Eosinophilic Esophagitis: A hidden cause of dysphagia

Causes of Dysphagia

- GERD/Peptic Stricture
- Esophageal webs and rings
- Achalasia/Motility disorders
- Mass
- Eosinophilic esophagitis

Eosinophilic Esophagitis

- A chronic, immune-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation.

- First cases described in late 70’s
- 1982 eosinophils described in GERD
- Adult cases described 1990s
  - 12 adults with dysphagia, no anatomic obstruction, no esophagitis
  - All with dense infiltration of eosinophils
  - 11/12 with normal esophageal acid exposure on 24 hr pH monitoring
Increased Diagnosis of Eosinophilic Esophagitis Over the Years

**Eosinophilic Esophagitis**

Richard J. Noel, M.D., Ph.D.
Philip E. Putnam, M.D.
Marc E. Rothenberg, M.D., Ph.D.
Cincinnati Children’s Hospital Medical Center
Cincinnati, OH 45229

Eosinophil-associated gastrointestinal disorders: A world-wide-web based registry

Juan P. Gasque, MD, Ainsley V. Morgan, MB, BS, Jennifer A. Redhe, RN, Margaret M. Gallon, MD, PhD, Leslie B. Reisman, MD, Ainsley V. Morgan, MB, BS

**GI Eosinophil-Related Publications**


Truly Increasing Incidence or Increased Recognition?

- Epidemic phenomenon?
- Environmental factors?
- Increasing incidence of allergic diseases?
- Greater clinical awareness?
- Increased diagnostic testing/detection?

Increased Incidence?
Increased Recognition?

Epidemiology

World-Wide Detection

Epidemiology

- Widely distributed
  - All racial and ethnic groups

- Prevalence in US estimated 0.44%
  - In patients with dysphagia 10-15%
  - 11-55% food impactions in adult series
  - 1-4% of PPI refractory GERD

- Strong familial association
  - Family history of EoE reported in 7% to 10% of patients, and 5% had siblings with EoE.
  - Personal or family history of allergic diseases in 50% to 91% of EoE patients.

Patient Characteristics

- Male predominant in adults (3:1)
- Third or fourth decade
- May have peripheral eosinophilia or increased IgE levels
- Patients often have a family history or personal history of atopy

Food Allergies in EoE

- 19-80% of pediatric patients with EoE had positive skin test result to a panel of food allergens and aeroallergens
  - Do not always have direct correlation between positive food allergy test result and response to treatment
  - Less prominently reported in adults (13-40%)
- Commonly implicated foods: milk, eggs, soybeans, wheat, nuts
- IgE mediated v. delayed hypersensitivity

Aeroallergens

- Cases where symptoms vary by season
- Pattern of inflammatory cells and cytokine expression in EoE is similar to that seen in allergic airway disorders.
- Pulmonary exposure to these inhaled antigens has been hypothesized to result in mast cell activation in the esophagus.
- Additionally, aeroallergens may be swallowed.

Pathogenesis

Role of Eosinophils in EoE

- Esophagus normally devoid of eosinophils.
- In vitro studies have shown that eosinophil granule constituents are toxic to a variety of tissues
  - increase smooth muscle reactivity
  - induce degranulation of mast cells and basophils
  - upregulate fibroblast growth factor

Key Players

- IL-5
  - Induce experimental EoE
  - Primes eosinophils to react to chemoattractants
  - Promotes development, activation and migration of eosinophils
- Eotaxin
  - Eosinophilic chemotactic factor, promotes accumulation and adhesion
- IL-13
  - Upregulates IgE
  - Important for eosinophil recruitment and survival

Eosinophil Activation

- Major basic protein.
  - Diminishes tight junctions in epithelial cells.
  - Induces organ contraction.
  - Remodeling
  - Stimulates mast cell and basophil degranulation.
- Leukotrienes.
  - Increases mucus secretion and vascular permeability.
  - Stimulates smooth muscle contraction.
- Cytokines.
  - Potentiates the inflammatory response.
  - Inhibits acetylcholine release leading to dysmotility.
  - Chronic inflammation leads to fibrosis and remodeling.
Other causes of esophageal eosinophilia

- GERD
- Crohn’s Disease
- Collagen vascular disease
- Infectious esophagitis
- Drug-induced injury
- Hypereosinophilic syndrome
- Eosinophilic gastroenteritis
- Scleroderma

How is the diagnosis of EoE made?

Proposed Diagnostic Guidelines

- **Clinicopathologic diagnosis**
  - Clinically characterized by symptoms related to esophageal dysfunction
  - Pathologically, 1 or more biopsy specimens must show eosinophil-predominant inflammation
  - Isolated to esophagus
  - Other causes of esophageal eosinophilia should be excluded, specifically PPI-responsive esophageal eosinophilia
  - Disease should remit with treatments of dietary exclusion, topical corticosteroids or both

Clinical Features

- Dysphagia
- Esophageal food impaction
- GERD-like symptoms
- Chest pain
- Abdominal pain
- Odynophagia
- Diarrhea
- Weight loss
Symptoms stratified by age

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTT</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8</td>
</tr>
<tr>
<td>Heartburn</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>18</td>
</tr>
<tr>
<td>Chest pain</td>
<td>22</td>
</tr>
<tr>
<td>Food impaction</td>
<td>25</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>30</td>
</tr>
</tbody>
</table>

Endoscopic Appearance of EoE

- Known as “ringed esophagus” or “corrugated esophagus.”
- Classic endoscopic appearance of EoE.
- Multiple concentric rings.

Feline Esophagus

Adherent White Papules

- White papules (1-2 mm in diameter) that do not wash off.
- Loss of vascular pattern.
- Focal areas of eosinophilic infiltration/microabscesses.

Small Caliber Esophagus

- Narrow, fixed internal diameter.
- Poor expansion on air insufflation.
- Proximal and/or distal stenosis.

“Crepe Paper” Mucosa

- Fragile mucosa.
- Mucosal abrasions or tear with minimal contact.
- Potentially responsible for high frequency of tears/perforations post dilation.

Other Endoscopic Findings

- Esophageal furrows.
  - Vertical and lateral esophageal lines.
- Normal Esophagus.
  - Reported in about 12% to 33% of cases.
Histopathology of Eosinophilic Esophagitis

- Increased number of intraepithelial eosinophils in an esophageal biopsy.
- Significant variability in the diagnostic criteria for eosinophilic esophagitis exists.

How Many Biopsies?

- Intraesophageal pH monitoring.
  - Normal results reported in 82% of adults with EoE.
  - Potentially useful in excluding GERD.

- Esophageal manometry.
  - Abnormal results in 53% of adults with EoE.
  - Most frequent abnormality observed was non-specific peristaltic movements.

- EUS.
  - Thickening of the individual tissue layers of the esophagus.

Other Diagnostic Modalities

Histology

- Increased number of intraepithelial eosinophils in an esophageal biopsy.
- Significant variability in the diagnostic criteria for eosinophilic esophagitis exists.
What features distinguish EoE from GERD?

Differentiation of GERD from EoE

- Greater density of mucosal eosinophilia in EoE.
- GERD associated with 5-10 eos/HPF.
- Involvement of multiple segments of the esophagus in EoE, whereas GERD is typically confined to the distal esophagus.
- Distinguishing histological features such as eosinophilic microabscesses, basal cell hyperplasia, and lamina propia eosinophils noted in EoE.
- Immunohistology

### Table 4

Multivariate model predicting EoE

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at biopsy</td>
<td>0.98</td>
<td>0.95–1.00</td>
<td>0.09</td>
</tr>
<tr>
<td>Dysphagia (symptom)</td>
<td>11.8</td>
<td>3.77–36.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Food allergy (documented)</td>
<td>11.2</td>
<td>2.79–45.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Rings seen on EGD</td>
<td>9.9</td>
<td>1.93–51.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Linear furrows seen on EGD</td>
<td>6.4</td>
<td>0.62–65.5</td>
<td>0.12</td>
</tr>
<tr>
<td>White plaques seen on EGD</td>
<td>5.4</td>
<td>0.49–58.5</td>
<td>0.17</td>
</tr>
<tr>
<td>Hiatal hernia present on EGD</td>
<td>0.21</td>
<td>0.04–1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Maximum eosinophils count</td>
<td>1.01</td>
<td>1.01–1.02</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Degranulating eosinophils</td>
<td>4.81</td>
<td>1.52–15.2</td>
<td>0.008</td>
</tr>
</tbody>
</table>

*Multivariate logistic regression with a backwards elimination strategy was used to develop model variables.

*Odds ratio represents the odds of being a case for a 1 year increase in age at biopsy.

*Odds ratio represents the odds of being a case for a one cell increase in eosinophil count.

Role of PPI

- Two potential roles:
  - Part of diagnostic evaluation
  - May have concomitant GERD

- Gastric acid is not thought to be the primary mediator associated with EoE pathogenesis.

- Even if pathologic reflux is not present, acid exposure has potential to irritate the inflamed esophagus.

- Recent data suggest that PPIs may have an anti-inflammatory effect

Treatment Options for Eosinophilic Esophagitis

- Acid Suppression.
- Dietary Modifications.
- Corticosteroids.
- Leukotriene Receptor Antagonists.
- Biologics.
- Endoscopic Dilation.
Dietary Therapy

- Removal of food antigens has clearly been demonstrated to treat successfully both the symptoms and the underlying histopathology in children. Scarce data in adults.

- Several therapeutic regimens
  - Amino acid based formula can be utilized, thus removing all potential food allergens
  - Specific food elimination based on allergy testing and clinical history
  - Simply remove foods most likely to cause EoE
    - (milk, egg, soy, wheat, nuts, and seafood).

Six Food Elimination Diet: Adults

- Patients underwent 6 weeks of a six food elimination diet (milk, egg, soy, wheat, nuts, and seafood).
  - If patients had resolution of esophageal eosinophilia then 1 food was added back every 2 weeks.
  - Nearly 80% of patients had histological improvement with diet.

**Esophageal Eosinophil Count/HPF**

P<0.05  P<0.05

Gonsalves N, et al. A Prospective Clinical Trial of Six Food Elimination Diet and Reintroduction of Causative Agents in Adults with Eosinophilic Esophagitis. (abstract).

**Gastroenterology** 2008; 134 (Suppl): A104-5.

Six Food Elimination Diet: Adults

- Significant improvement in symptom scores (94%).
- Endoscopic improvement observed in 78% of patients.
- All patients had return of their symptoms and endoscopic abnormalities after reintroduction of foods.

**Esophageal Eosinophil Count/HPF**

P<0.05  P<0.05

Gonsalves N, et al. A Prospective Clinical Trial of Six Food Elimination Diet and Reintroduction of Causative Agents in Adults with Eosinophilic Esophagitis. (abstract).

**Gastroenterology** 2008; 134 (Suppl): A104-5.

Possible diagnostic and treatment algorithm for dietary intervention alone in adults with eosinophilic esophagitis (EE).


© 2007 Mayo Foundation for Medical Education and Research
Corticosteroids

- Systemic steroids effective but associated with significant adverse events
  - 1998: use of systemic steroids significantly improved both clinical symptoms and histology of 20 of 21 children with EoE
- Swallowed topical steroids administered by metered dose inhaler or viscous solution
  - Improvement in histology, symptoms, esophageal remodeling
- In RCT in kids, swallowed fluticasone and oral prednisone had comparable efficacy
  - Reserve systemic steroids for severe cases: small-caliber esophagus, weight loss and hospitalization
- High relapse rate, up to 70% require repeat treatment

**References**

Topical Steroids

- Fluticasone 440-800ug bid
  - Administer the MDI without the use of a spacer. MDI should be inserted into the mouth, sprayed with lips sealed around the device.
  - The powder should then be swallowed and not rinsed.
  - Patients should not eat or drink for at least 30 minutes.
  - Goal is to swallow approximately 80% of the medication
- Budesonide
  - 2 small RCTs from Switzerland showed improvement
  - Regimen continued for 6-8 weeks and then individualize need for long-term therapy

**References**

Leukotriene Receptor Antagonists and Mast Cell Stabilizers

- Cromolyn sodium has never been formally studied in patients with EoE prospectively. In a review, 14 patients treated, nobody improved clinically or histologically
- Leukotriene receptor antagonists
  - 7/8 complete symptom resolution, 1 with partial
  - 6/8 recurrence within 3 weeks
  - Minimal adverse effects
  - No significant improvement in histology
  - Not enough data to support use

**References**
- Liacouras et al J Allergy Clin Immunol July 2011

Biologic Agents

- Monoclonal antibody anti-IL-5: Mepolizumab
  - Open-label phase I/II study
    - 4 pts with EoE, 16 weeks of treatment with follow-up esophageal biopsies at week 20.
    - Improvement in symptoms, QOL and eosinophilia
  - Straumann et al 2010 RCT
    - 11 pts, significant reduction in eos but not sx’s
  - Multicenter RCT 2011
    - 59 children, different doses
    - Reduced eos in 90%
Endoscopic Dilation

- Esophageal dilation has proven successful in improving patient symptoms of dysphagia.
- Reports of easier mucosal tearing, significant pain, and reports of esophageal perforation.
  - Older studies reported 5% perforation, 7% hospitalization for chest pain
- Systematic review 1975-2010:
  - 92% improved symptoms for 1-2 years
  - Improvement of dysphagia independent of eos
  - Post-procedure pain for several days is common
  - Perforation rate <0.1%
- Dilation does not affect underlying eosinophilic inflammation.

Natural History

- Dysphagia:
  - 23% increasing sx's over time, 37% stable, 37% better
  - 50% make minor lifestyle changes
  - Eosinophilia may decrease over time
  - Endoscopic appearance does not change over time
  - Peripheral eosinophilia predicts worse course
- No malignant potential reported
- Normal life expectancy

Monitoring

- Not well established. No association with the development of esophageal malignancy.
- Main aim is to prevent progressive esophageal dysfunction and detect complications with therapy
- Kids- periodic endoscopy
- No clear role for surveillance endoscopy in adults
  - can more accurately report symptoms
- Consensus: regular clinic visits and question symptoms and compliance with therapy
- Consider EGD q 2-3 years to evaluate for progressive disease

Conclusion

- EoE is an emerging/increasingly recognized disease.
- Should be considered in patients with history of food impaction, dysphagia, refractory GERD, especially if fit typical profile.
- Clinicopathologic diagnosis (can be a hidden cause).
- Consider PPI trial in patients without warning symptoms
- Refer for EGD if dysphagia, food impaction, refractory heartburn symptoms
- No malignant potential, normal life expectancy.
Thank you!