EOSINOPHILIC ESOPHAGITIS

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Grand Rounds Presentation
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Outline

- History of the disease
- Epidemiology and Demographics
- Pathophysiology
- Workup and Findings
- Complications
- Treatment
First described in 1978 but GERD was thought to be the driving force (1)

1982 Winter et al. (2)
- Correlated intraepithelial eosinophils (>1 eos/hfp) with PH, manometry, endoscopy and histologic findings suggestive of reflux

1985 Lee et al. (3)
- Found that 91% of patients (n=11) with >5 eos/hpf had evidence of reflux esophagitis
1993 Attwood et al. (4)

- Retrospective review of 12 patients
- All had undergone esophogram, PH monitoring, and manometry
- Characterized as
  - Low-grade (<20 eos/hpf)
  - High-grade (>20 eos/hpf)
  - On average patients had 56 eos/hpf
- 92% had high-grade eosinophilia but normal PH monitoring
- 58% had allergies or asthma
- Compared data to 90 normal controls with 24-hour PH proven GERD and only 48% had intraepithelial eosinophilia with an average of 3.3 eos/hpf
Kelly et al (5)
- 75 pediatric patients resistant to medical therapy for reflux
- 31% had persistent eosinophilia
- 6 week elemental diet for 12 patients
  - 80% complete resolution of symptoms
  - 60% complete resolution of endoscopy findings
  - 70% of patients also had asthma or eczema
  - Average eosinophilia dropped from 41 to 0.5 eos/hpf
- 10 underwent reintroduction of foods
  - Symptoms returned within 1 hour (median)
  - Cow milk, soy, wheat, peanut, egg
Case report of 21y/o with EE, asthma and allergy. Documented eosinophilia on biopsy that:

- Resolved in the winter season
- Relapsed in the pollen season (Fall/Spring)
Spontaneous resolution of symptoms

150 eos/hpf

12 eos/hpf
Further evidence for allergy

- 1999 Ruchelli et al (7)
  - 56% of patients failing anti-reflux treatment had:
    - Wheezing
    - Atopic
    - Rhinitis
  - 16 patients in failure group
    - 8 completely resolved with corticosteroids
    - 4 improved with elemental diet
Further evidence for allergy

- 2003 Markowitz et al (8)
  - 51 children with documented EE
  - Placed on elemental diet for 4 weeks
  - 96% improvement in vomiting, abdominal pain, dysphagia
  - Mean time to improvement of 8.5 days
  - Showed a drop of 33.7 to 1.0 eos/hpf after diet
### 2007 Diagnostic Criteria (9)

| **Histology** | 1. Esophageal biopsies ≥15 eos/HPF  
2. Normal gastric and duodenal biopsies  
3. Patients must have biopsies after 6–8 weeks of twice daily acid suppression with proton pump inhibitors or have a documented negative pH study |
|---|---|

| **Presence of symptoms** | **Adults**  
Dysphagia  
Food impaction  
Heartburn  
Regurgitation  
Chest pain  
Odynophagia | **Children**  
Abdominal pain  
Heartburn  
Regurgitation  
Nausea/vomiting  
Dysphagia  
Failure to thrive |
Reflux ruled out as the culprit

Allergy assumed to play a role

Diagnostic criteria had been set

Who does this affect and what happens to those affected?
Epidemiology

- Seems to be relegated to westernized world
- Incidence (10)
  - Random population survey of 3000 adults
  - 1563 invited to have endoscopy
  - 1000 agreed and had esophageal biopsies
  - Eosinophilia present in 5%
  - 1% met histologic criteria for EE
- Prevalence is increasing (11)
  - 0.5/100,000 in 1995
  - 8.9/100,000 in 2004
  - Mirrors increases in atopic and allergic disease
  - 50-70% with EE also have atopic disease
Males represent 60-80% of cases
Age 30-50 in adults and 5-10 in children
Genetics
- 7% have a parent with EE or a stricture
- 5% have a sibling with EE
- Eotaxin-3 has been implicated
Children have proven more affected by foods than adults (70% vs 30%)
Considerations in Children (1)

- Children present with more systemic symptoms
- Those with IgE-mediated forms do not respond as well to corticosteroids
- Strictures rarely reported in children
  - Supports the idea that the disease is chronic
- Common for children with eosinophilic esophagitis to have parents with longstanding dysphagia, documented strictures or eosinophilia on biopsy as well
Lag of 4.3 years between onset of symptoms and diagnosis

Restricted to the esophagus

Chronic disorder that cannot be outgrown
- Chronic Persistent
- Chronic Relapsing

Prolonged disease leads to remodeling of the esophagus

Not associated with premalignant or malignant transformation

17 year database shows no mortality related to EE
Quality of Life (12)

- No lifestyle changes (47%)
  - Most learn to cope with symptoms

- Minor lifestyle changes (50%)
  - Influenced food choices
  - Refuse solid foods without liquid chasers

- Major lifestyle change (3%)
  - Engineer required to change jobs because his current jog required eating lunch with clients on a regular basis
Rhinosinusitis in 19-25% of patients with EE
62% of children have personal or FH of allergy
EE implicated in
- Rhinosinusitis
- Laryngitis
- Subglottic Stenosis
- Recurrent croup
  - Major Basic Protein (MBP)
  - Eosinophilic Cationic Protein (ECP)
Pathophysiology
Players in the Pathogenesis of EE

(14)

- Environmental exposure
  - Food or aeroallergens
- Drugs
- Sensitization-Th2 Activation
  - Allergic Genetic Background
- Eosinophilic Esophagitis Genetic Predisposition
  - SNP in the 3'UTR of eotaxin-3 gene
Allergic disease common in EE but not everyone has them

Only a minority present with anaphylaxis
  - Therefore classical IgE mediated mast cell activation is not the common pathway

Seasonal variation has led to studies of food and aeroallergens
  - Allergens have been shown to increase IL-5 and IL-13 suggesting a Th-2 associated pathway
  - IL-5 and IL-13 are important in growth, chemotaxis, and activation of eosinophils
Epicutaneous exposure does not induce EE and lung inflammation unless a nasal challenge is also performed (15,16)

- Despite:
  - Strong systemic Th-2 response
  - Chronic cutaneous exposure
  - Bone marrow eosinophilopoiesis
  - Circulating eosinophilia

Knockout mice with loss of STAT 6, IL-13, IL-4, and IL-5 do not develop EE to external triggers unless intratracheal IL-13 is used (17,18)

- Intratracheal IL-13 induces airway and esophageal eosinophilia

*Therefore both external triggers and a strong intrinsic Th2 response are required making this a multifactorial disease process.
Genetics (14,18)

- **Eotaxin 3**
  - Signature gene for eosinophilic esophagitis
  - Powerful eosinophil activator and chemoattractant
  - Induced in all patients with EE regardless of allergy status or gender
  - Only one SNP (eotaxin-3) has been identified with EE using microarray technology
    - 50x more elevated than normal controls
  - IL-13 induces eotaxin-3 in keratinocytes through the STAT6 pathway → epithelial proliferation and fibrosis
  - Mice with genes targeted against CCR3 (the eotaxin-3 receptor) are protected from development of EE.

- **IL-13**
  - Two chains for the IL-13 receptor located on chromosome X
  - 70% of patients with EE are male
Esophageal Epithelium (19)

- Esophagus is the only GI segment devoid of eosinophils
- Epithelium is squamous but not keratinized
  - Keratinocytes directly exposed to esophageal contents
  - Esophageal epithelium may play a role in the induction of esophageal inflammation
Most specific cytokine for eosinophil
- Growth
- Differentiation
- Activation
- Survival
- Migration from marrow to blood

Overexpressed in the esophagus of patients with EE

Animal studies have shown:
- Overexpression of IL-5 is present in esophageal biopsies
- No esophageal response to antigens in mice deficient IL-5
IL-13 (19)

- Implicated in:
  - Asthma
  - Eczema/Atopic dermatitis
  - Allergic Rhinitis

- Overexpression leads to:
  - Eosinophilia
  - Mucous overproduction
  - Airway hyper responsiveness

- Intratracheal IL-13 induces pulmonary inflammation and is associated with the development of EE.
Eosinophils (19)

- Crystalloid Core
  - Major Basic Protein (MBP)
- Matrix
  - Eosinophil cationic protein (ECP)
  - Eosinophil-derived neurotoxin (EDN)
  - Eosinophil peroxidase (EPO)
- Effects of these proteins
  - Cytotoxic effects on epithelium
  - Increases smooth muscle reactivity
  - Degranulation of mast cells
Mast Cells (IgE) and Eosinophils (Non-IgE) in EE

- Release lipid mediators
  - Smooth muscle contraction
  - Vascular permeability
  - Mucous secretion
- Leukotriene release
  - Recruit inflammatory cells
- TGF-B
  - Tissue fibrosis
Mechanism (19)

Allergens -> APC -> Antigen Presenting Cells

Blood:
- B-cell
- Eosinophil
- T-cell

Esophagus:
- IgE
- Mast cell
- IL-18
- T-cell
- IL-5
- Eotaxin
- GF
- Muscle cell
- Collagen Accumulation
- Epithelial cell hyperplasia
- Fibroblast proliferation
Time to Take a Step Back

- What is the Differential?
- How do we get to this Diagnosis?
**Differential Diagnosis**

- Food allergy
- GERD
- Candida esophagitis
- Inflammatory bowel disease
- Celiac disease
- Parasitic infection
- Churg-Strauss syndrome
- Connective tissue disease (Scleroderma)
- Drug allergy
- Hypereosinophilic syndrome
- Autoimmune enteropathy
- Viral esophagitis (CMV/HSV)
Important Historical Question

- Is there any food avoidance?
- Do you eat very slowly?
- Do you chew your food excessively?
- Do you have to drink after each bite of food?
- Other GI complaints? (nausea, vomiting, diarrhea)
Physical Findings

- Due to the isolation of the esophagus, findings on physical exam are seldom

- We therefore rely on history and endoscopy with biopsy to make the diagnosis
Further Workup

- Laboratory Testing
- pH monitoring
- Esophageal manometry
- Radiography
- Endoscopy with biopsy
- Allergy Testing
Peripheral Eosinophilia
- 5-50% of patients with EE

IgE levels
- Elevated in 70% with eosinophilia
- Respond less to corticosteroid treatment

*Neither test is diagnostic
*Neither test can predict disease progression
Reported in 20 studies of patients with EE

- Of 228 Adults
  - 40% were evaluated with PH studies
  - 82% were normal

- Of 223 children
  - 78% were evaluated with PH studies
  - 90% were normal

*Recommended that pH testing or PPI therapy for 6 weeks required before diagnosis can be made*
Schematic of pH monitoring

Esophageal pH Monitoring

LES = lower esophageal sphincter

pH probe
Esophageal Manometry (9)

- Esophageal manometry reported in 10 studies
  - LES in 77 adults:
    - Normotensive in 66
    - Hypotensive in 10
    - Hypertensive in 1
  - Peristaltic abnormalities 30/77 patients
    - 28/30 nonspecific peristaltic abnormalities
    - 1/30 distal esophageal spasms
    - 1/30 nutcracker esophagus
  - Overall 41/77 (53%) had abnormal manometric exams
- All 14 children evaluated had normal manometry.

*Recommendation that manometry does not provide diagnostic value in EE*
Esophageal Manometry Tracing

Ineffective oesophageal motility

Low amplitude contraction

Non-transmitted contraction
Very nonspecific and can be discordant with Endoscopy findings

Can identify:
- Strictures
- Small caliber esophagus
- Malrotation
- Hiatal Hernia

*Recommended as ancillary test in pediatric patients with negative endoscopy
Patient returns after 6-8 weeks of therapy and still is complaining of symptoms
## Diagnostic Criteria (9)

| **Histology** | 1. Esophageal biopsies ≥15 eos/HPF  
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Regurgitation  
Nausea/vomiting  
Dysphagia  
Failure to thrive |
Mucosal changes are diverse and there are no "cardinal signs"

Thus making the diagnosis is difficult with endoscopy alone

This is why biopsy is included in the evaluation
Endoscopic Findings of EE

- Linear furrowing
- White plaques
- Edema
- Shearing
- Friability
- Crepe paper mucosa
- Small caliber esophagus
- Concentric mucosal rings

*30% of children and 9% of adults will have visually normal endoscopy exams (22,23)
Smooth contour, whitish pink color

Narrow band imaging with green/blue light showing glycogenic acanthosis
Abnormal Findings (21)

**Concentric Rings**
- Linear furrowing occurs in 25-100% of patients
- Loss of Vascularity occurs in 93% of patients
Specificity of 95%
Clustered Eosinophils or micro abscesses breaking through mucosa
Sensitivity of 30% to 50%
Specificity of 95%
Erosions at the GE junction

Furrowing and absent vascularity in proximal esophagus

Erosions at the GE junction
Proximal strictures related to eosinophilic esophagitis

Distal strictures more common for GERD or a combination of effects
Number and Location of Biopsies

- **Location**
  - If you biopsy just the distal esophagus you will miss 20\% of diagnoses (24)
  - Therefore you must biopsy the distal and proximal esophagus

- **Number**
  - Children require 4 biopsies (25) and Adults require 5 biopsies (24) to achieve a sensitivity of 100\%
  - Therefore biopsy in four quadrants both distally and proximally

**Distal is 5cm above squamocolumnar junction and proximal is 10cm above the distal mark**
Histological Findings

- >15 eso/hpf
- Basal layer thickening
- Superficial layering
- Micro abscesses (>4 eos clustered together)
- Eosinophilic degranulation
Thickened Basal Layer

Eosinophils close to luminal surface
More Histology (9)

Superficial Layering

Large Micro abscesses

Small Micro abscess
Role of Allergy Testing

- Skin prick testing (IgE mediated)
  - Standardized and very consistent results
  - Commonly identifies egg, milk, soy, wheat, peanuts, beans, rye, and beef

- Atopy patch testing (non-IgE mediated)
  - More variable in preparations and methodologies
  - Identifies corn, soy, and wheat
50% (13/26) had ≥1 food allergen

93% (14/15) had allergy to ≥1 aeroallergen

- Overall 81% had ≥1 allergy

Most common food allergens

- Peanut
- Egg white
- Soybean
- Cow’s milk
- Tree nuts
Complications of EE
Endoscopy reports suggest strictures in 57%

Radiographic reports suggest 77% Strictures can occur early in disease rather than as a long term consequence

*Much less common in children at 6% (6)
Food Impaction

- Occurs in about 60% of patients and about 50% of patients with esophageal food impactions are diagnosed with EE (1)
- Dry rice and meats
- Characterized by:
  - Retrosternal discomfort
  - Delayed passage
  - Hypersalivation
- Obstruction can persist for hours
Chronic eosinophilic esophagitis is the most common cause of food impaction
Secondary GERD

- Chronic inflammation leads to dysfunction of LES
- Remedios et al. (27)
  - 10/26 patients with EE had reflux diagnosed by PH monitoring
  - 8/10 with reflux also showed reduced pressures of the LES on motility studies
Candidiasis is a well known result of steroid therapy but occurs spontaneously in those with EE.

- Leads to exacerbations in dysphagia.
- Antifungal treatment significantly improves symptomatology.
Biopsy proven candida at presentation

Near resolution at 6 weeks. Biopsy showed 38 eos/hpf
Esophageal Rupture (Boerhaave’s, 1)

- 3 cases of spontaneous rupture reported
  - 2 after repetitive vomiting for GI infection
  - 1 after retching due to impacted food bolus

- Although uncommon still must be aware of this complication especially in those with longstanding disease
Treatment

- Dietary Modifications
- Oral and Topical Corticosteroids
- Leukotriene Inhibitors
- Recurrent dilation
- Acid Suppression
Dietary Modifications (28)

- No RCT evaluating dietary therapy
- Case series data shows that 92-98% patient response to elemental diet (symptomatic and histologic improvement)
- Food is reintroduced starting with least antigenic food first and adding one new food weekly
- EGD is repeated after every 5-7 new foods
- This is very daunting psychosocially
Dietary Modifications (28)

- More easily tolerated than elemental diets
- Based on the most allergic foods
  - Dairy
  - Soy
  - Egg
  - Wheat
  - Beef
  - Peanut
  - Corn
- 74% of patients will respond symptomatically and histologically to this diet
Systemic Corticosteroids

- Used for acute exacerbations and refractory cases
- Often used in combination with topical steroids
- Prednisone 1mg/kg/d, maximum 60mg/day
- Success (28)
  - 95% improvement in symptoms and histology
  - 90% recurrence upon cessation of therapy
- Side effects
  - Osteoporosis, poor growth, mood changes, adrenal suppression
Randomized Prospective Trial
80 patients evaluated

Treatment
- Prednisone (2mg/kg/d)
- Fluticasone (880ug/d 1-10 y/o; 1760ug/d >10y/o)
- Treated for 4 weeks with 8 week weaning protocol

Symptoms improved in F(32/32) and P(35/36)
Histology improved in F(30/32) and P(32/34)
- No significant differences in groups

45% of patients relapse by 24 week follow up
Topical Corticosteroids

- First line treatment after dietary changes
- Clinical and histologic resolution within weeks

Drugs
- Fluticasone propionate or Budesonide
- Dosing is orally either BID or QID
- Start with high dose induction followed by low dose maintenance

Side effects
- Oral Candidiasis in 15% (29)
The role of Anti-inflammatory Drugs

- **Cromolyn Sodium**
  - Has not been shown to be effective

- **2008 Attwood et al. (30)**
  - 8 patients treated with 100mg Montelukast with maintenance of 20-40mg daily for 14 months
    - Symptom relief in 7/8
    - 6/8 recurred within 3 weeks of stopping meds
  - Repeat endoscopy was not performed therefore eosinophilia response cannot be elucidated
Monoclonal Antibodies

- Mepolizumab (Anti-IL-5)
  - Several clinical trials have shown good results
- Anti-TNF-β
  - Prevent hyper vascularity and fibrosis

Awaiting larger clinical trials
Stricture Dilation

- Last resort when medical treatment fails or when patient has food impaction
- Risk of esophageal perforation or tearing has been reported
- 2008 Schoepfer et al. (31)
  - Retrospective analysis of 10 patients resistant to topical therapy
  - 1 stricture (8pts), 2 strictures (1pt), 3 strictures (1 pt)
  - Prompt relief in all patients with only post procedural odynophagia
  - No complications
  - Sustained response for 6 months
2010 Jacobs and Spechler (32)

- Systematic Review of all papers describing esophageal dilations for EE.
- 18 reports, 468 patients, 671 dilations
- 11/18 reports described tears during dilation
- Only 1 perforation described due to dilation itself (0.1%)
Balloon pull-through technique for esophageal dilation in eosinophilic esophagitis

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Non-invasive markers of disease
Studies defining long-term management strategies
Studies defining treatment of patients resistant to standard therapy
Should we treat the symptoms or the eosinophilia?
Should we be empirically treating all patients with PPI’s?
Treat patients with 6-8 weeks worth of PPI therapy, but what if it’s not GERD?
2009 Reimer et al. (33)
- Randomized, Double Blinded, Placebo controlled trial of 120 normal patients
  - 12 weeks of placebo
  - 8 weeks of Nexium 40mg/day then 4 weeks placebo
- Measured GI symptom rating scores (GSRS) weekly
- Results
  - Both groups similar at baseline
  - Higher GSRS (worse) score at 10, 11, 12 weeks
  - 44% vs 15% reported >1 acid related symptom week 9-12

*If you start a PPI, you may not be able to stop it*
Summary

- Diagnosis of Exclusion
- Becoming more prevalent
- Multifactorial Pathogenesis
- History and Endoscopy with biopsy are the keys to diagnosis
- Disease cannot be outgrown and therefore symptom relief is the mainstay of treatment
- Treatment recommendations are still evolving, but many will still require PPI therapy
## Types of Hypersensitivity Reactions

Table 2. Gell And Coombs Classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>Effector Mechanism</th>
<th>Typical Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (Immediate)</td>
<td>IgE</td>
<td>Anaphylaxis, angioedema, urticaria</td>
</tr>
<tr>
<td>Type II (Cytotoxic)</td>
<td>IgM, IgG, complement, phagocytosis</td>
<td>Cytopenia, nephritis</td>
</tr>
<tr>
<td>Type III (Immune Complex)</td>
<td>IgM, IgG, complement, precipitins</td>
<td>Serum sickness, vasculitis</td>
</tr>
<tr>
<td>Type IV (Delayed)</td>
<td>T-Lymphocytes</td>
<td>Contact dermatitis</td>
</tr>
<tr>
<td>Other Idiopathic</td>
<td>Varies</td>
<td>Non-specific rash</td>
</tr>
</tbody>
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References

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