasia – needs action</td>
<td>Expert confirmation then selective resection, better EMR, ? for some endoscopy every three months (looking for invasive carcinoma)</td>
</tr>
</tbody>
</table>
Is there Dysplasia?

1. Architectural pattern
2. Nuclear Pattern
3. Surface maturation
Inter-observer Agreement - Cleveland Clinic

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Kappa</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade dysplasia</td>
<td>0.04</td>
<td>Poor to fair</td>
</tr>
<tr>
<td>High grade dysplasia</td>
<td>0.47</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sub-mucosal carcinoma</td>
<td>0.38</td>
<td>Fair</td>
</tr>
<tr>
<td>Sub-mucosal carcinoma</td>
<td>0.13</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Is there dysplasia?

• Problems:
  1. Over diagnosis of LGD
  2. Over diagnosis of HGD (if one relies on focal cytology only)
  3. Not recognizing the possibility of adjacent carcinoma
What about p53?

Sporadic nuclear staining is considered negative (-).

Nuclear staining in continuity indicates clonal expansion of mutated cells (+).
## p53 Role in Diagnosing Barrett’s

<table>
<thead>
<tr>
<th></th>
<th>Non dysplastic</th>
<th>Low grade dysplasia</th>
<th>High grade dysplasia</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.4 %</strong></td>
<td>1.4 %</td>
<td>30%</td>
<td>68%</td>
<td>72%</td>
</tr>
<tr>
<td><em>(0-10%)</em></td>
<td><em>(0-10%)</em></td>
<td><em>(0-60%)</em></td>
<td><em>(50-100%)</em></td>
<td><em>(45-100%)</em></td>
</tr>
</tbody>
</table>

Table shows gradual increase in p53 expression as dysplasia increases.

**Why is p53 use controversial?**

Because of the considerable overlap in expression between and within categories.
Kaplan-Meier progression 'p53 status'
Am J Gastroenterol 2002;97:2508–2513
p53 in Diagnosing Dysplasia in Barrett’s

Though controversial, alterations in p53 expression can facilitate the interpretation of an epithelial abnormality.
Q: Barrett’s Mucosa Predictive of Associated Carcinoma

<table>
<thead>
<tr>
<th>Histologic Feature</th>
<th>Carcinoma in Resection Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcerated high-grade dysplasia</td>
<td>83%</td>
</tr>
<tr>
<td>Neutrophils in dysplasia</td>
<td>80%</td>
</tr>
<tr>
<td>Cribriform/solid growth</td>
<td>73%</td>
</tr>
<tr>
<td>Dilated tubules/necrotic debris</td>
<td>79%</td>
</tr>
<tr>
<td>Invasion of squamous epithelium</td>
<td>100%</td>
</tr>
</tbody>
</table>

Zhu et al Am J Clinical Pathology 2009
Dysplastic tubules appear to extend into squamous epithelium

Zhu et al Am J Clinical Pathology 2009
Cribiform architecture

Zhu et al Am J Clinical Pathology 2009
Superficial ulcer

Zhu et al Am J Clinical Pathology 2009
Dysplasia – when in doubt?

1. Ask for bigger pieces
2. Ask for more biopies
3. Ask for a second opinion
Second opinion
Progression to high-grade dysplasia/carcinoma

1 pathologist
2 pathologists agreed
3 pathologists agreed
Take home message

• GERD diagnosis does not require endoscopy
• Endoscopy is for treatment failure and to rule out complications
• GERD definition is changing to include all columnar lined mucosa
Any questions
Any questions