Mucosal Defense and Eosinophils in Esophageal Disease

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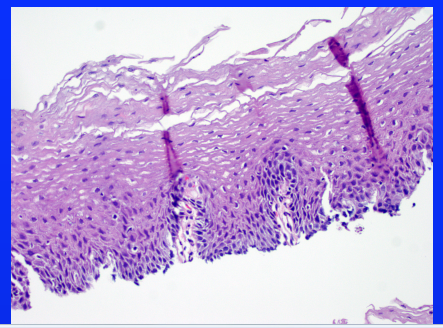
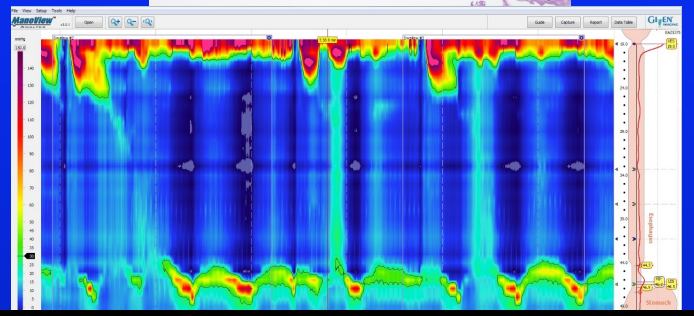
A 29 year-old man with heartburn and dysphagia

- Treated empirically with PPIs for suspected GERD
  - Symptoms only slightly improved
- Endoscopy (on PPIs)
  - Normal esophageal mucosa



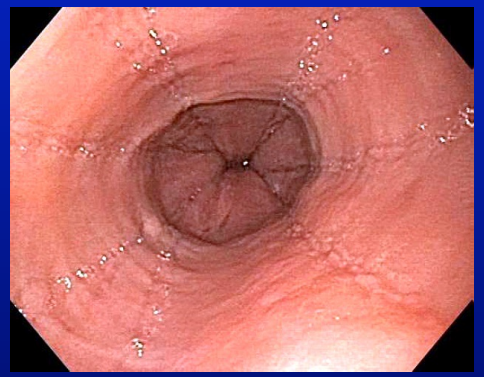
- Manometry suggests achalasia
  - 100% failed peristalsis
  - IRP upper limits of normal

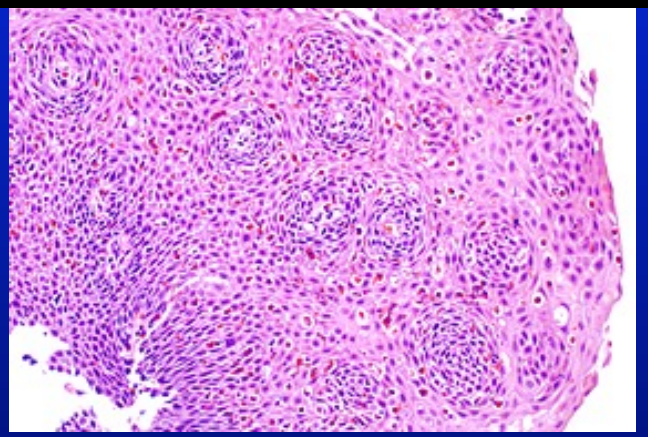


Endoscopy performed on PPIs cannot rule out EoE.

- PPIs stopped, EGD repeated

Furrows, Rings

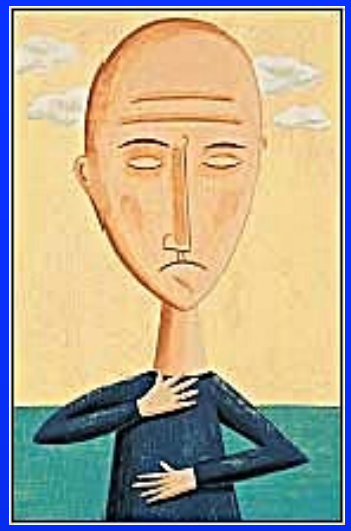




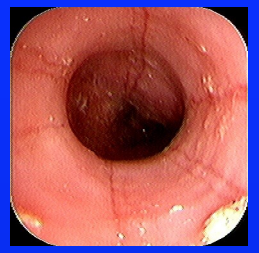
>50 eos/HPF

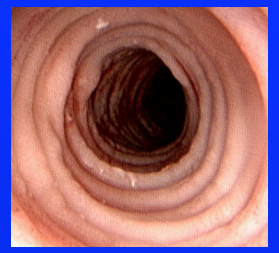
Odiase E et al. Gastroenterology 2018; 54:1217-21.

Eosinophilic Esophagitis and Achalasia



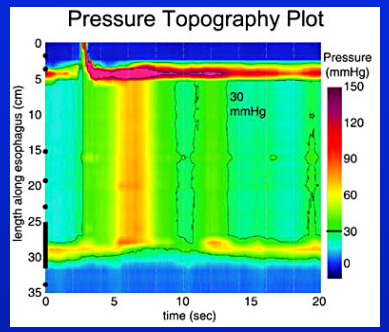
- **Eosinophilic Esophagitis**

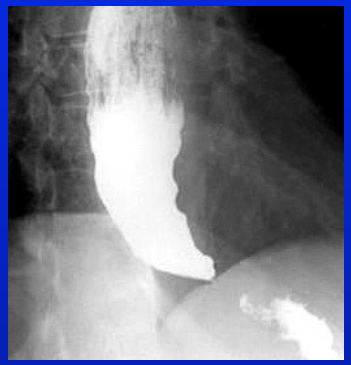




  - Allergen-driven
  - Recognized by mucosal manifestations
  - *Eosinophils **can** infiltrate all layers of esophageal wall including muscularis propria*

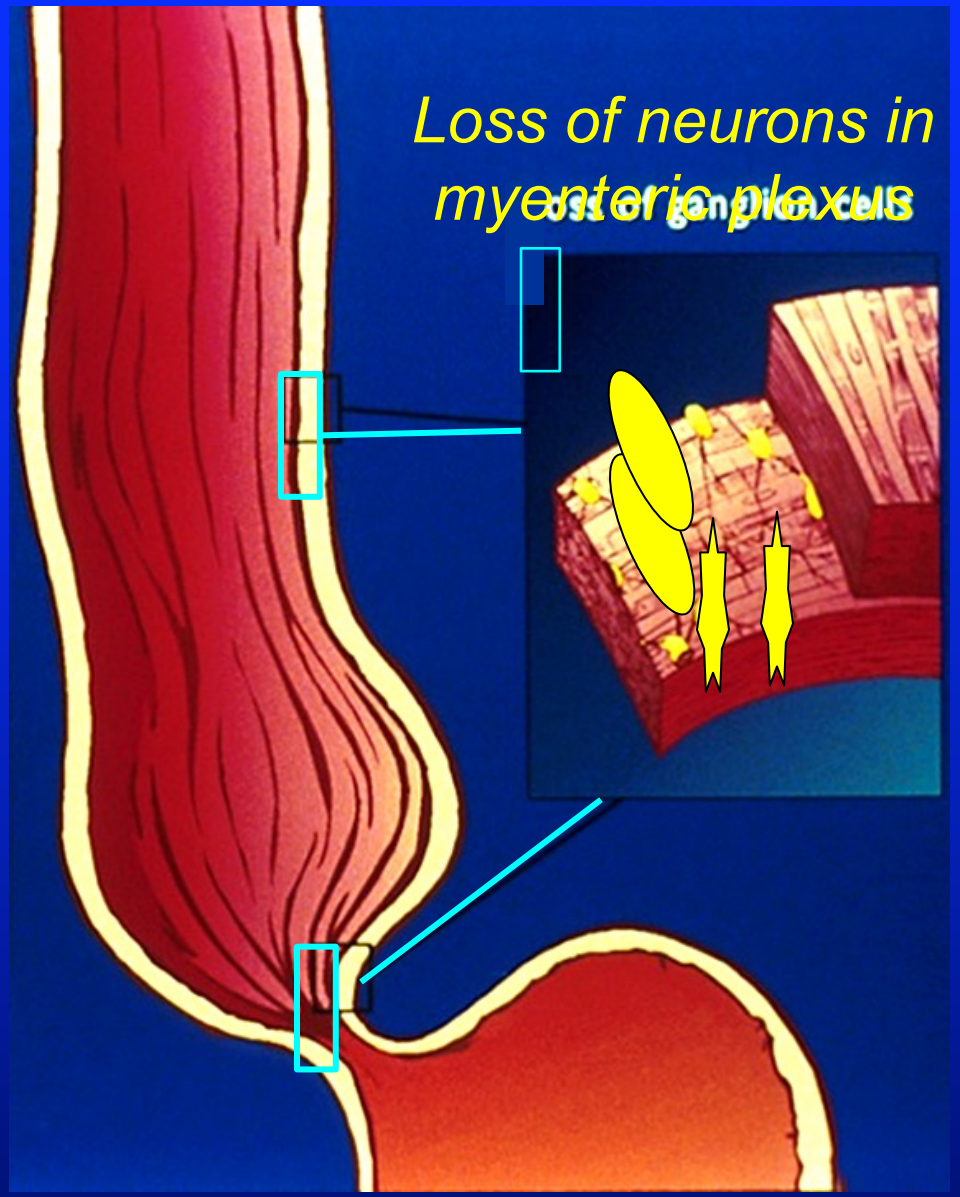
- **Achalasia**





  - Esophageal motility disorder
  - Recognized by esophageal muscle dysfunction
  - *Eosinophils **often** found infiltrating esophageal muscularis propria*

Current Concept: *Achalasia is a Disease of Neurons (Ganglion Cells) in the Esophageal Myenteric Plexus*



- Loss of neurons in the esophageal body impairs peristalsis
- Loss of neurons in the LES impairs its relaxation with swallowing

- Notion that achalasia is caused by destruction of esophageal neurons first proposed in a report by Sir Arthur Hurst in 1930

Hurst AF, Rake GW. Quarterly Journal of Medicine, Volume os-23, Issue 92, July 1930, Pages 491-508.

Sir Arthur Hurst

Founder of the British Society of Gastroenterology

Described post-mortem examinations of esophagus of 8 patients with end-stage achalasia

"The fact of greatest importance was the disappearance of all ganglion cells."

Current Hypothesis: Achalasia is an autoimmune disease targeted at esophageal neurons.

Achalasia Is Associated with Atopy

- Population-based retrospective cohort study assessing associations between achalasia and atopic disease, autoimmune disease, and neurodegenerative disease
- 2,593 patients with achalasia (median age 57 years, 52% male) matched to 10,402 controls
  - Achalasia cohort ***less*** likely to have neurodegenerative disease
    - 17 achalasia subjects (1.6%) vs 105 controls (2.4%); adjusted **OR 0.57** (95% CI 0.33–0.97, P=0.037).
  - Achalasia cohort ***more*** likely to have autoimmune disease
    - 57 achalasia subjects (9%) vs 176 controls (6%); adjusted **OR 1.39** (95% CI 1.02–1.90, P=0.039).
  - Achalasia cohort (<age 40) ***more*** likely to have atopy
    - 76 achalasia subjects (39%) vs 240 controls (30%); adjusted **OR 1.40** (95% CI 1.00–1.95, P=0.047).

- Suggests an atopic etiology of achalasia in younger patients

King D et al. Am J Gastroenterol 2021;116:416-9.

Esophageal Eosinophilia and Achalasia

- Eosinophil cationic protein (ECP) found in biopsies of esophageal muscularis propria (taken during Heller myotomy) in 9 of 9 primary achalasia patients

Tottrup A et al. Dig Dis Sci 1989;34:1894.

- Study of esophagectomy specimens from 42 achalasia patients
  - All had eosinophils and lymphocytes infiltrating myenteric plexus
  - 22 (52%) had eosinophilia of muscularis propria

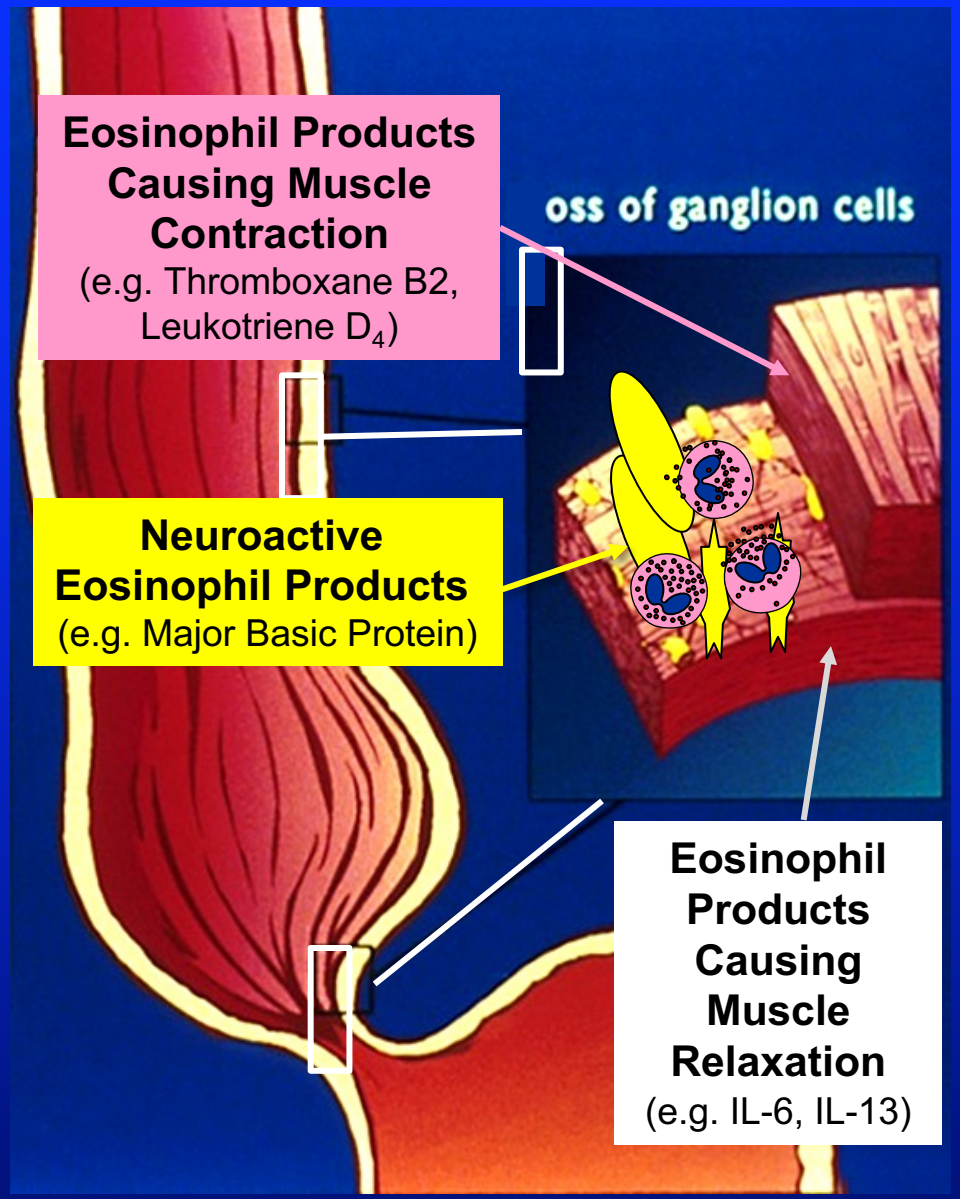
Goldblum JR et al. Am J Surg Pathol 1994;18:327.

- Study of esophageal muscle biopsies taken during POEM from 28 achalasia patients
  - 24 (86%) had immunoreactivity for eosinophil major basic protein (MBP) and eosinophil-derived neurotoxin (EDN)

Jin H et al. Med Sci Monitor 2018;24:2377.

Potential Mechanism To Explain the Association of Achalasia and Esophageal Eosinophilia

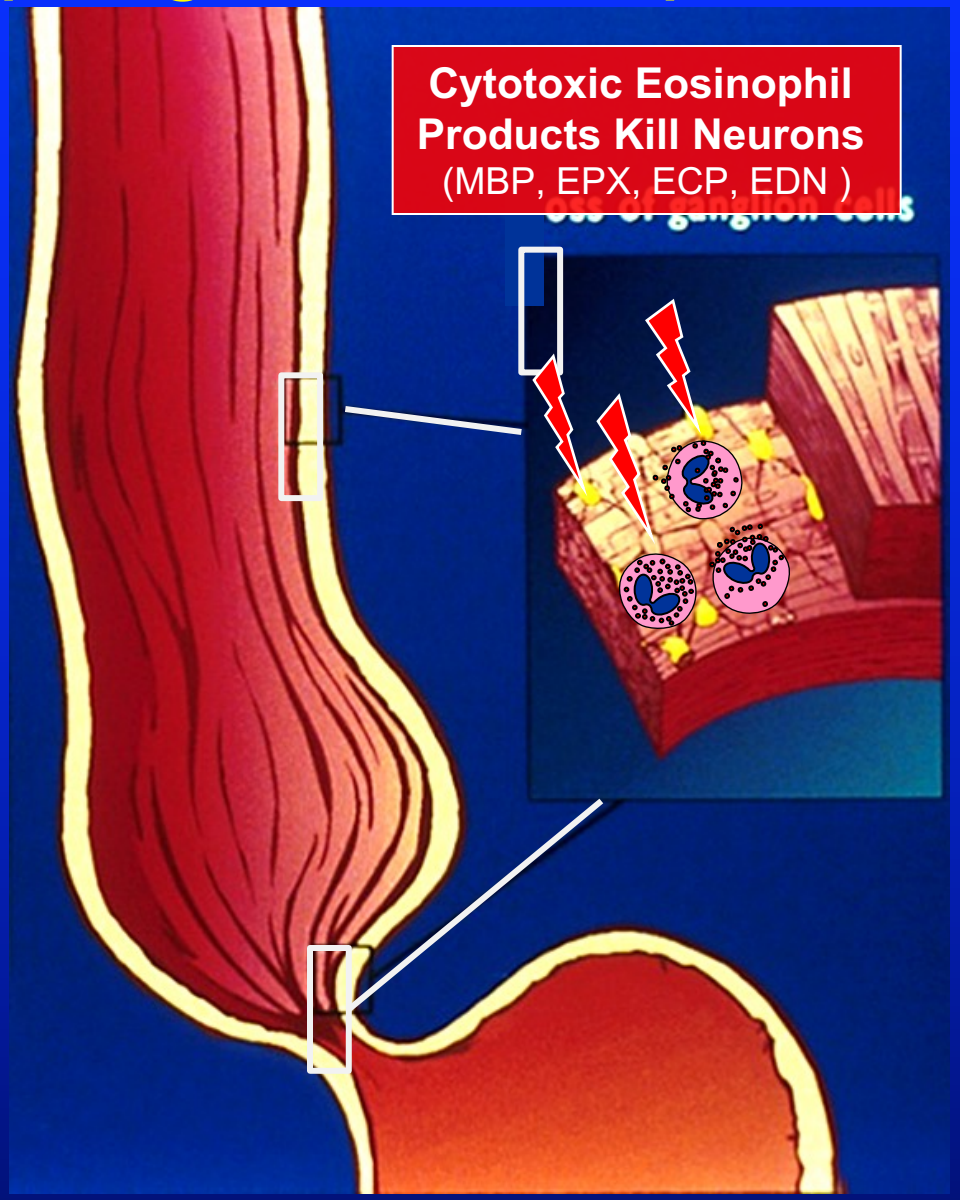
- **Eosinophilia causes motility abnormalities**
  - Myoactive or neuroactive eosinophil secretory products disrupt peristalsis and interfere with LES relaxation



Spechler SJ, Konda V, Souza R. Am J Gastroenterol 2018;113:1594-9.

Potential Mechanism To Explain the Association of Achalasia and Esophageal Eosinophilia

- **Eosinophilia causes neuronal destruction**
  - Pro-inflammatory and cytotoxic eosinophil secretory products cause destruction of neurons in the esophageal myenteric plexus



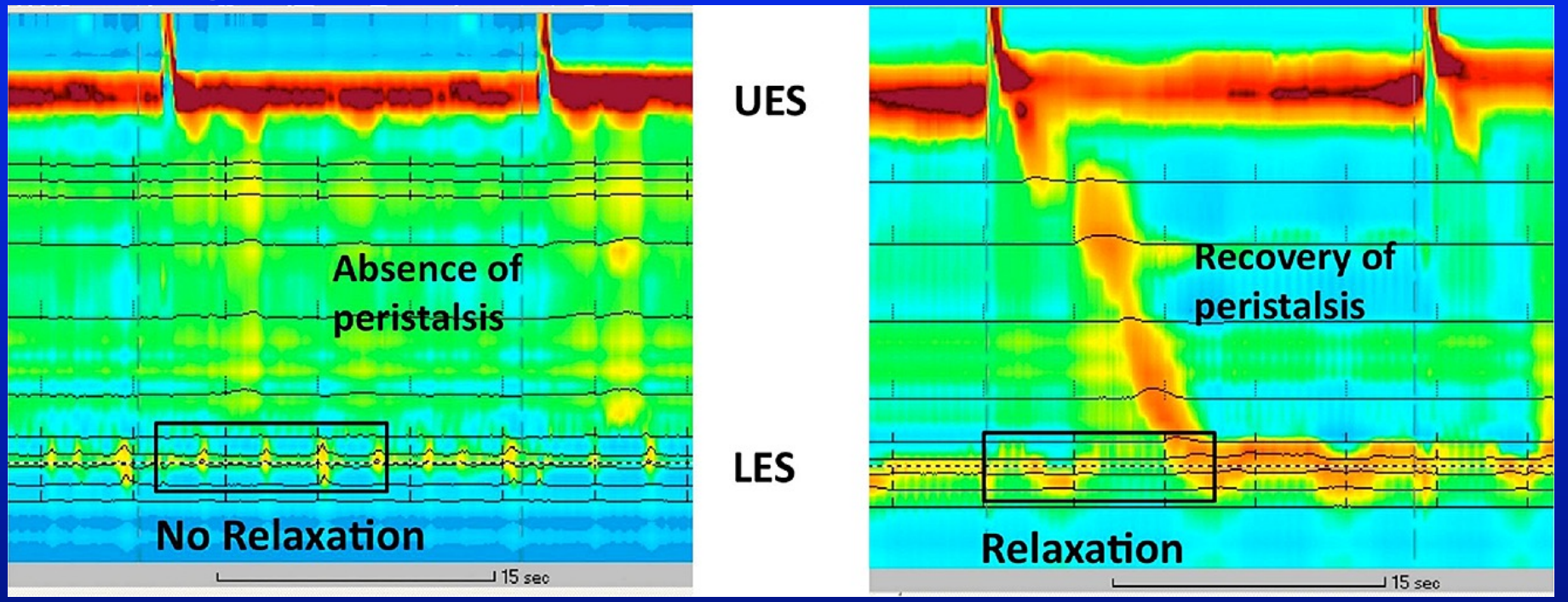
Spechler SJ, Konda V, Souza R. Am J Gastroenterol 2018;113:1594-9.

Evidence that Esophageal Eosinophilia Can Cause Reversible Motility Abnormalities

Eosinophils in the esophagus can cause reversible esophageal motility abnormalities.

Pre-Treatment Esophageal Biopsy: >50 eosinophils/hpf

Biopsy:<15 eosinophils/hpf



Savarino E et al. Clin Gastroenterol Hepatol 2011;9:1104.

Hypothesis

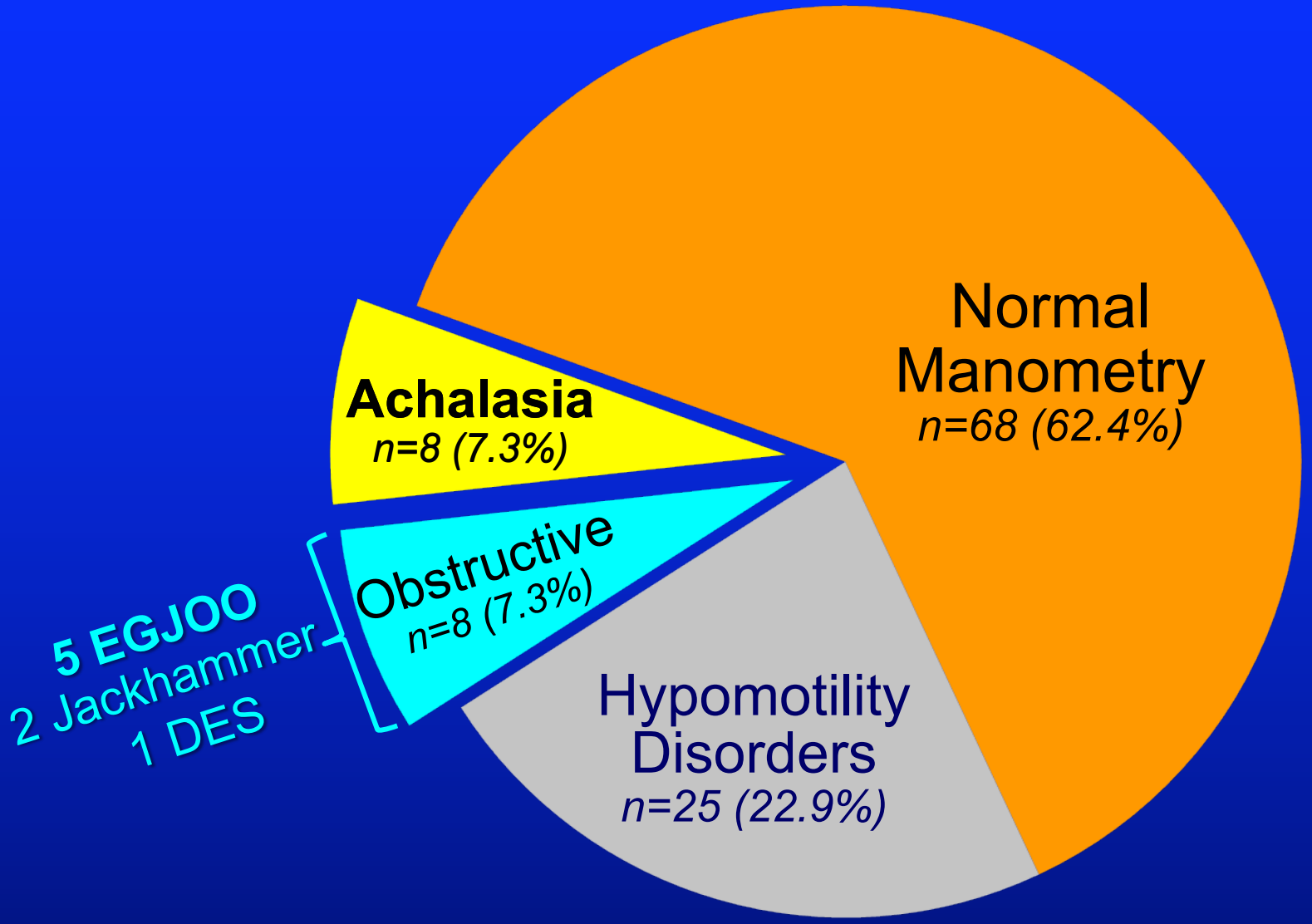
EoE can have mucosal-predominant and muscle-predominant forms, and muscle-predominant EoE can underlie achalasia and other esophageal motility disorders.

Achalasia might develop from a muscle-predominant form of eosinophilic esophagitis.

- Supporting evidence
  - Eosinophils and mast cells have multiple secretory products that can relax or contract esophageal muscle.
  - Reports document normalization of motility abnormalities, including achalasia, with treatment that reduces esophageal eosinophilia.
  - Achalasia is thought to be caused by neuronal destruction, and eosinophils secrete proteins that can destroy neurons.
  - Eosinophils and/or their degranulation products have been found in esophageal muscle of patients with achalasia and other esophageal motility disorders, even when mucosal eosinophils are absent.

Spechler SJ, Konda V, Souza R. Am J Gastroenterol 2018;113:1594-9.

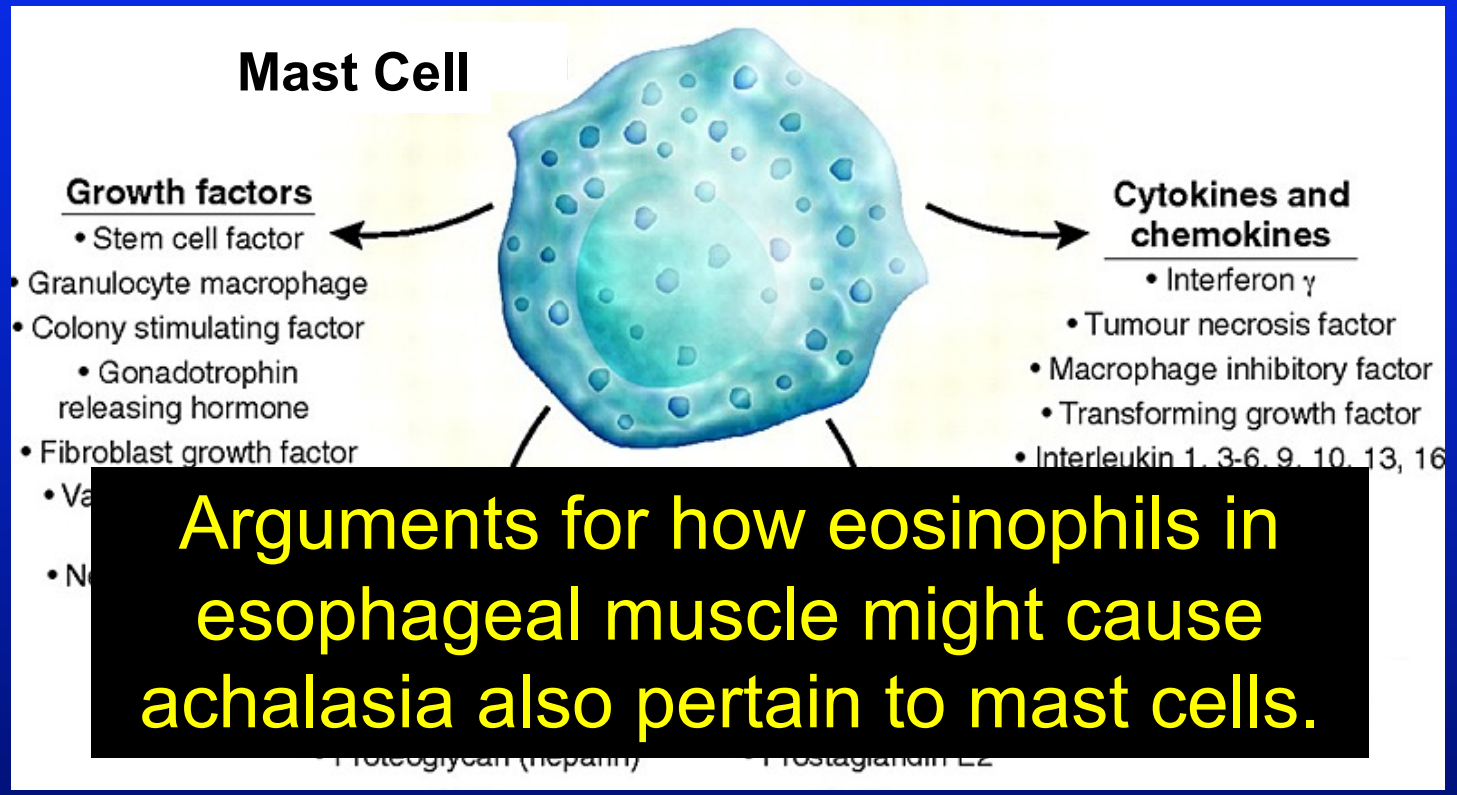
High Resolution Manometry Findings in 109 Consecutive EoE Patients



Ghisa M et al. Clin Gastroenterol Hepatol 2021;19:1554-63.

Mast Cells

- Immune cells that arise from bone marrow, circulate, and differentiate after migrating into tissue.
  - Initiate inflammation and repair in response to tissue insults
  - Best known for their role in allergic diseases.
- In EoE, esophageal mucosal biopsies show increased mast cell numbers and activation.
- Like eosinophils, mast cells contain proinflammatory, myoactive, neuroactive, and cytotoxic products.



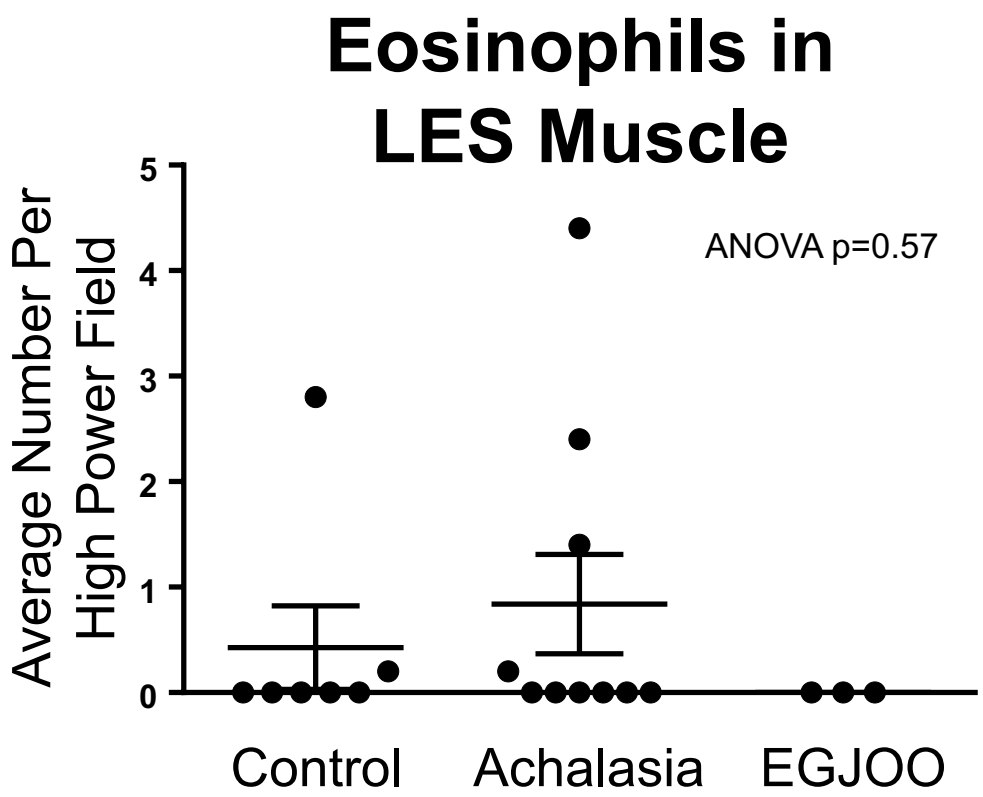
Arguments for how eosinophils in esophageal muscle might cause achalasia also pertain to mast cells.

Study Exploring Hypothesis that Achalasia Is an EGID (Eosinophilic GI Disorder)

- LES muscle biopsies taken during Heller myotomy from 10 achalasia patients and 3 EGJOO patients
  - 7 men, 6 women; median age 59 (range 26-77 years)
- Control LES biopsies taken from 7 heart-beating, deceased organ donors without esophageal disease
  - 4 men, 3 women; median age 42 (range 20-53 years)
- LES muscle stained with H&E and for tryptase
- LES muscle evaluated by qPCR for genes mediating smooth muscle Ca^{2+} handling and contraction

Nelson M, Zhang X et al. Neurogastroenterol Motil 2021;33:e14055.

Eosinophils are Rare, but Mast Cells are Plentiful in LES Muscle



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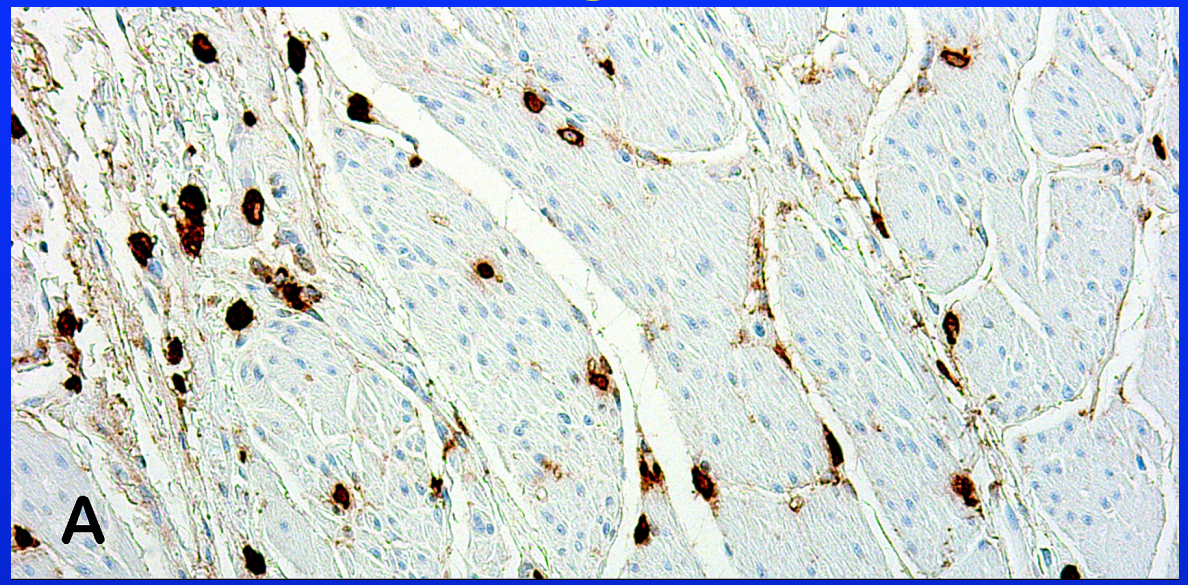
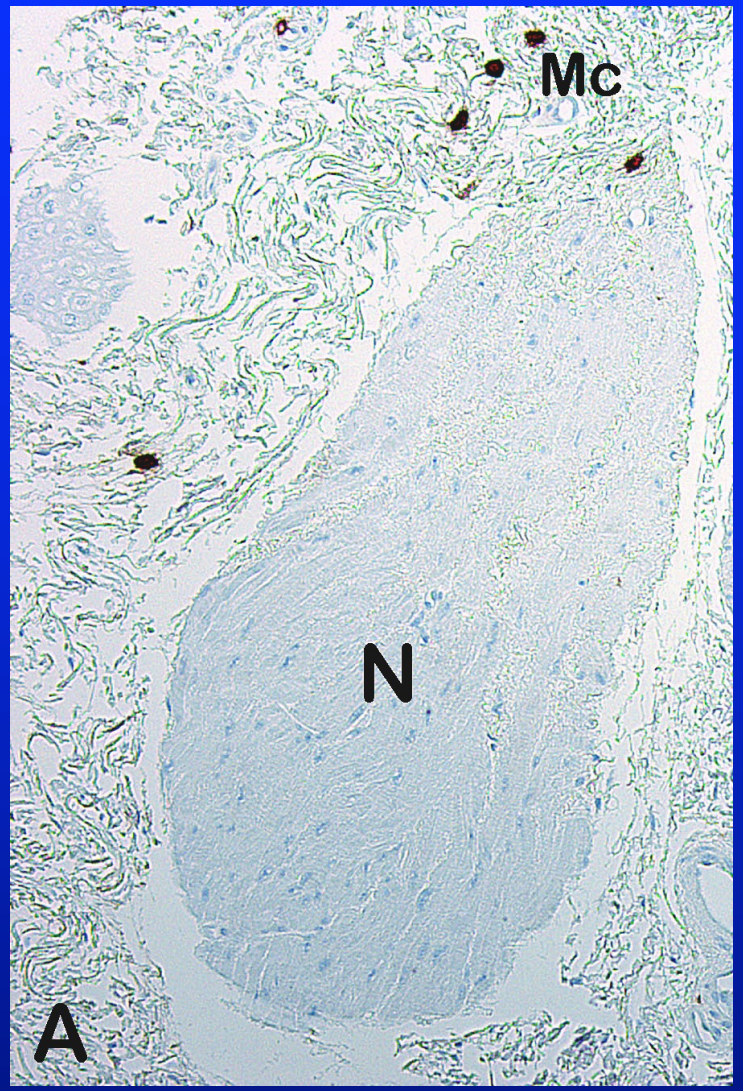
Achalasia LES Muscle Exhibits Profound Mast Cell Degranulation in Perimysium



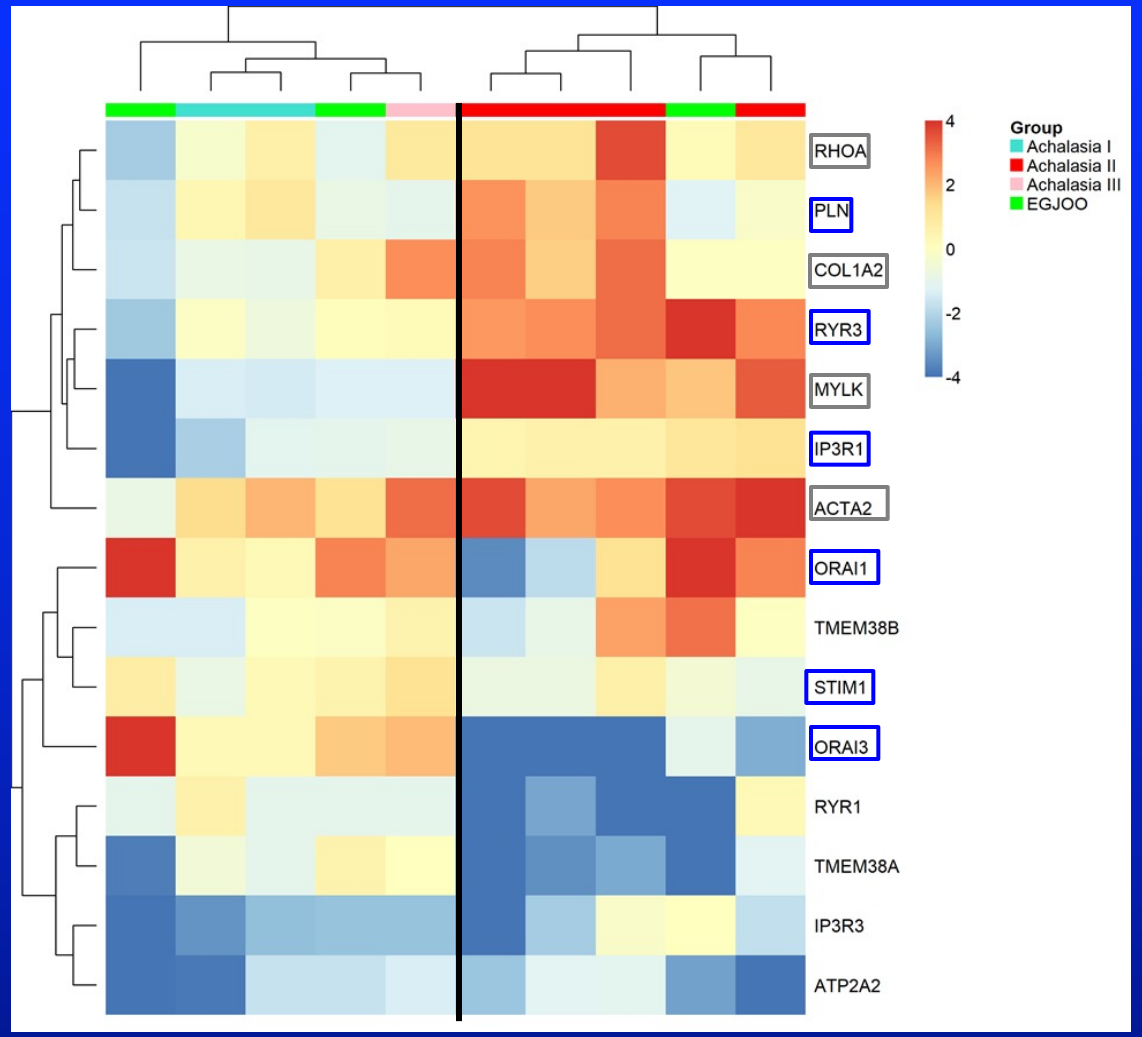
Organ Donor Control

Achalasia LES Muscle Exhibits Profound Mast Cell Degranulation Around Nerves



Organ Donor Control

Hierarchical Clustering Analysis of qPCR Data Reveals 2 "Mototype" LES Gene Expression Patterns



Mototype Cluster 1 **Mototype Cluster 2**

All achalasia II patients clustered in Mototype 2

- Upregulation of calcium handling genes (PLN, RYR3, IP3R1)
- Upregulation of smooth muscle contractility genes (RHOA, COL1A2, MYLK, ACTA2)

- Achalasia I and III patients clustered in Mototype 1
  - Upregulation of calcium handling genes (ORAI1, ORAI3, STIM1)

Nelson M, Zhang X et al. Neurogastroenterol Motil 2021;33:e14055.

Study Conclusions

- LES muscle of patients with achalasia and EGJOO exhibits striking mast cell degranulation
  - Supports our hypothesis that achalasia might be allergy-driven
- Patients with different achalasia manometric phenotypes exhibit different LES patterns of expression for genes mediating Ca^{2+} handling and muscle contraction

Nelson M, Zhang X et al. Neurogastroenterol Motil 2021;33:e14055.

Hypothesis

There is a form of achalasia caused by activated eosinophils and/or mast cells in esophageal muscle.

- Neuro- and myoactive eosinophil and mast cell products in esophageal muscle cause motility disturbances of achalasia
- Hypothesis strongly supported by reports of achalasia-like motility disturbances in EoE patients resolving with steroids
  - Difficult to reconcile with concept of achalasia as a neurodegenerative disorder
- When patients acquire EGID-mediated achalasia, genetic mototype might determine the manometric phenotype
- Ganglion cell destruction in achalasia may not represent a primary pathogenetic event, but late-stage “collateral damage” inflicted by chronic release of cytotoxic and pro-inflammatory cytokines from eosinophils and/or mast cells.


EGAD!
I’ve got
an
EGID.