Common Inflammatory Gastrointestinal Disorders:
Endoscopic and Pathologic Correlations

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Disclosure

Financial relationship with Aerie Pharmaceutical
Basics of Pathology...
It Helps to Know Some Pathology

- Knowledge of endoscopic/pathologic correlations can
  - Guide biopsy sampling
  - Help pathologists interpret findings

- Accurate diagnosis of inflammatory disorders is usually possible based upon endoscopic findings, histology and disease distribution
Esophagus

Lumen

Base

Papillae
Esophagitis

• A 30 year-old man with history of asthma presented with difficulty swallowing
Esophageal Biopsy

- Lots of eosinophils with eosinophil microabscesses (circles)
- Luminal orientation of eosinophils
- Eosinophil-rich inflammation at multiple levels of the esophagus
Eosinophilic Esophagitis

Intracellular edema (spongiosis)

Sheets of eosinophils
“scale crust”
Gastroesophageal Reflux Disease

Biopsy of the distal esophagus
# Eosinophilic Esophagitis vs. GERD

<table>
<thead>
<tr>
<th>Features</th>
<th>Eosinophilic Esophagitis</th>
<th>GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophil density</td>
<td>Usually $\geq 15$/hpf</td>
<td>Usually $&lt; 15$/hpf</td>
</tr>
<tr>
<td>Macrosopic distribution</td>
<td>Patchy</td>
<td>More severe distally</td>
</tr>
<tr>
<td></td>
<td>Mulitple levels of the</td>
<td></td>
</tr>
<tr>
<td></td>
<td>esophagus</td>
<td></td>
</tr>
<tr>
<td>Microscopic distribution</td>
<td>Luminally oriented</td>
<td>Evenly dispersed</td>
</tr>
</tbody>
</table>
Eosinophilic Esophagitis
Diagnostic Issues

- Numbers of eosinophils
  - > 15 eosinophils per high-power field is most commonly used (ACG practice guidelines)
  - Overlap with gastroesophageal reflux disease
    - Many eosinophils does not exclude reflux
    - Especially in single samples
    - Especially in the distal esophagus
## Eosinophilic Esophagitis vs. GERD

<table>
<thead>
<tr>
<th>Feature</th>
<th>Eosinophilic Esophagitis</th>
<th>GERD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of eosinophils</td>
<td>Range: 51-204</td>
<td>Range: 20-168</td>
<td>Rodrigo*</td>
</tr>
<tr>
<td></td>
<td>Range: 15-609</td>
<td>Range: 0-377</td>
<td>Dellon</td>
</tr>
<tr>
<td></td>
<td>Range: 7-125</td>
<td>Range: 0-13</td>
<td>Parfitt</td>
</tr>
<tr>
<td>Eosinophils at multiple levels</td>
<td>67%</td>
<td>55%</td>
<td>Rodrigo*</td>
</tr>
<tr>
<td></td>
<td>34%</td>
<td>11%</td>
<td>Dellon</td>
</tr>
<tr>
<td>Eosinophil microabscesses</td>
<td>83%</td>
<td>54%</td>
<td>Rodrigo*</td>
</tr>
<tr>
<td></td>
<td>67%</td>
<td>19%</td>
<td>Dellon</td>
</tr>
<tr>
<td></td>
<td>42%</td>
<td>0%</td>
<td>Parfitt</td>
</tr>
<tr>
<td>Fibrosis of subepithelial tissue</td>
<td>39%</td>
<td>7%</td>
<td>Parfitt</td>
</tr>
<tr>
<td></td>
<td>57%</td>
<td>0%</td>
<td>Chehade</td>
</tr>
<tr>
<td></td>
<td>89%</td>
<td>38%</td>
<td>Li-Kim-Moy</td>
</tr>
</tbody>
</table>

* >20 eosinophils/hpf was an inclusion criterion

Proton Pump Inhibitor Responsive Esophageal Eosinophilia

• Patients with clinical, endoscopic, and histologic findings indistinguishable from eosinophilic esophagitis

• Symptoms remit with proton pump inhibitor therapy

• No distinguishing features identified to date

• Similar molecular signature to eosinophilic esophagitis

• May represent a point on the spectrum between extreme reflux and eosinophilic esophagitis
Patchy Distribution

One specimen from the mid-esophagus of one patient

1-2 eosinophils/hpf

>60 eosinophils/hpf

Up to 5 eosinophils/hpf

0 eosinophils/hpf
Sampling Recommendations

- American College of Gastroenterology (ACG) recommends multiple biopsies (at least 2-4) from the proximal and distal esophagus

- Submitted separately

- Sample abnormal and normal-appearing mucosa
Barrett Esophagus

- A 70 year-old man with chronic gastroesophageal reflux disease and endoscopy suspicious for Barrett esophagus
Barrett Esophagus

- Premalignant condition characterized by replacement of squamous epithelium by glandular mucosa
- Cancer risk: 0.2-0.5% per year
- Jobs for the pathologist
  - Document the presence of goblet cells
  - Detect dysplasia and early carcinoma
Barrett Esophagus

- A brief word about definitions
  - The presence of intestinal metaplasia, in the form of intestinal type goblet cells, is required for a diagnosis
  - At least here and many other (but not all) places
  - At least for now
Diagnosis of Barrett Esophagus

- Well-developed Barrett esophagus with numerous goblet cells
Diagnosis of Barrett Esophagus

- Often a hybrid epithelium with gastric foveolar cells intermixed with non-goblet epithelium
Sampling to Detect Barrett Esophagus

- ACG and American Gastroenterological Association (AGA) Guidelines
  - At least 8 biopsy samples OR
  - At least 4 per centimeter in patients with short (1-2 cm) abnormal segments
Sampling to Detect Dysplasia

- Patients *without* a history of dysplasia
- Detection rates of dysplasia and adenocarcinoma using non-systematic *versus* systematic sampling of Barrett esophagus (Abela *et al.*).

<table>
<thead>
<tr>
<th>Method</th>
<th>Low-grade Dysplasia</th>
<th>High-grade Dysplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-systematic</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Systematic</td>
<td>19%</td>
<td>3%</td>
</tr>
</tbody>
</table>

- Surveillance biopsies at 1-cm intervals in 45 patients *with high-grade* dysplasia in Barrett esophagus (Reid *et al.*)
  - 37 (82%) cancers were present at only 1-cm increment
  - 31 (69%) were present in only one tissue sample
  - 50% would have been undetected by sampling at 2-cm intervals

Sampling to Detect Dysplasia

- Four quadrant biopsies
  - At 2 cm intervals in patients without dysplasia
  - At 1 cm intervals in patients with prior dysplasia
Barrett Esophagus, Negative for Dysplasia

Small, uniform, basally-oriented nuclei

Apical cytoplasm or mucin vacuole
Barrett Esophagus with Low-grade Dysplasia

Crowded, overlapping nuclei – still oriented to the basement membrane (cell polarity preserved)

Nuclear-to-cytoplasmic ratio

Normal density of glands
Barrett Esophagus with High-grade Dysplasia

Crowded, haphazard arrangement of glands
Glands are irregular in size and shape

Loss of cell polarity
Prominent nucleoli
Large nuclei
Indefinite for Dysplasia

- Provisional category when features are equivocal
- NOT a point on the spectrum of dysplasia
- Usually used when low-grade dysplasia is in the differential diagnosis
- Features do not typically overlap with high-grade dysplasia
Barrett Esophagus, Indefinite for Dysplasia

Nuclear-to-cytoplasmic ratio

Surface atypia overlaps with dysplasia, but it is inflamed
Barrett Esophagus, Indefinite for Dysplasia

Gland atypia overlaps with dysplasia, but surface is mature.
Endoscopic Mucosal Resection

• Now the preferred modality for sampling and treating visible abnormalities
• Much better for patients
• Enhances the ability of pathologists to accurately classify intraepithelial neoplasia and stage early carcinomas
  – Presumably, the availability of more tissue leads to less over- and under-reporting.
Pathologists Should…

• Grade dysplasia
• Report on the status of lateral mucosal and deep margins.
  – Status of deep margin often determines subsequent management
• Adenocarcinoma should be assessed for tumor differentiation, depth of invasion, presence of lymphovascular invasion, margin involvement.
Handle with Care

• Should be pinned and fixed prior to sectioning
  – Retraction compromises quality of sections and assessment of margins
Endoscopic Mucosal Resection
Endoscopic Submucosal Dissection

Submucosal glands
Endoscopic Submucosal Dissection
Infectious Esophagitis

- A 56 year-old man who recently underwent stem cell transplant for treatment of acute myeloid leukemia complains of severe dysphagia
Infectious Esophagitis

- Esophagitis in immunosuppressed patients
  - Viral
    - Cytomegalovirus
    - Herpes
  - Fungal
    - Candida

- What is the best area to biopsy?
Cytomegalovirus Infection

Viral inclusions in stromal and endothelial cells (ulcer bed)
Nuclear “owl’s eye” inclusions (black arrows)
Granular cytoplasmic inclusions (green arrows)
Herpes Esophagitis

Viral inclusions in squamous epithelial cells (edge of ulcer)
Nuclear inclusions: “multiple, marginated, molded”
Candida Esophagitis
Candida Esophagitis

Superficial neutrophilic infiltrate
“Shredded wheat keratin”
Hyphae perpendicular to long access of squamous cells “shish kabob”
Infectious Esophagitis
Sampling Recommendations

- CMV: sample the ulcer bed
- HSV: sample the ulcer edge
- Candida: sample the exudate/plaque
Stomach

Antral Mucosa

Body and Fundic (Oxyntic) Mucosa
Chronic Gastritis

- A 55 year-old woman with nausea, vomiting and dyspepsia
- Labs show anemia
Gastric Body Biopsy
Autoimmune Gastritis

- Body-based gastritis
- Deep or full thickness inflammation
- Loss of oxyntic gland “antralization”
Autoimmune Gastritis

Negative gastrin stains tells us we are not in the antrum
Chromogranin stains highlights ECL cell hyperplasia
Helicobacter pylori Gastritis

Antrum-based gastritis
Luminally oriented lymphoplasmacytic infiltrate in lamina propria
Neutrophils in the epithelium
Curvilinear organisms attached to epithelial cells and within mucin

Courtesy R. Pai, MD
Autoimmune vs. *H. pylori* Gastritis

<table>
<thead>
<tr>
<th>Features</th>
<th>Autoimmune</th>
<th><em>H. pylori</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammatory infiltrate</td>
<td>Lymphoplasmacytic infiltrate</td>
<td>Lymphoplasmacytic infiltrate</td>
</tr>
<tr>
<td></td>
<td>Lymphoid aggregates</td>
<td>Lymphoid aggregates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neutrophils in epithelium</td>
</tr>
<tr>
<td>Macrosopic distribution</td>
<td>Body/Fundus predominant</td>
<td>Antrum predominant</td>
</tr>
<tr>
<td>Microscopic distribution</td>
<td>Deep or full thickness</td>
<td>Superficial, band-like</td>
</tr>
<tr>
<td>Diagnostic findings</td>
<td>Loss of oxyntic glands, ECL cell hyperplasia</td>
<td>Adherent bacillary organisms</td>
</tr>
</tbody>
</table>
Chronic Gastritis
Sampling Recommendations

• Updated Sydney system: 5 mucosal biopsy specimens to evaluate chronic gastritis
  • 2 antral samples (greater and lesser curvature)
  • 2 corpus samples (greater and lesser curvature)
  • 1 sample from incisura angularis
Chronic Gastritis

- Sydney system may fail to detect intestinal metaplasia and dysplasia in some cases

<table>
<thead>
<tr>
<th>Finding</th>
<th>Sydney compliant</th>
<th>Seven Biopsies</th>
<th>Nine Biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal metaplasia</td>
<td>90%</td>
<td>95%</td>
<td>97%</td>
</tr>
<tr>
<td>Dysplasia or carcinoma</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Duodenum
Celiac Disease

- A 45 year-old woman with type I diabetes presents with chronic diarrhea, weight loss, and iron deficiency anemia.

- Serology reveals positive TTG and anti-gliadin antibodies.

![Image of Celiac Disease pathology](image-url)
Celiac Disease

Normal villous architecture
Increased intraepithelial lymphocytes
Celiac Disease

Near-complete villous blunting
Increased chronic inflammatory cells in the lamina propria
Marked intraepithelial lymphocytosis
Celiac Disease
Diagnostic Issues

• Broad spectrum of histologic changes

• Patchy nature of villous blunting
  • Approximately half of patients have varying degrees of villous blunting in samples from different parts of the duodenum

• Intraepithelial lymphocytes are usually increased in all samples, but that may be seen in other disorders [H. pylori infection, drug (NSAIDs), peptic duodenitis]

Duodenal Bulb Biopsies

• Sampling historically discouraged
• Normal histologic features of the proximal duodenum overlap with features of celiac disease
• Peptic duodenitis overlaps with celiac disease
Duodenal Bulb Biopsies

• Biopsies of duodenal bulb increase sensitivity for celiac disease detection in some studies

• May be the only site with diagnostic findings, especially in pediatric patients

• Submit bulb biopsies separately or specify which sites are included in a single specimen (e.g. “Duodenum, 2nd and bulb”)

Celiac Disease
Sampling Recommendations

- ACG clinical practice guidelines
  - 1-2 biopsies of the bulb
  - At least 4 from post-bulbar duodenum
Summary and Conclusions

• Judicious, but adequate sampling of the gastrointestinal tract results in high-yield, informative biopsies

• It helps to know some pathology (and it is fun to look at)

• Some abnormalities may be missed even if practice guidelines are adhered to, so the endoscopist’s judgment is paramount

• Tell your pathology colleagues
  • What you saw
  • What you sampled
  • What you are looking for

• Come and see for yourself!
Thanks and Good Luck!