Eosinophilic Esophagitis

DR. FRITZ POTGIETER
GASTROENTEROLOGIST
PRETORIA EAST HOSPITAL

Definition

- Eosinophilic esophagitis (EoE) is defined as "a chronic, immune/antigen-mediated, esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation"

EPIDEMIOLOGY

- Incidence has increased by 0.35 per 100,000 population between 1991 and 1995 to 9.45 per 100,000 between 2001 and 2005.
- Majority of affected adults have been men in their 20s or 30s
- Mean age at diagnosis was 34 years (range 14 to 77 years)
- Symptoms (predominantly dysphagia) had been present for an average of 4.5 years prior to diagnosis.
- Significantly more likely to be Caucasian (84 percent compared with 73 percent.)

NATURAL HISTORY

- 30 untreated patients followed for an average of 7.2 years, dysphagia persisted in 29 (97 percent). During follow-up, symptoms increased in 23 percent, were stable in 37 percent, and decreased in 37 percent. Attacks of dysphagia occurred more frequently in patients with blood eosinophilia or with pronounced findings on endoscopy.

CLINICAL MANIFESTATIONS

- Dysphagia (Most common)
- Food impaction (up to 54 percent of patients.)
- Chest pain that is often centrally located and does not respond to antacids
- Gastroesophageal reflux disease-like symptoms/refractory heartburn (1-4 % of patients with refractory reflux)
- Upper abdominal pain
- Esophageal strictures have been noted in up to 31 percent of patients.
- Esophageal dysmotility may also be observed.

ASSOCIATIONS WITH OTHER DISORDERS

- Strong association with allergic conditions
- 28 to 86 percent of adults and 42 to 93 percent of children with eosinophilic esophagitis have another allergic disease.
- In one series, 10 of 13 patients (77 percent) had a history of an allergic disorder. Twelve of 13 patients (92 percent) had an absolute peripheral eosinophilia.
- 9 of 12 patients (75 percent) had concurrent eosinophilic gastroenteritis.

- Association with celiac disease has been reported in multiple studies
- Association with connective tissue disorders, caustic injury and antibiotic exposure in infancy has been described.

DIAGNOSIS

- Based upon symptoms, endoscopic appearance, and histological findings.
- first diagnostic test is typically an upper endoscopy with esophageal biopsies following two months of treatment with a proton pump inhibitor.

Esophageal eosinophilia

- Esophageal eosinophilia is the finding of eosinophils in the squamous epithelium of the esophagus.
- Seen in association with multiple conditions.

- Gastroesophageal reflux disease (GERD)
- Eosinophilic esophagitis (EoE)
- Eosinophilic gastrointestinal diseases (EGIDs)
- Celiac disease
- Crohn's disease
- Infection
- Hypereosinophilic syndrome (HES)

Eosinophilic esophagitis

- The most recent guideline, issued in 2013 by the American College of Gastroenterology, proposed the following.

- Symptoms related to esophageal dysfunction
- Eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of ≥15 eosinophils per high power field
- Mucosal eosinophilia is isolated to the esophagus and persists after two months of treatment with a proton pump inhibitor (PPI) trial
- Secondary causes of esophageal eosinophilia have been excluded.
- A response to treatment (dietary elimination; topical glucocorticoids) supports the diagnosis but is not required.

PPI-responsive esophageal eosinophilia

- Patients with clinical and histologic features compatible with eosinophilic esophagitis but who respond histologically to a PPI have been described as having PPI-responsive esophageal eosinophilia.
- Pathogenesis of esophageal eosinophilia in such patients is not well understood.

THE CHALLENGE OF DISTINGUISHING PROTON-PUMP INHIBITOR-RESPONSIVE ESOPHAGEAL EOSINOPHILIA AND EOSINOPHILIC ESOPHAGITIS: ARE THEY THE SAME DISEASE?

- In 2013, two studies conducted in adults, including 66 and 103 patients with >15 eos/HPF, respectively, failed to find distinguishing clinical, endoscopic, and histological features between patients ultimately found to have EoE or PPI-REE
- Levels of eotaxin-3,interleukin (IL)-5, and IL-13 expression in the distal and proximal esophagus in 40 adult patients with >15 eos/HPF (60% EoE and 40% PPI-REE) were indistinguishable between the two patient groups.

- Of these (75 percent) had a clinicopathologic remission on treatment with a PPI.
- Thus using histologic criteria alone to diagnose eosinophilic esophagitis may lead to an overestimation of the prevalence of the disorder.
- Because of the association of GERD with esophageal eosinophilia, biopsies for eosinophilic esophagitis should be obtained after two months of treatment with a PPI or after an esophageal pH study has excluded reflux.

A recent promising genetic tool, the EoE

diagnostic panel, showed a sensitivity and specificity of >95% in identifying paediatric and adult EoE, and in distinguishing between EoE patients in remission and controls. This still needs further validation.

ADVANCES IN UNDERSTANDING PROTON-PUMP INHIBITOR-RESPONSIVE ESOPHAGEAL EOSINOPHILIA

PATHOPHYSIOLOGY

- Epithelial barrier impairment and
- Potential anti-inflammatory effects of PPI therapy.

ANTI-INFLAMMATORY EFFECTS OF PROTON-PUMP INHIBITOR THERAPY

- Eotaxin-3 is a potent eosinophil chemo attractant.
- Expression of eotaxin-3 is stimulated by Th2 cytokines, such as IL-4 and IL-13.
- PPIs inhibited in-vitro IL-4 and IL-13 signalling through STAT6.
- Omeprazole blocks Th2 cytokine-stimulated eotaxin-3 expression in oesophageal squamous cell cultures from both GERD and EoE patients

Effect of proton-pump inhibitor therapy on esophageal eosinophilia-related epithelial barrier impairment

- Coexisting GERD might be the primary event, allowing the potential entry of food-derived allergenic molecules through acid-induced epithelial barrier damage in the esophagus.
- GERD-induced epithelial damage could expose the deeper layers of the esophageal squamous epithelium to antigens that ordinarily could not penetrate a normal mucosa.

- Acid and weak acidic perfusion of the distal esophagus has been shown to impair mucosal integrity in both the exposed distal esophagus and proximal, non-exposed esophagus.

PPI-REE in summary

- PPI-REE occurs commonly in adult patients with an EoE phenotype.
- At baseline (before a PPI trial), PPI-REE is indistinguishable from EoE.
- PPI-REE is more common in patients with concomitant GERD, but GERD (or at least, pathological acid exposure) is not necessary for PPI-REE to occur.

- Esophageal barrier impairment may occur with exposure to acidic and weakly acidic reflux, therefore calling into question the validity of a rigid classification of PPI-REE patients (GERD and non-GERD patients) based upon pH monitoring results.
- Studies have demonstrated in-vitro and in-vivo anti-inflammatory effects of PPI through modulation of the Th2 pathway, independent of acid suppression.

DISTINCTION FROM GERD

- The most common consideration in the differential diagnosis of eosinophilic esophagitis is GERD
- Large numbers of eosinophils (>100/HPF) may be seen in association with GERD.
- In a study of 712 patients with upper gastrointestinal symptoms undergoing endoscopy, 35 (5 percent) had ≥15 eosinophils/HPF on biopsies obtained from the upper-middle esophagus.

- Histologic features suggestive of eosinophilic esophagitis rather than GERD include:
- Large numbers of intraepithelial eosinophils on histologic examination
- presence of more than 20 eosinophils/HPF
- Patients with eosinophilic esophagitis are also more likely to have ≥15 eosinophils/HPF in three or more biopsies taken at different levels.

- proximal esophageal involvement
- subepithelial and lamina propria fibrosis
- eosinophilic abscesses
- more severe basal cell hyperplasia
- activated mucosal mast cells/increased epithelial tryptase density
- degranulating eosinophils

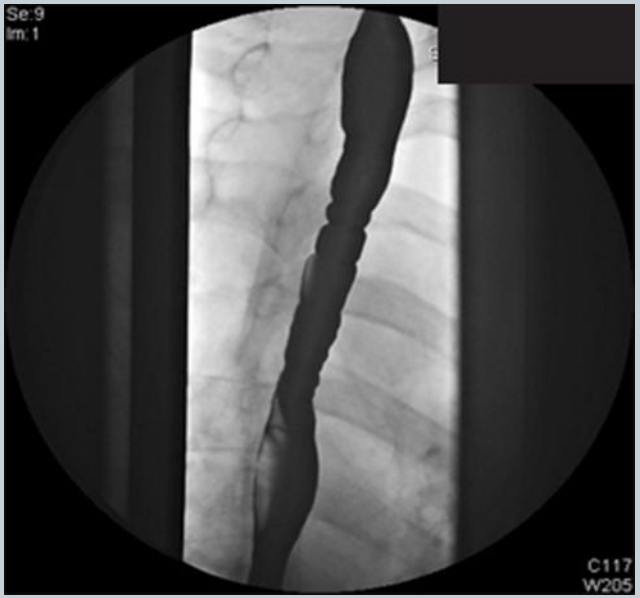
ENDOSCOPIC FINDINGS

- Stacked circular rings (“feline” esophagus): 44 percent
- Strictures (particularly proximal strictures): 21 percent
- Attenuation of the subepithelial vascular pattern: 41 percent
- Linear furrows: 48 percent
- Whitish papules (representing eosinophil microabscesses): 27 percent
- Small calibre esophagus: 9 percent

HISTOLOGY

- The vast majority of patients have at least 15 eosinophils per high power field (peak value) in at least one biopsy specimen after taking a proton pump inhibitor
- Esophageal eosinophilia in the absence of clinical features is not sufficient to make a diagnosis of eosinophilic esophagitis.
- should be obtained from the distal esophagus as well as either the mid or proximal esophagus.

RADIOLOGY



- can help characterize anatomic abnormalities and provide information on the length and diameter of strictures.
- Findings described in patients with eosinophilic esophagitis undergoing barium studies include strictures and a ringed esophagus.

LABORATORY TESTS

- 50 to 60 percent of patients with eosinophilic esophagitis will have elevated serum IgE levels (>114,000 units/L)
- Peripheral eosinophilia is seen in 40 to 50 percent of patients but is generally mild

TREATMENT OF EoE

- dietary, pharmacological, endoscopical and experimental therapies.

DIETARY THERAPY

- effective first-line treatment for eosinophilic esophagitis in children and adults.
- Testing-directed elimination diet
- Skin prick testing (SPT) and atopy patch testing (APT)
- Empiric elimination diet
- six-food elimination diet
- milk, egg, soy, wheat, peanuts/tree nuts, fish/shellfish
- fish/shellfish and peanuts/tree nuts are rare triggers for EoE, and foods such as grains and meats are more common triggers.

- Elemental diet
- The patient is placed on an elemental formula, which eliminates all potential food allergens.

PHARMACOLOGIC THERAPY

- Acid suppression
- one-third of patients with suspected eosinophilic esophagitis have a good clinical and histologic response to PPIs alone, suggesting that GERD, or a PPI-responsive form of esophageal eosinophilia, may be responsible.

- In a randomized trial, 42 patients with newly diagnosed eosinophilic esophagitis were randomly assigned to treatment with aerosolized swallowed fluticasone (440 mcg twice daily) or esomeprazole (40 mg daily) for eight weeks followed by an upper endoscopy with biopsies
- In patients without coexisting GERD, there was no significant difference in resolution of esophageal eosinophilia between the esomeprazole and fluticasone treatment arms (18 versus 24 percent). In contrast, among patients with GERD, those treated with esomeprazole were significantly more likely to have resolution of esophageal eosinophilia as compared with fluticasone (100 versus 0 percent).

Fluticasone

- Patients ≥11 years of age (including adults): 220 mcg inhaler, two sprays twice daily.
- A 2013 guideline issued by the American College of Gastroenterology (ACG) suggested that the dose in adults can range from 880 to 1760 mcg/day in divided doses.
- Patients who are destined to respond tend to do so quickly (within one week and often within one to two days). In patients who respond, treatment is given for eight weeks.

- Patients frequently relapse when treatment is stopped, with reported relapse rates of 14 to 91 percent.
- patients who relapse, we treat and discuss maintenance topical glucocorticoids or a trial of a dietary approach. For patients who do not respond to fluticasone, options include a higher dose of fluticasone, a change to oral viscous budesonide, or a dietary approach.

Budesonide

- Appears to be effective for treating eosinophilic esophagitis.
- 36 adults and adolescents with active eosinophilic esophagitis were randomized to budesonide 1 mg twice daily or placebo for 15 days.
- Patients who received budesonide were more likely to have significant improvements in dysphagia compared with those who received placebo (72 versus 22 percent).

Topical vs. systemic steroids

- Trial included 80 children with eosinophilic esophagitis who were randomly assigned to oral prednisone or swallowed fluticasone
- Almost all of the patients, regardless of treatment, were symptom free by four weeks. Histologic improvement was seen to a greater degree in the prednisone group.

MAINTENANCE THERAPY

- Maintenance therapy with topical steroids and/or dietary restriction should be considered for all patients especially the following group

- Severe dysphagia or food impaction
- High-grade esophageal stricture
- Rapid symptomatic/histologic relapse following initial therapy.
- Maintenance dose of fluticasone (880 mcg daily in divided doses) or oral viscous budesonide (1 mg daily).

Experimental and ineffective therapies

- Antihistamines- Little benefit has been seen in patients treated with medications aimed at controlling allergies, including antihistamines.
- Montelukast- symptoms improved but no improvement noted in esophageal eosinophilia.

PROGNOSIS

- Untreated, patients may remain symptomatic or have episodic symptoms. Symptoms frequently recur in patients treated with a short course of topical glucocorticoids.
- 30 adults who were followed for an average of seven years.
- The majority of patients had persistent dysphagia
- Attacks of dysphagia were more common in patients who had peripheral eosinophilia
- Eosinophilic infiltration persisted in all symptomatic patients, but the degree of tissue eosinophilia appeared to decrease.

- Thank you.