UPDATE ON ESOPHAGITIS

GIPS Forum, March 17 2018

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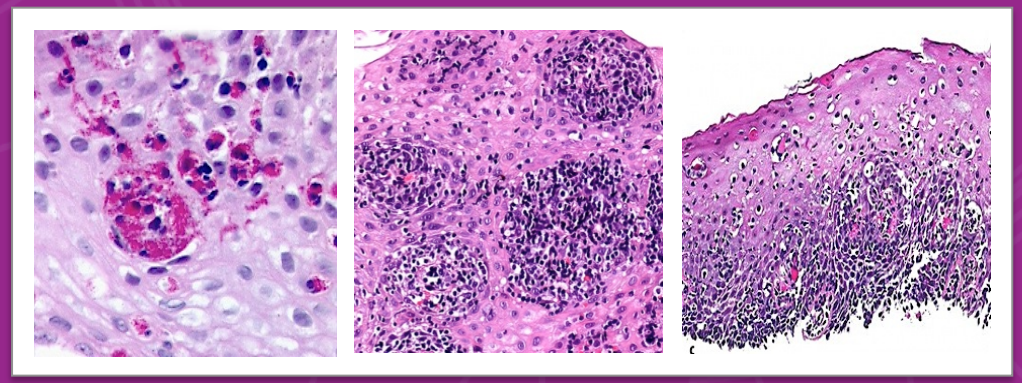
Mount Sinai Hospital, University of Toronto



107TH ANNUAL MEETING
GEARED TO LEARN

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Creating a Better Pathologist

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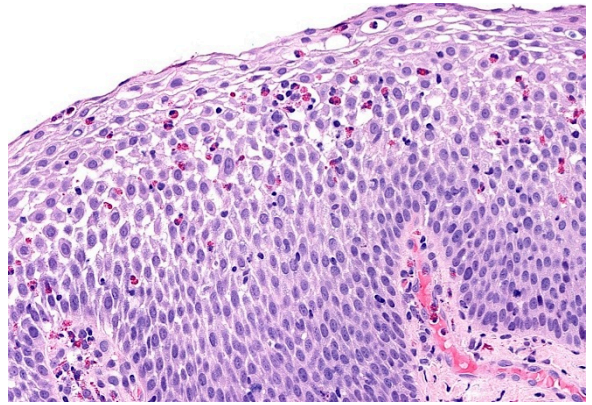
The following faculty reported no relevant financial relationships: (Richard Kirsch)

USCAP staff associated with the development of content for this activity reported no relevant financial relationships.

Outline

1. Esophageal eosinophilia

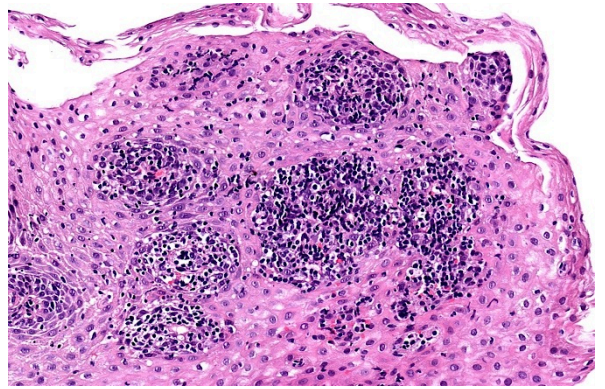
- What is PPI responsive eosinophilia?
- Which features should be reported?
- Should reports provide differential diagnosis or just be descriptive?



2. Intraepithelial lymphocytes in esophageal biopsies

3. Some of the newer forms of esophagitis

- Lymphocytic esophagitis
- Esophageal lichen planus
- IgG4 related esophagitis



4. Significance of epidermoid metaplasia

What is PPI responsive esophageal eosinophilia?

INTERNATIONAL DATELINE

THE RED SECTION

Am J Gastroenterol 2017; 112:1770–1773

Proton Pump Inhibitor Therapy for Eosinophilic Esophagitis: A Paradigm Shift

Javier Molina-Infante, MD, PhD[1,2] and Alfredo J. Lucendo, MD, PhD[2,3]

Am J Gastroenterol 2017; 112:1770–1773; doi:10.1038/ajg.2017.404; published online 31 October 2017

Eosinophilic esophagitis (EoE) is a chronic local immune-mediated esophageal disease, characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation (≥15 eosinophils per high power field) (1). First described in the early 90s (2), it currently constitutes the most prevalent cause of chronic esophagitis after gastroesophageal reflux disease (GERD) and the leading cause of dysphagia and food impaction in children and young adults (1). Without question, the consideration of proton pump inhibitor (PPI) therapy within the diagnostic and/or therapeutic algorithm has been the most evolving topic over the past decade in the field of EoE. Major advances in this field have been accomplished or endorsed by European researchers, especially from Spain. This study aims to provide a historical view on these challenging changes, which are summarized in **Table 1**.

histologic esophageal abnormalities normalized following the treatment with a PPI, implicating acid reflux as the underlying cause."

It is important to stress that 2007 recommendations established a dichotomous distinction between patients, which could be diagnosed with either GERD or EoE upon response to PPI therapy/pH results, but could not have both disorders concomitantly. These diagnostic criteria were counterintuitive, since the likelihood of coexistence of GERD and EoE (more common in young male population) was *a priori* high. By that time, some visionary authors posed the possibility that this rigid distinction between GERD and EoE could be simplistic, given the potential mechanisms of interaction between both disorders (5).

2017 EOE guidelines

Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults

Alfredo J Lucendo[1,2], Javier Molina-Infante[2,3], Ángel Arias[2,4], Ulrike von Arnim[5], Albert J Bredenoord[6], Christian Bussmann[7], Jorge Amil Dias[8], Mogens Bove[9], Jesús González-Cervera[2,10], Helen Larsson[9], Stephan Miehlke[11], Alexandra Papadopoulou[12], Joaquín Rodríguez-Sánchez[13], Alberto Ravelli[14], Jukka Ronkainen[15], Cecilio Santander[2,16], Alain M Schoepfer[17], Martin A Storr[18], Ingrid Terreehorst[19], Alex Straumann[20] and Stephen E Attwood[21]

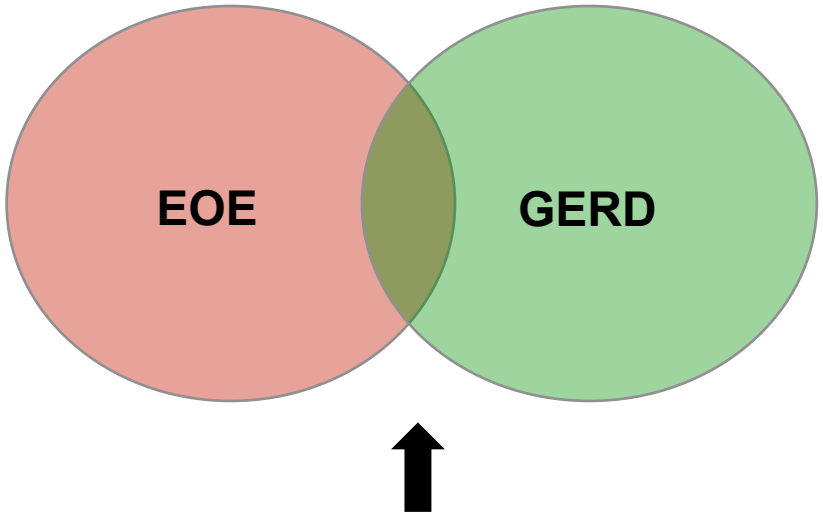
UNITED EUROPEAN GASTROENTEROLOGY ueg journal

United European Gastroenterology Journal
2017, Vol. 5(3) 335–358

Re-evaluation of PPI-REE as a distinct entity

Historical perspective

Distinction between EOE and GERD a diagnostic challenge



Assumption:
Only GERD should respond to PPIs

2007

AGA INSTITUTE

GASTROENTEROLOGY 2007;133:1342–1363

Eosinophilic Esophagitis in Children and Adults: A Systematic Review and Consensus Recommendations for Diagnosis and Treatment

Sponsored by the American Gastroenterological Association (AGA) Institute and North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition

GLENN T. FURUTA,* CHRIS A. LIACOURAS,‡ MARGARET H. COLLINS,§ SANDEEP K. GUPTA,‖ CHRIS JUSTINICH,¶ PHIL E. PUTNAM,# PETER BONIS,** ERIC HASSALL,‡‡ ALEX STRAUMANN,§§ MARC E. ROTHENBERG,‖‖ and Members of the First International Gastrointestinal Eosinophil Research Symposium (FIGERS) Subcommittees##

Diagnostic Guidelines

Clinical symptoms of esophageal dysfunction
≥15 Eosinophils in 1 high-power field
Lack of responsiveness to high-dose proton pump inhibition (up to 2 mg/kg/day) or
Normal pH monitoring of the distal esophagus

3rd group of patients

- Clinical
- Endoscopic
- Histologic

} features of EOE

But responded to PPI

2011

Eosinophilic esophagitis: Updated consensus recommendations for children and adults

J Allergy Clin Immunol 2011;128:3-20

Chris A. Liacouras, MD, Glenn T. Furuta, MD, Ikuo Hirano, MD, Dan Atkins, MD, Stephen E. Attwood, MD, FRCS, FRCSI, MCh, Peter A. Bonis, MD, A. Wesley Burks, MD, Mirna Chehade, MD, Margaret H. Collins, MD, Evan S. Dellon, MD, MPH, Ranjan Dohil, MD, Gary W. Falk, MD, MS, Nirmala Gonsalves, MD, Sandeep K. Gupta, MD, David A. Katzka, MD, Alfredo J. Lucendo, MD, PhD, Jonathan E. Markowitz, MD, MSCE, Richard J. Noel, MD, Robert D. Odze, MD, FRCP, Philip E. Putnam, MD, FAAP, Joel E. Richter, MD, FACP, MACG, Yvonne Romero, MD, Eduardo Ruchelli, MD, Hugh A. Sampson, MD, Alain Schoepfer, MD, Nicholas J. Shaheen, MD, MPH, Scott H. Sicherer, MD, Stuart Spechler, MD, Jonathan M. Spergel, MD, PhD, Alex Straumann, MD, Barry K. Wershil, MD, Marc E. Rothenberg, MD, PhD,* and Seema S. Aceves, MD, Ph[

Inclusion of the term PPI-responsive esophageal eosinophilia.

Diagnostic guideline

EoE is a clinicopathologic disease. Clinically, EoE is characterized by symptoms related to esophageal dysfunction. Pathologically, 1 or more biopsy specimens must show eosinophil-predominant inflammation. With few exceptions, 15 eosinophils/hpf (peak value) is considered a minimum threshold for a diagnosis of EoE. The disease is isolated to the esophagus, and other causes of esophageal eosinophilia should be excluded, specifically PPI-responsive esophageal eosinophilia.

PPI-REE
New disease phenotype

2013

ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE)

PRACTICE GUIDELINES

Evan S. Dellon, MD, MPH[1,6], Nirmala Gonsalves, MD[2,6], Ikuo Hirano, MD, FACG[2,6], Glenn T. Furuta, MD[3], Chris A. Liacouras, MD[4] and David A. Katzka, MD, FACG[5]

Am J Gastroenterol 2013; 108:679–692;

Recommendations

Proton-pump inhibitor esophageal eosinophilia (PPI-REE) should be diagnosed when patients have esophageal symptoms and have histologic findings of esophageal eosinophilia, but demonstrate symptomatic and histologic response to proton-pump inhibition. At this time, the entity is considered distinct from EoE, but not necessarily a manifestation of GERD. (Recommendation conditional, evidence low)

PPI responsive esophageal eosinophilia

Evidence accumulated:

- PPI-REE
- EOE

} Virtually indistinguishable

- *Cheng E et al. Gut. 2013: 62:824-32*
- *Molina-Infante J et al Aliment Pharm Ther. 2014;40:955-65*
- *Van Rhijn B et al. Clin Gastroenterol Hepatol. 2014;12:1815-23*
- *Wen T et al. J. Allergy Clin Immunol. 2015; 135:187-97*
- *Lucendo AJ et al. J. Allergy Clin Immunol. 2016; 137:931-34*
- *Sodikoff J et al. J. Allergy Clin Immunol. 2016; 137:631-33*
- *Shoda T et al. J Allergy Clin Immunol 2017; 139 : 2010-13*

Transcriptome analysis of proton pump inhibitor–responsive esophageal eosinophilia reveals proton pump inhibitor–reversible allergic inflammation

Ting Wen, PhD,[a] Evan S. Dellon, MD,[b] Fouad J. Moawad, MD,[c] Glenn T. Furuta, MD,[d] Seema S. Aceves, MD, PhD,[e]* and Marc E. Rothenberg, MD, PhD[a]* *Cincinnati, Ohio, Chapel Hill, NC, Bethesda, Md, Aurora, Colo, and La Jolla, Calif*

J Allergy Clin Immunol 2015;135:187-97

- Very similar pattern of gene up- and down-regulation in EOE & PPI-REE
- Distinct from that of GERD
- Almost completely reversed following PPI monotherapy

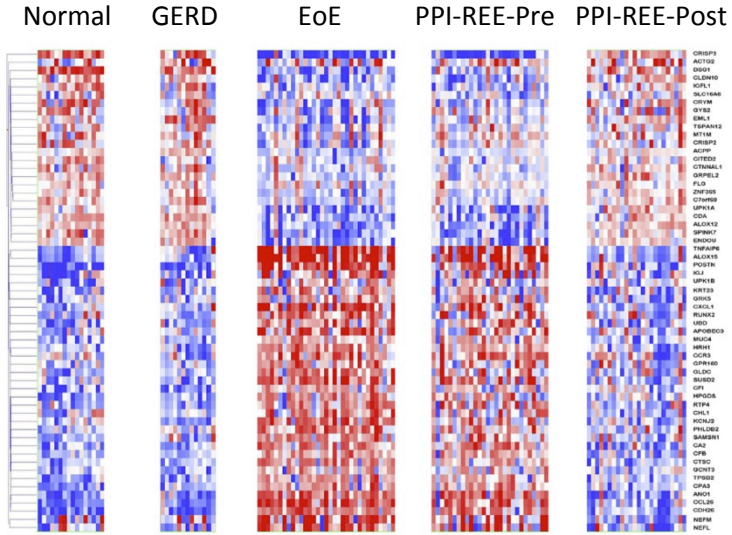


FIG 1. Comparison of esophageal transcriptomes of study cohorts. A total of 114 samples from 5 centers were analyzed by using the EDP. Heat maps were generated on the basis of the 59 EoE genes that passed a greater than 50% call rate of the EDP's 77 significant genes (F59). *Red* indicates higher expression (upregulation), and *blue* represents lower expression (downregulation). *NL*, Healthy control subjects; *PPI-REE-post*, posttherapy PPI-responsive esophageal eosinophilia; *PPI-REE-pre*, pretherapy PPI-responsive esophageal eosinophilia.

Including hallmark EOE genes:

- **CCL26** (eosinophil chemotaxis)
- **DSG1** (barrier molecule)
- **POSTN** (tissue remodeling)
- **CPA3** (mast cells)

PPI: Th_2 allergic inflammation & mucosal integrity

- PPI monotherapy downregulates Th2 allergic inflammation & restores mucosal integrity in PPI-REE

- Similar to that seen in EOE after topical steroid Rx

Proton pump inhibitor-responsive oesophageal eosinophilia correlates with downregulation of eotaxin-3 and Th2 cytokines overexpression

J. Molina-Infante*, M. D. Rivas†, M. Hernandez-Alonso*, G. Vinagre-Rodríguez*, J. M. Mateos-Rodríguez*, C. Dueñas-Sadornil*, B. Perez-Gallardo*, L. Ferrando-Lamana‡, N. Fernandez-Gonzalez‡, R. Bañares§ & J. Zamorano†

Aliment Pharmacol Ther 2014; **40**: 955–965

Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD

Edaire Cheng,[1] Xi Zhang,[2] Xiaofang Huo,[2] Chunhua Yu,[2] Qiuyang Zhang,[2] David H Wang,[2] Stuart Jon Spechler,[2] Rhonda F Souza[2]

Gut 2013;**62**:824–832.

Proton Pump Inhibitors Partially Restore Mucosal Integrity in Patients With Proton Pump Inhibitor–Responsive Esophageal Eosinophilia but Not Eosinophilic Esophagitis

Bram D. van Rhijn,*,‡ Pim W. Weijenborg,*,‡ Joanne Verheij,§ Marius A. van den Bergh Weerman,§ Caroline Verseijden,‡ René M. J. G. J. van den Wijngaard,*,‡ Wouter J. de Jonge,*,‡ Andreas J. P. M. Smout,* and Albert J. Bredenoord*

Clinical Gastroenterology and Hepatology 2014;12:1815–1823

PPI in diet & steroid responsive EOE

- EOE patients who initially responsive to dietary elimination & topical steroid therapy

- Also responded to PPI therapy

Dual response to dietary/topical steroid and proton pump inhibitor therapy in adult patients with eosinophilic esophagitis

Alfredo J. Lucendo, MD, PhD, FEBGH[a]
Ángel Arias, BSc, MSc[b]
Jesús González-Cervera, MD[c]
José María Olalla, MD[d]
Javier Molina-Infante, MD[e]

J Allergy Clin Immunol 2016;137:931–4.e2.

Proton pump inhibitor–responsive esophageal eosinophilia does not preclude food-responsive eosinophilic esophagitis

Jamie Sodikoff, MD
Ikuo Hirano, MD

J Allergy Clin Immunol 2016;137:631–33.

2017 EOE guidelines

Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults

Alfredo J Lucendo[1,2], Javier Molina-Infante[2,3], Ángel Arias[2,4], Ulrike von Arnim[5], Albert J Bredenoord[6], Christian Bussmann[7], Jorge Amil Dias[8], Mogens Bove[9], Jesús González-Cervera[2,10], Helen Larsson[9], Stephan Miehlke[11], Alexandra Papadopoulou[12], Joaquín Rodríguez-Sánchez[13], Alberto Ravelli[14], Jukka Ronkainen[15], Cecilio Santander[2,16], Alain M Schoepfer[17], Martin A Storr[18], Ingrid Terreehorst[19], Alex Straumann[20] and Stephen E Attwood[21]

United European Gastroenterology Journal
2017, Vol. 5(3) 335–358

Abandoned the term PPI-REE

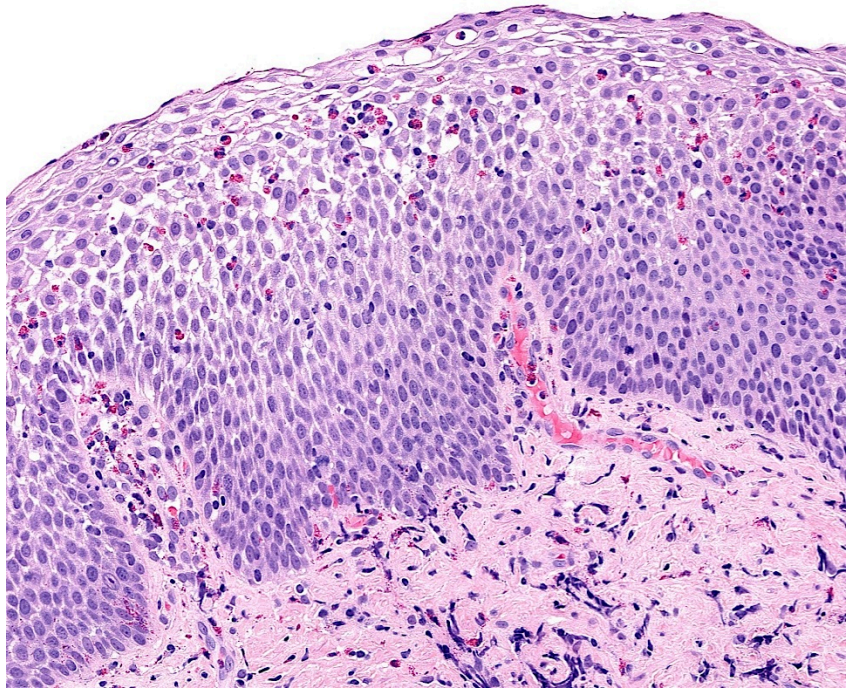
Considers PPI a first line therapeutic option in EOE rather than a diagnostic tool

- United European Gastroenterology (UEG)
- European Society of Pediatric Gastroenterol, Hepatol & Nutrition (ESPGHAN)
- European Academy of Allergy and Clinical Immunology (EAACI)
- European Society of Eosinophilic Oesophagitis (EUREOS)

Which features should be reported in esophageal biopsies with eosinophilia?

Which features should be reported?

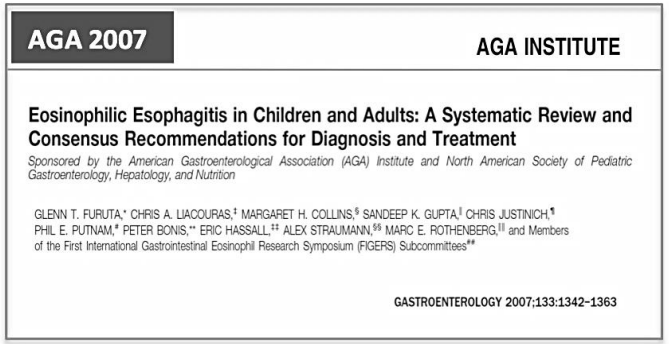
- **Just peak eosinophil count (PEC)?**
- **Other features?**
  - Basal cell hyperplasia?
  - Spongiosis?
  - Lamina propria fibrosis?
  - Lamina propria eosinophils?
  - Eosinophil microabscesses

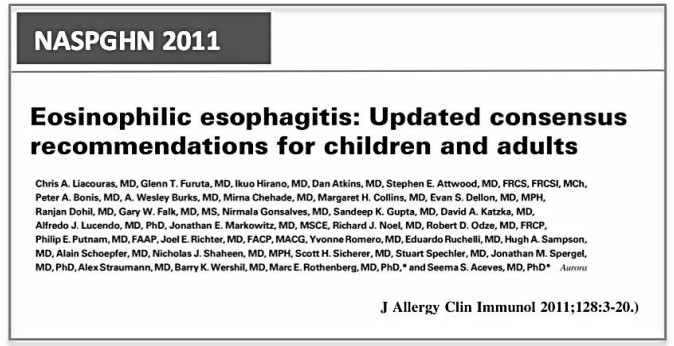


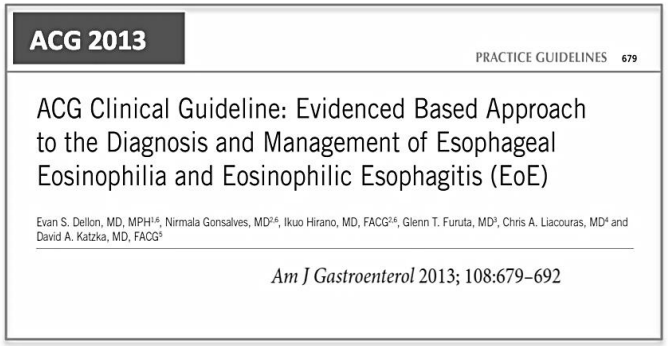
Peak eosinophil count (PEC)

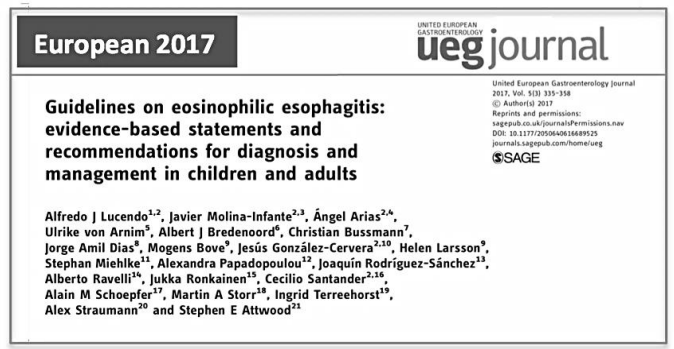
- PEC 15+/HPF defines EOE in appropriate clinical setting
- Distinguishes EOE from GERD in vast majority

Dellon ES et al. Mod Pathol. 2015;28:383-390









Peak eosinophil count (PEC)

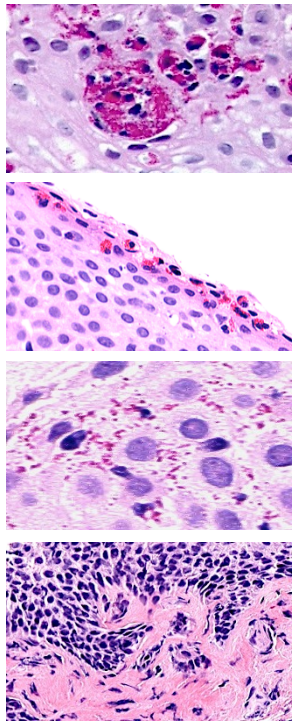
- PEC 15+/HPF defines EOE in **appropriate clinical setting** →
  - Symptoms of **esophageal dysfunction**
  - Eosinophilia **isolated** to **esophagus**
  - **Secondary causes excluded**
- Distinguishes EOE from GERD in vast majority

Dellon ES et al. Mod Pathol. 2015;28:383-390

Features other than PEC

Compared to GERD, EOE far more likely to show:

- Microabscesses
- Surface layering
- Degranulation
- Lamina propria fibrosis

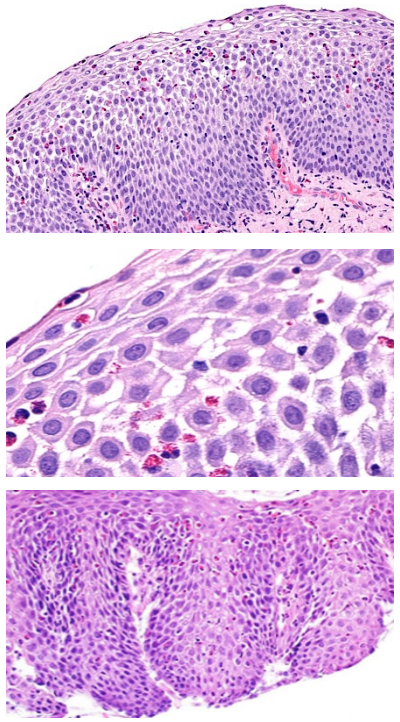


- *Parfitt JR et al. Mod Pathol. 2006; 19:90-96*
- *Walsh SV et al. Am J. Surg. Pathol. 1999; 23:390-6*
- *Desai TK et al. Gastrointest Endosc 2005;61:795-801*
- *Dellon ES et al. Am J Gastroenterol. 2014:107:1503-11.*
- *Dellon ES et al. Mod Pathol. 2015;28:383-390*

Features other than PEC

More frequent and pronounced:

- Basal cell hyperplasia
- Spongiosis
- Elongated vascular papillae



Parfitt JR et al. Mod Pathol. 2006; 19:90-96
Dellon ES et al. Am J Gastroenterol. 2014:107:1503-11.

2013

ACG Clinical Guideline: Evidenced Based Approach to the Diagnosis and Management of Esophageal Eosinophilia and Eosinophilic Esophagitis (EoE)

PRACTICE GUIDELINES

Evan S. Dellon, MD, MPH[1,6], Nirmala Gonsalves, MD[2,6], Ikuo Hirano, MD, FACG[2,6], Glenn T. Furuta, MD[3], Chris A. Liacouras, MD[4] and David A. Katzka, MD, FACG[5]

Am J Gastroenterol 2013; 108:679–692;

It is important that histologic features besides the absolute eosinophil count, such as eosinophil microabscess formation, superficial layering of eosinophils, extracellular eosinophil granules, basal cell hyperplasia, rete-peg elongation, subepithelial lamina propria fibrosis, and increases in other cell types, such as lymphocytes, be evaluated and noted in pathology reports (47). Although these features are not specific to EoE, they do add information to the overall clinicopathologic assessment of the patient.

Eosinophilic esophagitis: current perspectives from diagnosis to management

Fouad J. Moawad,[1] Edaire Cheng,[2] Alain Schoepfer,[3] Sahar Al-Haddad,[4] Andrew M. Bellizzi,[5] Heather Dawson,[6] Hala El-Zimaity,[7] Maha Guindi,[8] Roberto Penagini,[9] Ekaterina Safrooneva,[10] and Mirna Chehade[11]

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES 2016;1380(1):204-217

Histological reporting of biopsies

Histological reports should include an eosinophil peak count. They should also include descriptions of the degree of epithelial hyperplasia and spongiosis (e.g., mild, moderate, marked) and should note, if present, eosinophil surface layering and clustering and lamina propria fibrosis, if the lamina propria is present in the biopsies obtained. These reports not only support an initial diagnosis of EoE (or esophagitis with eosinophilia, depending on the relationship of the biopsy to PPI therapy), they also facilitate assessment of response to therapy on subsequent biopsies.

Newly developed and validated eosinophilic esophagitis histology scoring system and evidence that it outperforms peak eosinophil count for disease diagnosis and monitoring

M. H. Collins,[1] L. J. Martin,[2] E. S. Alexander,[3,6] J. Todd Boyd,[1] R. Sheridan,[1] H. He,[2] S. Pentiuk,[4] P. E. Putnam,[4] J. P. Abonia,[5] V. A. Mukkada,[4] J. P. Franciosi,[4] M. E. Rothenberg[5]

ISDE The International Society for Diseases of the Esophagus

Diseases of the Esophagus (2017) **30**, 1–8

EOE specific histologic scoring system (EOE-HSS)

- Eosinophil density
- Basal zone hyperplasia
- Dilated intercellular spaces
- Eosinophil abscesses
- Eosinophil surface layering
- Surface epithelial alteration
- Dyskeratotic epithelial cells
- Lamina propria fibrosis

Severity & extent scored (0-3) → **Composite histologic score** outperformed PEC in predicting Rx status in EOE

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M. H. Collins,[1] L. J. Martin,[2] E. S. Alexander,[3,6] J. Todd Boyd,[1] R. Sheridan,[1] H. He,[2] S. Pentiuk,[4] P. E. Putnam,[4] J. P. Abonia,[5] V. A. Mukkada,[4] J. P. Franciosi,[4] M. E. Rothenberg[5]

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- Eosinophil density
- Basal zone hyperplasia
- Dilated intercellular spaces

Correlated best with Rx status

- Eosinophil abscesses
- Eosinophil surface layering
- Surface epithelial alteration
- Dyskeratotic epithelial cells
- Lamina propria fibrosis

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EOE-HSS reported to be:

- Reproducible with minimal training
- Strong-to-moderate agreement (3 pathologists)
- Completed within 1 minute

Reliability of histologic assessment in patients with eosinophilic oesophagitis

M. J. Warners[1] | C. A. Ambarus[1] | A. J. Bredenoord[1] | J. Verheij[1] | G. Y. Lauwers[2] | J. C. Walsh[3] | D. A. Katzka[4] | S. Nelson[3] | T. van Viegen[3] | G. T. Furuta[5] | S. K. Gupta[6] | L. Stitt[3] | G. Zou[3] | C. E. Parker[3] | L. M. Shackelton[3] | G. R. D`Haens[1,3] | W. J. Sandborn[3,7] | E. S. Dellon[8] | B. G. Feagan[3] | M. H. Collins[9] | V. Jairath[3] | R. K. Pai[10]

WILEY AP&T Alimentary Pharmacology & Therapeutics

Aliment Pharmacol Ther. 2018;1–11

- Four GI pathologists
- 45 slides (EOE)
- Near perfect reliability

	Reliability ICC (95% CI)	
	Intra-rater	Inter-rater
EoE HSS—Grade	0.92 (0.87, 0.95)	0.84 (0.76, 0.89)
EoE HSS—Stage	0.92 (0.88, 0.95)	0.88 (0.82, 0.91)

(ICC: Intra-class correlation coefficients)

EOE-HSS: Utility in diagnostic practice?

Further prospective studies linking composite scores to:

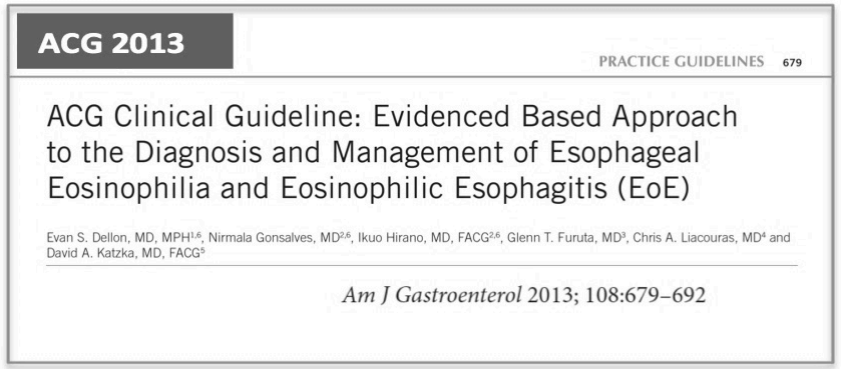
- Symptoms
- Treatment response

} NB for applicability in future Dx practice

Do we need to provide a DDx or should we be descriptive?

Reporting of esophageal eosinophilia

Guidelines: EOE should <u>not</u> be diagnosed based on pathology alone



"EoE is clinicopathologic disorder diagnosed by clinicians taking into consideration both clinical and pathologic information without either of these parameters interpreted in isolation."

"Clinical manifestations or pathologic data should not be interpreted in isolation"

Reporting of esophageal eosinophilia

PEC 15+/HPF: No clinical history

DIAGNOSIS:

Esophagitis with abundant eosinophils (peak eosinophil count 30/HPF)

COMMENT :

This meets the threshold for EOE in the appropriate clinical context, although occasionally other conditions, especially GERD, may produce similar findings. Sampling the proximal esophagus can be helpful in making this distinction

Reporting of esophageal eosinophilia

Comment more specific:

- Clinical history supportive of EOE
- Mid or proximal biopsies show marked eosinophilia

Reporting of esophageal eosinophilia

Eosinophils admixed with neutrophils:

- GERD
- Candida
- Pill esophagitis
- Crohn’s
- Drug hypersensitivity
- Others

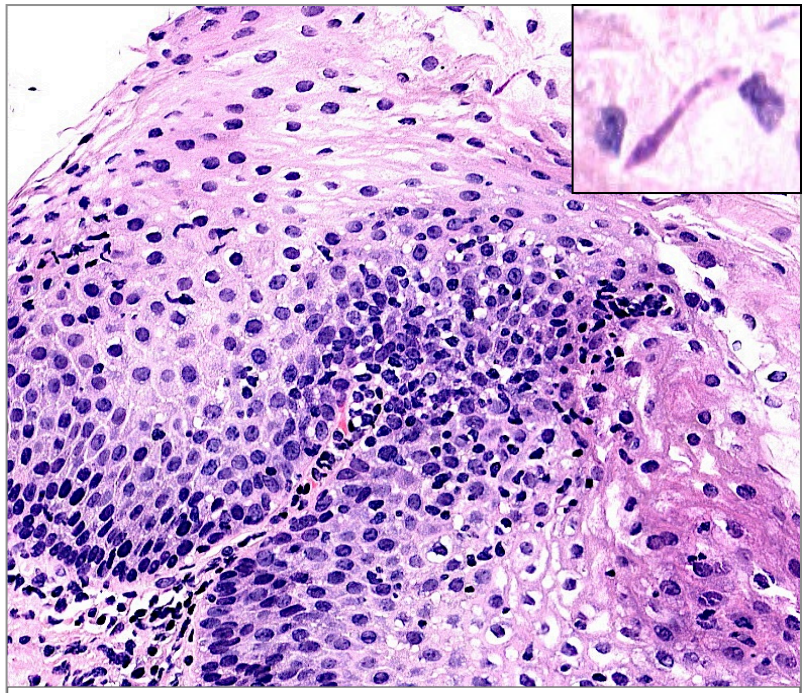
Intraepithelial lymphocytes in esophageal biopsies

Intraepithelial lymphocytes esophageal bx

- IEL normally present in small numbers
- Increased in variety of conditions

Conditions associated with increased IEL in esophageal squamous mucosa
Lymphocytic esophagitis
GERD
EOE
Infection (e.g. Candida, viral)
Crohn's
Lichen planus
Achalasia
Post-ablation
Immunodeficiency (e.g. CVID)

Intraepithelial lymphocytes esophageal bx



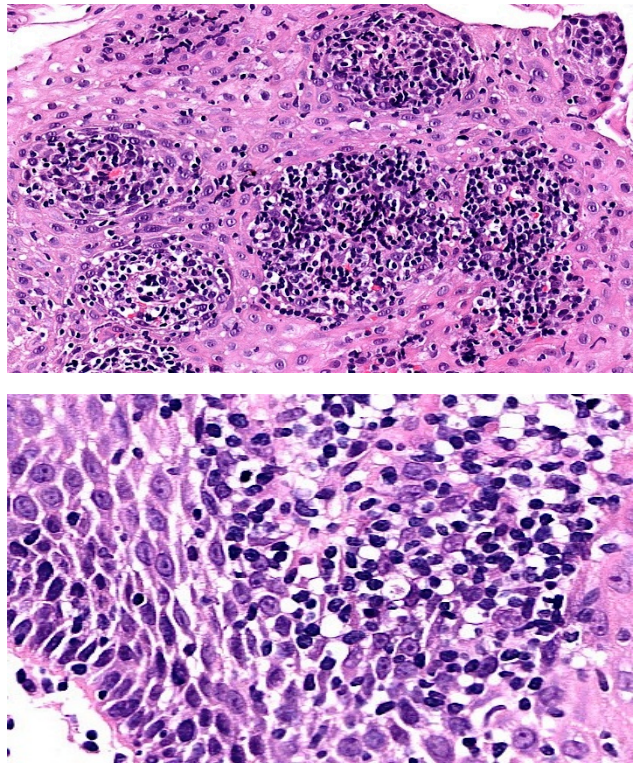
Candida esophagitis with IEL

Conditions associated with increased IEL in esophageal squamous mucosa
Lymphocytic esophagitis
GERD
EOE
Infection (e.g. Candida, viral)
Crohn’s
Lichen planus
Achalasia
Post-ablation
Immunodeficiency (e.g. CVID)

Lymphocytic esophagitis

Distinctive histologic pattern

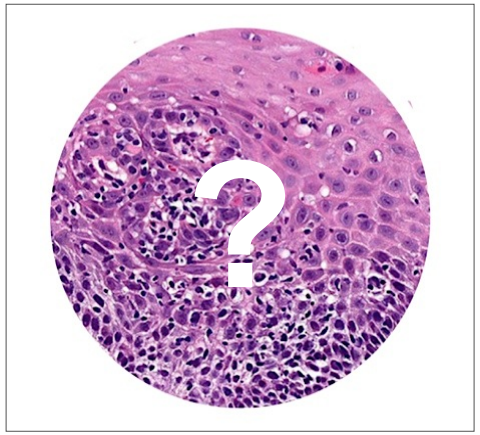
- Prominence of peri-papillary lymphocytes
- Spongiosis
- Absent or rare granulocytes



Lymphocytic esophagitis

Diagnostic thresholds for IEL

- 12 to 50 per HPF
- No numerical threshold
- Epithelial damage (spongiosis)



- *Conner, J.R. et al. Mod. Pathol. 2014; 27: 169A.*
- *Ebach, D.R. et al. Inflamm. Bowel Dis. 2011. 17: 45–49.*
- *Sutton, L.M. et al. Inflamm. Bowel Dis. 2014. 20: 1324–28.*
- *Putra J et al. Am J Surg Pathol. 2016; 40:1679-85.*
- *Haque S, Genta RM. Gut. 2012; 61: 1108–1114.*

Lymphocytic esophagitis

Diagnostic thresholds for IEL

- 12 to 50 per HPF
- No numerical threshold
- Epithelial damage (spongiosis)

Most published data on **normal IEL numbers** derived from patients with **upper GI symptoms**

- *Conner, J.R. et al. Mod. Pathol. 2014; 27: 169A.*
- *Ebach, D.R. et al. Inflamm. Bowel Dis. 2011. 17: 45–49.*
- *Sutton, L.M. et al. Inflamm. Bowel Dis. 2014. 20: 1324–28.*
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- *Haque S, Genta RM. Gut. 2012; 61: 1108–1114.*

Lymphocytic Esophagitis in Nonachalasia Primary Esophageal Motility Disorders

Improved Criteria, Prevalence, Strength of Association, and Natural History

Juan Putra, MD, Kristen E. Muller, MD,* Zilla H. Hussain, MD,† Siddhartha Parker, MD, Scott Gabbard, MD,† Elizabeth B. Brickley, PhD,‡ Brian E. Lacy, MD, PhD,† Richard Rothstein, MD,† and Mikhail Lisovsky, MD, PhD**

Am J Surg Pathol 2016;40:1679–1685

17 healthy volunteers, with normal:

- Endoscopy
- Histology
- Esophageal pH studies

Distance from GEJ	Mean peak IEL ± SD	Upper limit of normal (mean + 2SD)
10 cm	23 ± 9	41
5 cm	24 ± 11	46
0-2 cm	26 ± 18	64

IEL counted in a 40x objective field (0.24 mm^2)

Lymphocytic esophagitis

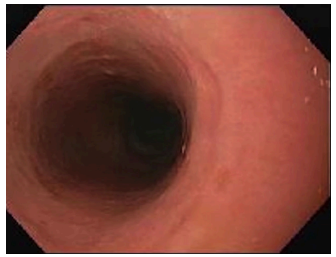
Clinical presentation:

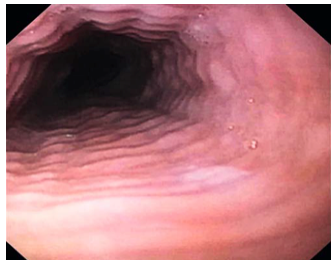
- Dysphagia (53-67%)
- GERD type symptoms
- Abdominal or chest pain
- Nausea

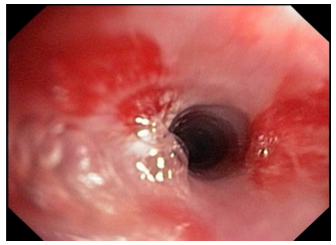
Lymphocytic esophagitis

Endoscopic findings:

- Normal (1/3)
- EOE type features (1/3)
  - *Rings, furrows, plaques, exudates etc*.
- Non-specific (1/3)
  - *Erythema, nodularity, fragility etc*.







Lymphocytic esophagitis

Associations:

- Crohn's disease in children
  - *Rubio, C.A et al. Am.J. Clin. Pathol. 2006; 125: 432–437.*
  - *Purdy, J.K. et al. Am. J. Clin. Pathol. 2008; 130: 508–513.*
  - *Ebach, D.R. et al. Inflamm. Bowel Dis. 2011; 17: 45–49.*
  - *Sutton, L.M. et al. Inflamm. Bowel Dis. 2014; 20: 1324–28.*
- Motility disorders in adults
  - *Xue, Y. et al. Am. J. Surg. Pathol. 2015; 39: 1558–67.*
  - *Putra J et al. Am J Surg Pathol. 2016; 40:1679-85.*

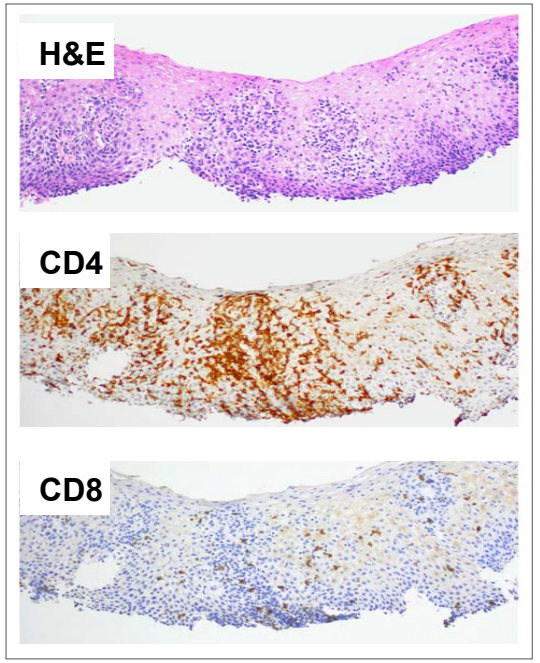
Lymphocytic Esophagitis With CD4 T-cell–predominant Intraepithelial Lymphocytes and Primary Esophageal Motility Abnormalities

A Potential Novel Clinicopathologic Entity

Yue Xue, MD, Arief Suriawinata, MD,* Xiaoying Liu, MD,* Zhongze Li, MS,†*
Scott Gabbard, MD,‡ Richard Rothstein, MD,‡ Brian Lacy, MD, PhD,‡
*and Mikhail Lisovsky, MD, PhD**

Am J Surg Pathol 2015;39:1558–1567

- 45 patients with lymphocytic esophagitis
- 64% CD4+ predominant infiltrates
- Dysmotility more prevalent with CD4+ infiltrates



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- 45 patients with lymphocytic esophagitis
- 64% CD4+ predominant infiltrates
- Dysmotility more prevalent with CD4+ infiltrates

Motility testing (n=21)

CD4+ predominant
88% had dysmotility (14/16)

CD8+ predominant
40% had dysmotility (2/5)

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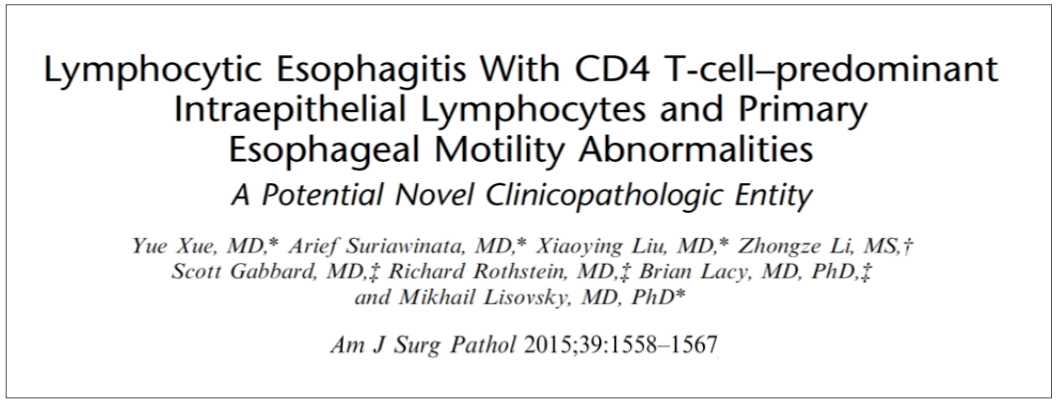
Am J Surg Pathol 2016;40:1679–1685

- **Compared esophageal biopsies**:
  - 69 patients with PEMD
  - 70 patients with severe GERD
- **Lymphocytic esophagitis found**:
  - 32% patients with PEMD
  - 4% patients with severe GERD

* Primary esophageal motility disorder

CD4+ predominant infiltrate found in:

- 64% with dysmotility associated LyE
- 25% with GERD associated LyE



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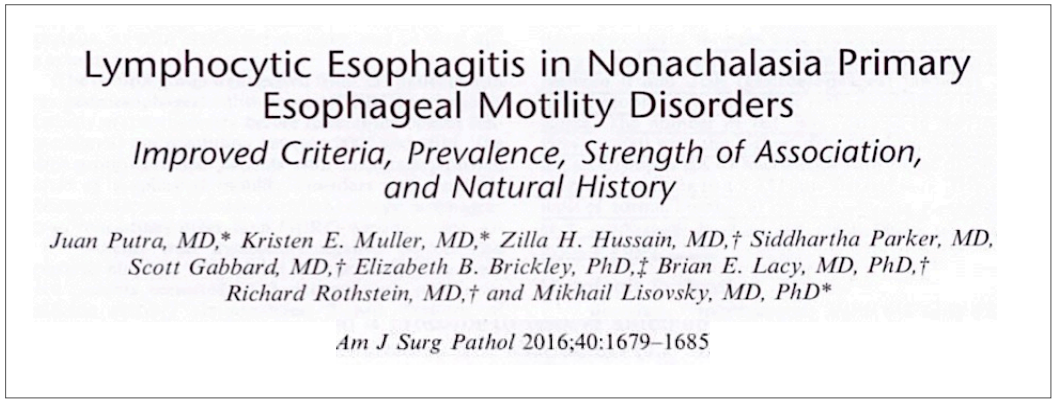

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Am J Surg Pathol 2016;40:1679–1685

Suggested that:

- Dysmotility associated LyE may represent a distinct disorder
- Preferentially associated with CD4+ predominant IELs
- Major form of LyE in adults

GERD & lymphocytic inflammation

- GERD may be associated with increased IEL
- Usually admixed PMN and/or eosinophils
- ~5% GERD: Histologic features of LyE

Basseri B et al. Dis Esophagus. 2010; 23: 368–376
Putra J et al. Am J Surg Pathol 2016;40:1679–1685

GERD & lymphocytic inflammation

Lymphocytic esophagitis reported in:

- Up to 7% of patients with BE
- Post ablation Bx for BE dysplasia (higher rates than pre-ablation)

- *Conner JR et al. Mod Pathol. 2014;27:169A*
- *Kissiedu J et al. Mod Pathol. 2016;29:599-606*

Should lymphocytic esophagitis be reported?

Reporting lymphocytic esophagitis

- Lack of standardized Dx criteria
- Unclear clinical significance
- Absence of specific therapies

Should LyE be reported at all?

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Lymphocytic esophagitis: a histologic pattern with emerging clinical ramifications

Mikhail Lisovsky,[1,a] Maria Westerhoff,[2,a] and Xuchen Zhang[3]

Ann. N.Y. Acad. Sci. 1381 (2016) 133–138

Reporting of LyE may be helpful:

- **Children:**
  - May prompt consideration of possible Crohn's disease
- **Adults:**
  - May prompt evaluation for a motility disorder
  - Plausible explanation for symptoms & endoscopic findings suggestive of EOE

Esophageal lichen planus

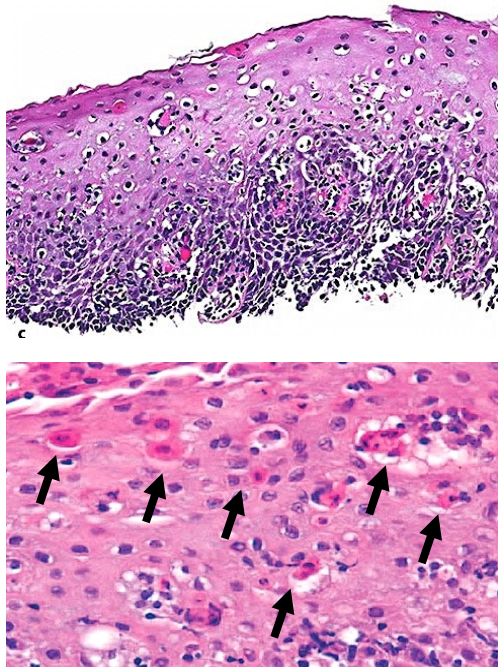
Esophageal lichen planus

- Under-recognized
- Middle aged females
- Mucocutaneous disease (+/-)

Esophageal lichen planus

Classical histologic findings:

- Dense band like infiltrate (interface)
- Basal epithelial damage
- Civatte bodies (dyskeratotic cells)



Salaria SN et al. Am J Surg Pathol. 2013; 37:1889-94
Franco D et al Case Rep Gastroenterol 2015;9:253–260

Esophageal lichen planus

Direct immunofluorescence findings:

- Globular IgM deposits (interface)
- Complement staining of Civatte bodies

Lichenoid Esophagitis

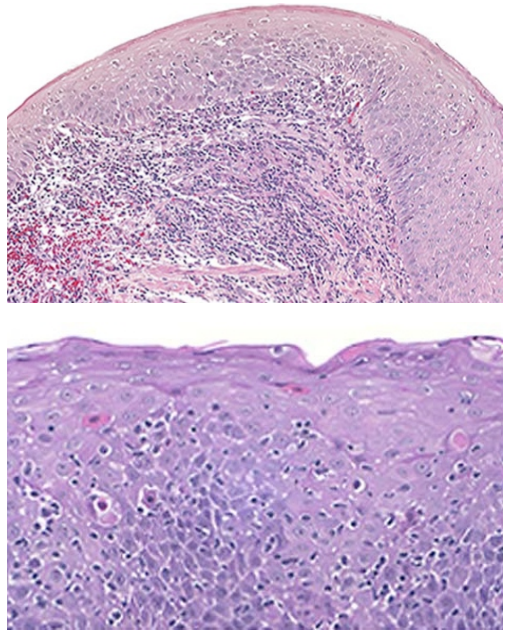
Clinicopathologic Overlap With Established Esophageal Lichen Planus

Safia N. Salaria, MD, Amer K. Abu Alfa, MD,*† Michael W. Cruise, MD, PhD,**
Laura D. Wood, MD, PhD, and Elizabeth A. Montgomery, MD**

Am J Surg Pathol 2013;37:1889–1894

- Identical histologic features
- Without mucocutaneous disease or positive IF
- Viral infection*, polypharmacy, rheumatological conditions

*HIV, hepatitis B & C



Esophageal lichen planus

Classical findings often absent or poorly developed

Fewer than 50% cases Dx as esophageal LP based on:

- Clinical
- Endoscopic
- Histologic

Classical histologic features on biopsy

Kern JS et al. Eur J Gastroenterol Hepatol. 2016: 28:1374–1382
Podboy A et al. Aliment Pharmacol Therapeutics. 2017;45:310-318

Clinical presentation

- Often assymptomatic until late
- Strictures
- Dysphagia
- Odynophagia

Cancer risk of *Lichen planus*: A cohort study of 13,100 women in Finland

Pia Halonen[1], Maija Jakobsson[1], Oskari Heikinheimo[1], Annika Riska[1], Mika Gissler[2,3] and Eero Pukkala[4,5]

Int. J. Cancer: **142**, 18–22 (2018)

Table 2. Observed (Obs) and expected (Exp) numbers of cancer cases and SIRs with 95% CIs among women with diagnosis of LP during 1969–2014

Cancer site	Obs	Exp	SIR	95% CI
Any site	1,520	1,326	1.15	1.09–1.20
Lip	18	3.48	5.17	3.06–8.16
Tongue	59	4.75	12.4	9.45–16.0
Oral cavity	163	20.5	7.97	6.79–9.24
Pharynx	5	3.49	1.43	0.47–3.34
Esophagus	19	9.75	1.95	1.17–3.04
Larynx, epiglottis	5	1.44	3.47	1.13–8.10

SIR: Standardized incidence ratio

Increased risk of cancer:

- Oral cavity
- Upper aerodigestive tract

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AP&T Alimentary Pharmacology and Therapeutics

Oesophageal lichen planus: the efficacy of topical steroid-based therapies

A. Podboy*, D. Sunjaya*, T. C. Smyrk†, J. A. Murray‡, M. Binder*, D. A. Katzka‡, J. A. Alexander‡ & M. Halland‡

Aliment Pharmacol Ther 2017; **45:** 310–318

Topical swallowed steroids (budesonide, fluticasone):

- Clinical response*: 62% (25/40)
- Endoscopic response: 73% (29/40)

**Resolution of dysphagia*

Other treatments options

- Systemic steroids & immunosuppressive therapies
- Esophageal dilatation

IgG4-related esophagitis

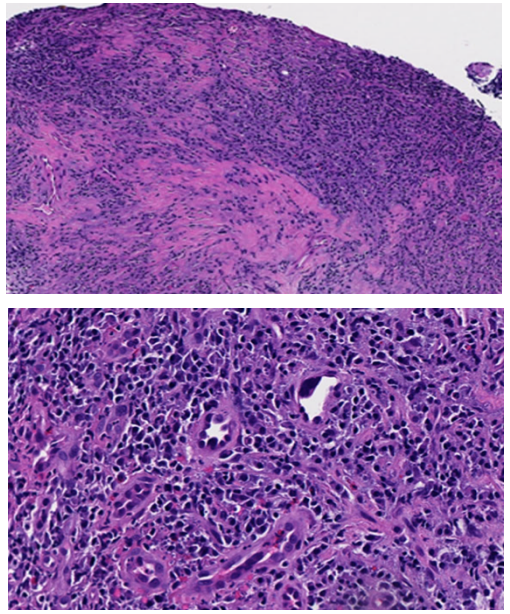
IgG4-related disease involving the esophagus: a clinicopathological study

I. Obiorah,[1] A. Hussain,[2] C. Palese,[2] N. Azumi,[1] S. Benjamin,[2] M. Ozdemirli[1]

[1] *Department of Pathology and* [2] *Division of Gastroenterology, Department of Internal Medicine, Medstar Georgetown University Hospital, Washington DC, USA*

Diseases of the Esophagus (2017) **30**, 1–7

- Largest series to date (n=8)
- At least 2 of 3 major criteria
- ≥50 IgG4 positive plasma cells/HPF
- IgG4:IgG ratio of at least 50%



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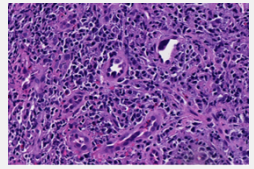
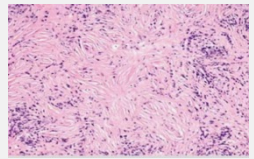
Major histologic criteria for IgG4 disease

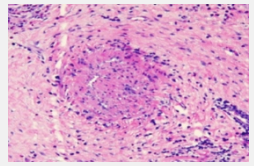
Dense plasma cell infiltrate



Storiform fibrosis



Obliterative phlebitis



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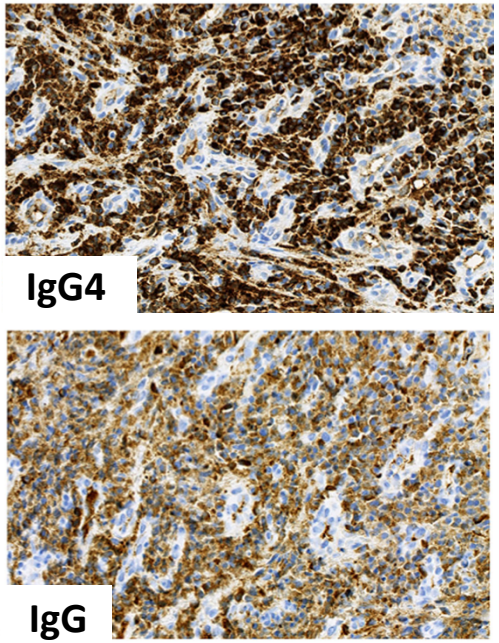
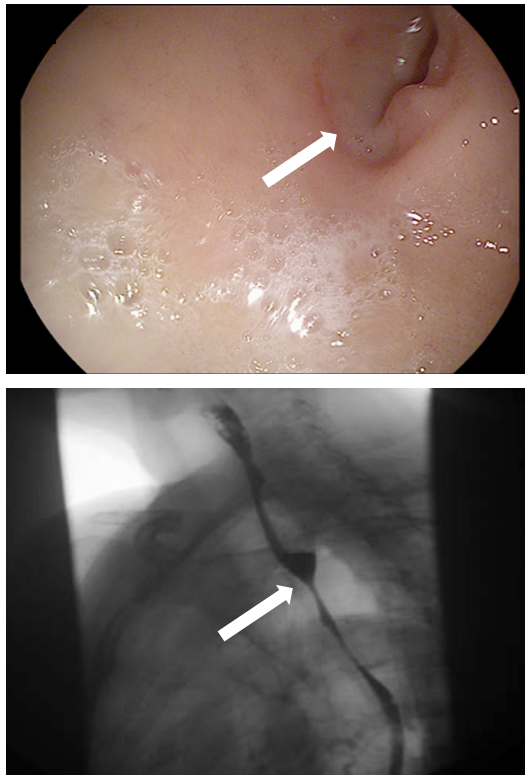


IgG4-related esophagitis

- Most male (11/14)
- Dysphagia (13/14)
- Strictures & erosive esophagitis
- Occasionally mass like lesions



- *Obiorah et al. Dis Esoph. 2017;30:1-7*
- *Dumas-Capagna et al. J Clin Med Res. 2014;6:295-8*

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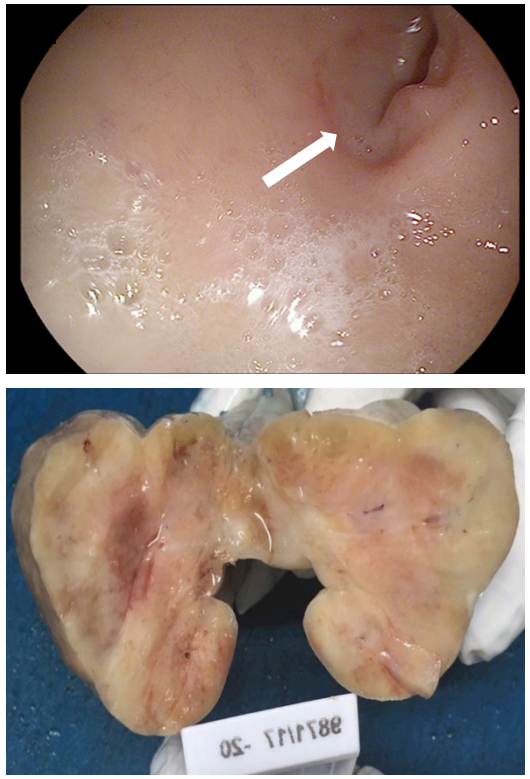


- *Obiorah et al. Dis Esoph. 2017;30:1-7*
- *Dumas-Capagna et al. J Clin Med Res. 2014;6:295-8*

IgG4-related esophagitis

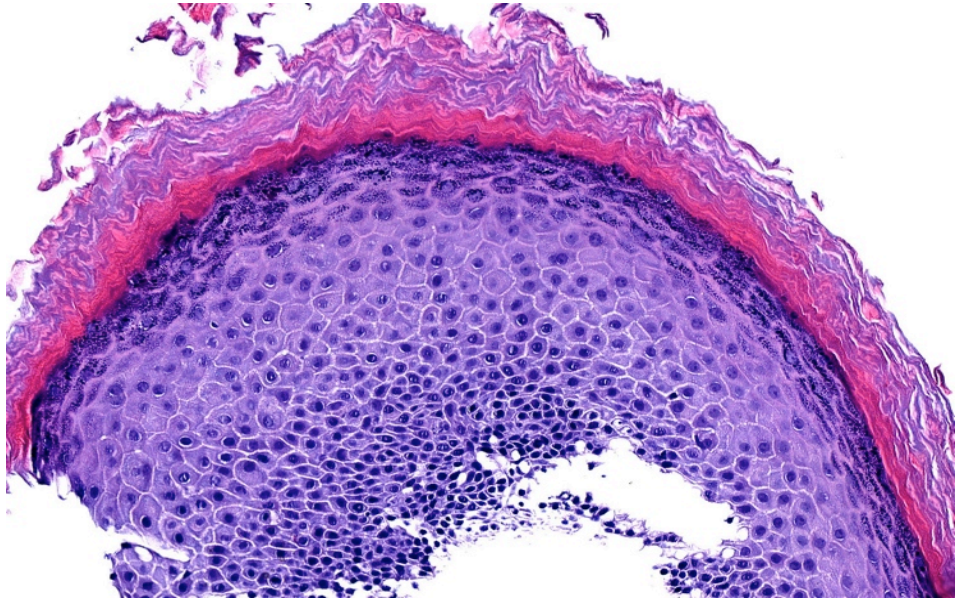
Treatment:

- Most respond initially to steroids (relapse common)
- Immunomodulators (e.g. MMF, MTX), biologics used
- Esophageal dilation

Epidermoid metaplasia of the esophagus

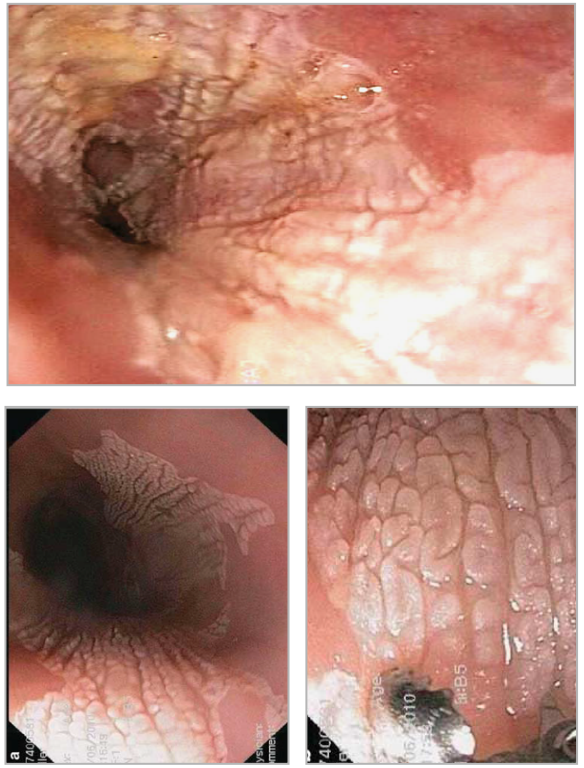
Epidermoid metaplasia

- Resembles epidermis of skin
- Strong association with tobacco
- Lesser degree with alcohol



Epidermoid metaplasia

- Well demarcated
- Patches and plaques
- Often multifocal
- Size: <1 mm to >20 cm



Cottreau J et al. Histopathology 2016;68:988-995
Singhi A et al. Mod Pathol. 2014; 27:38–43

Association with squamous neoplasia

- Association with synchronous & metachronous squamous neoplasia

  Cottreau J et al. Histopathology 2016;68:988-995
  Singhi A et al. Mod Pathol. 2014; 27:38–43
  Taggard M et al. Histopathol.2013, 63, 463–473

- Evidence for role as a precursor lesion recently established

  Singhi A et al. Mod Pathol. 2017;30:1613-21

Targeted next-generation sequencing supports epidermoid metaplasia of the esophagus as a precursor to esophageal squamous neoplasia

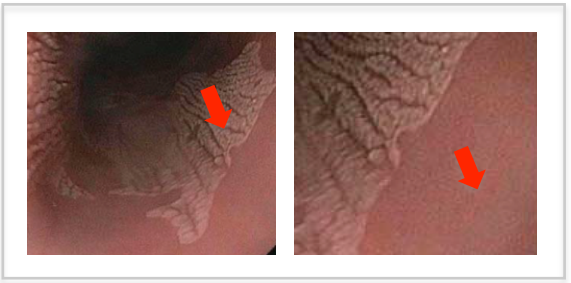
Aatur D Singhi[1], Christina A Arnold[2], Dora M Lam-Himlin[3], Marina N Nikiforova[1], Lysandra Voltaggio[4], Marcia I Canto[4], Kevin M McGrath[1] and Elizabeth A Montgomery[4]

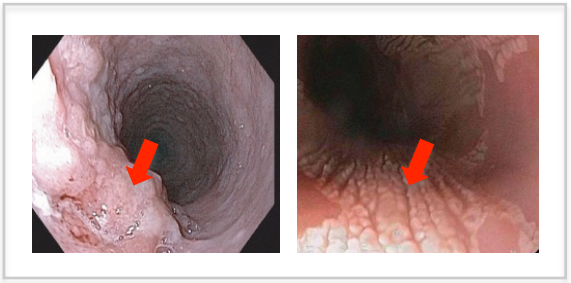
MODERN PATHOLOGY

MODERN PATHOLOGY (2017) 30, 1613–1621

Targeted next generation sequencing:

- Lesional & non-lesional mucosa of 18 patients
- Synchronous & metachronous HGD* & SCC* (5/18 patients)





*HGD: High grade dysplasia
*SCC: Squamous cell carcinoma

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MODERN PATHOLOGY

MODERN PATHOLOGY (2017) 30, 1613–1621

- 12/18 cases harboured alterations in genes associated with SCC
  - *TP53* (n=10)
  - *PIK3CA* (n=2)
  - *EGFR* (n=2)
  - *MYCN* (n-1)
  - *HRAS* (n=1)
  - *TERT* promoter (n=1)
- No genetic alterations in uninvolved esophageal squamous mucosa

Targeted next-generation sequencing supports epidermoid metaplasia of the esophagus as a precursor to esophageal squamous neoplasia

Aatur D Singhi[1], Christina A Arnold[2], Dora M Lam-Himlin[3], Marina N Nikiforova[1], Lysandra Voltaggio[4], Marcia I Canto[4], Kevin M McGrath[1] and Elizabeth A Montgomery[4]

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Associated **HGD & SCC** shared genetic alterations with **epidermoid metaplasia**

Table 2 Genetic alterations with mutational allelic frequencies detected in esophageal samples from 18 patients with esophageal epidermoid metaplasia

Patient	*Uninvolved esophageal mucosa*	*Esophageal epidermoid metaplasia*	*High-grade squamous dysplasia/squamous cell carcinoma*
1	No mutations found	*TP53* c.844C>T; p.R282W (4%) *PIK3CA* c.2176G>A; p.E726K (3%) *MYCN* c.793G>A; p.D265N (3%)	*TP53* c.844C>T; p.R282W (33%) *PIK3CA* c.2176G>A; p.E726K (36%) *MYCN* c.793G>A; p.D265N (21%) *CDKN2A* Homozygous Deletion
2	No mutations found	*TP53* c.734G>A; p.G245D (4%) *TP53* c.638G>A; p.R213Q (3%)	*TP53* c.734G>A; p.G245D (39%) *CDKN2A* Homozygous Deletion
3	No mutations found	*TP53* c.380C>A; p.H193R (3%) *TP53* c.559G>A; p.R248Q (3%)	*TP53* c.380C>A; p.H193R (10%) *TP53* c.559G>A; p.R248Q (8%) *CDKN2A* splice c.151-1G>A (8%)
4	No mutations found	*TP53* c.637C>T; p.R213* (4%)	*TP53* c.637C>T; p.R213* (14%)
5	No mutations found	*TP53* c.380C>A; p.S127Y (3%)	*TP53* c.380C>A; p.S127Y (10%) *TP53* c.559G>A; p.G187S (3%)

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- Provide strong support for epidermoid metaplasia as a precursor lesion
- Strengthens case for close endoscopic surveillance

THANK YOU