CAN PATHOLOGY SAMPLES DIFFER BETWEEN EE, GERD AND EGID?

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Disclosures
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- GSK
- Cephalon (formerly Ception)
- Meritage

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History of histopathology

• Small numbers of eosinophils were reported in esophageal biopsies of patients who had GERD, and eosinophils became pathognomonic of GERD.¹

• Subsequently, large numbers of intraepithelial eosinophils in esophageal biopsies were reported in adults and children who had normal pH probe tests/did not respond to therapy for GERD, and required/responded to dietary therapy.²,³
History of histopathology

• More complete descriptions of the histopathology of esophageal eosinophilia followed:\n  – Abscesses
  – Surface layering
  – Elongated papillae
  – Basal zone hyperplasia
  – Lamina propria fibrosis
History of histopathology

1982
History of histopathology
History of histopathology

1986
History of histopathology

1987
History of histopathology

1988
History of histopathology

• The histopathology of EoE is not new in either children or adults.\textsuperscript{6-10}

• Most studies conclude that the incidence of the histology has remained somewhat stable, but the prevalence has increased due to both increased recognition and increased numbers of endoscopies and biopsies.

• Even small numbers of intraepithelial eosinophils may indicate chronic disease.\textsuperscript{6}
How strict are the cut-off for EE?

- Restated: Does a peak eosinophil count \( \geq 15/\text{hpf} \) distinguish EoE from other causes of esophageal epithelial eosinophilia?
- No.
- Again: Do other diseases have \( \geq 15/\text{hpf} \)?
- Yes.
- **EoE is a clinicopathologic diagnosis. Histopathology must be interpreted in the clinical context.**
EoE vs GERD

PRIMARY EOSINOPHILIC ESOPHAGITIS

Materials and Methods

Patients

Between January 1, 1993, and July 1, 1995, 1,809 patients were evaluated for GERD disease. Each patient displayed chronic gastrointestinal symptoms (≥2 months’ duration) including abdominal–epigastric pain or regurgitation–vomiting, chest pain, dysphagia, nighttime coughing, choking, poor appetite, weight loss, or irritability. Upper gastrointestinal series or recurrent esophageal evaluation performed in all patients. Whenever symptoms persisted despite medical management (mechanical, feeding alteration, antacids, or H2 blockers) or when the symptoms were complicated by gastroesophageal bleeding, respiratory disease, or weight loss, an esophagogastroduodenoscopy (EGD) was performed by a board-certified pediatric gastroenterologist using an Olympus video endoscope (Olympus, Columbia, MD, USA) (N30, S30, or CIP 110—depending on the patient’s age). Patients with known gastrointestinal disorders (Crohn’s disease, ulcerative colitis, celiac disease), anatomic abnormalities (mucosal biopsy, hiatal hernia, duplication) or systemic disease (cancer, chronic renal disease, scleroderma) were excluded.

Five hundred eighty-three patients underwent EGD for GERD. Treatment consisted of ranitidine with metamizole or cipradine. These patients who improved during the study were considered to be the reference group of children with GER. If the patient’s symptoms worsened or if they did not show improvement with medication, the dose of ranitidine was increased to a maximum of 1 mg/kg twice daily, and four times daily. After 3 months, another EGD was performed if symptoms remained despite the therapy. Patients who continued to have histologic evidence of eosinophilic esophagitis continued receiving cipradine but with the addition of one of the other medications (1 mg/kg per day; minimum, 10 mg/day; maximum, 50 mg/day).

(1809) patients with GER symptoms

(583) with persistent symptoms = EGD

(165) normal EGD

(418) EGD + esophagitis

(214) + esophageal eos

(204) no esophageal eos

(184) improved with therapy

(30) no improvement (≥15 eos/HPF)

(8) + antral/duodenal eos

(22) esophageal eos only

(20) study patients

surgery

FIG. 1. Flow chart depicting the selection of study patients.
EoE vs GERD

- Early studies identified patients with ≥15 eosinophils/hpf who did not respond to anti-reflux therapy and who had abnormal pH probe studies.\textsuperscript{11}

- Some patients who respond to anti-reflux therapy, and may have abnormal pH probe studies, have EoE histology.\textsuperscript{12-15}
EoE vs GERD

• 712 adults with upper GI symptoms\textsuperscript{16}
• 35/712 (4.9\%) had \( \geq 15/\text{hpf} \) pretherapy in biopsies from upper/mid esophagus
• Treated with PPI; response = resolution of clinical symptoms with \(<5\) eosinophils/hpf on repeat biopsy
• 26/35 (74\%) responded to PPI
• 9/35 (26\%) did not = EoE
<table>
<thead>
<tr>
<th>Histopathologic findings, n (%)</th>
<th>PPPI-R 15-35/hpf N=17</th>
<th>PPI-R &gt;35/hpf N=9</th>
<th>EoE N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial distribution</td>
<td>5 (29%)</td>
<td>6 (66%)</td>
<td>5 (55%)</td>
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<tr>
<td>Degranulating eosinophils</td>
<td>12 (70%)</td>
<td>7 (77%)</td>
<td>7 (77%)</td>
</tr>
<tr>
<td>Eosinophils microabscesses</td>
<td>2 (11%)</td>
<td>3 (33%)</td>
<td>5 (55%)</td>
</tr>
<tr>
<td>Basal cell hyperplasia</td>
<td>12 (70%)</td>
<td>9 (100%)</td>
<td>8 (88%)</td>
</tr>
<tr>
<td>Papillae elongation</td>
<td>12 (70%)</td>
<td>7 (77%)</td>
<td>7 (77%)</td>
</tr>
<tr>
<td>Intercellular edema</td>
<td>15 (88%)</td>
<td>8 (88%)</td>
<td>8 (88%)</td>
</tr>
<tr>
<td>Lamina propria present</td>
<td>9 (52%)</td>
<td>4 (44%)</td>
<td>7 (77%)</td>
</tr>
<tr>
<td>Lamina propria fibrosis</td>
<td>6 (35%)</td>
<td>4 (44%)</td>
<td>7 (77%)</td>
</tr>
<tr>
<td>5 eo in lamina propia</td>
<td>3 (17%)</td>
<td>3 (33%)</td>
<td>6 (66%)</td>
</tr>
<tr>
<td>pH monitoring</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Normal/Pathologic</td>
<td>0/7</td>
<td>2/5</td>
<td>4/3</td>
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PATHOLOGY OF EoE

• Eosinophil-predominant inflammation, often with many more than 15 eosinophils/hpf, associated with abscesses, surface layering, epithelial hyperplasia, etc is highly characteristic but not pathognomonic of EoE.

• The distribution of the changes in the esophagus are also not pathognomonic of EoE.
Are there other criteria to use in questionable cases?

• Degranulation, microchips, gene expression?
  – Yes, these can be helpful, but require stains in addition to the usual H&E and are best considered research tools currently.
Are there other criteria to use in questionable cases?

- Extracellular eosinophil granules increase as the number of eosinophils increase, and mechanical factors may induce deposition.\(^{17,18}\)
- Extracellular deposits of eosinophil granule contents may be extensive even in biopsies with few intact eosinophils, and may identify EoE in questionable cases.\(^{15,19-21}\)
- The number of mast cells is increased in EoE compared to GERD.\(^{15,22}\)
Are there other criteria to use in questionable cases?

- IgE-positive cells are found in EoE biopsies but few if any are present in GERD.\textsuperscript{22-25}

- Genome-wide association studies have identified numerous genes upregulated in EoE, with confirmed increased mRNA and protein expression, including eotaxin-3, periostin and TSLP.\textsuperscript{26-30}
Are there other criteria to use in questionable cases?

- Down-regulated genes include filaggrin and involucrin that are essential for epithelial barrier integrity.\textsuperscript{31}
- IL-5 gene expression (determined by mRNA) is detected only in EoE.\textsuperscript{30}
How do you distinguish the person who comes in already on empiric therapy?

- Biopsies from patients on empiric therapy can be problematic.
- Biopsies from patients on anti-reflux therapy only that show the characteristic histopathology of EoE fulfill the criteria for a diagnosis of EoE.
- Biopsies from patients on anti-reflux therapy and EoE therapy that show the histopathology of EoE fulfill the criteria for diagnosis of EoE.
How do you distinguish the person who comes in already on empiric therapy?

- Biopsies from patients on anti-reflux therapy and therapy for EoE that do not show eosinophil-predominant inflammation could represent either disease. Repeat biopsy after discontinuing EoE therapy may be required.
How to make the diagnosis of EG/EC?

• Eosinophils normally exist in colon and stomach.
• Eosinophils normally exist everywhere in the GI tract except the esophagus.
• Early descriptions of eosinophilic GI disease were mostly based on bowel resections that emphasized changes in the wall.
How to make the diagnosis of EG/EC?

• Few studies have attempted to establish norms for eosinophil concentrations in mucosa throughout the GI tract.\textsuperscript{18,32,33}

• Histologic criteria for diagnosis of eosinophilic disorders in sites other than the esophagus do not exist.

• Nonhistologic markers, such as abnormalities of gene structure or expression, do not exist for eosinophilic diseases other than EoE.
How to make the diagnosis of EG/EC?

• In my own practice, numerous eosinophils without signs of epithelial invasion or chronic changes is referred to as mucosal eosinophilia, and biopsies that show eosinophil-predominant inflammation associated with infiltration and damage are diagnosed as eosinophilic gastritis or enteritis or colitis. The presence of any acute inflammatory cells raises the possibility of idiopathic inflammatory bowel disease.
SELECTED REFERENCES
5 Straumann A, et al. Natural history of primary eosinophilic esophagitis: A follow-up of 30 adult patients for up to 11.5 years. Gastroenterology 2003;125:1660


8 Vanderheyden AD, et al. Emerging eosinophilic (allergic) esophagitis: increased incidence or increased recognition? Arch Pathol Lab Med 2007;131:777


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