EOSINOPHILIC GASTROINTESTINAL DISEASES

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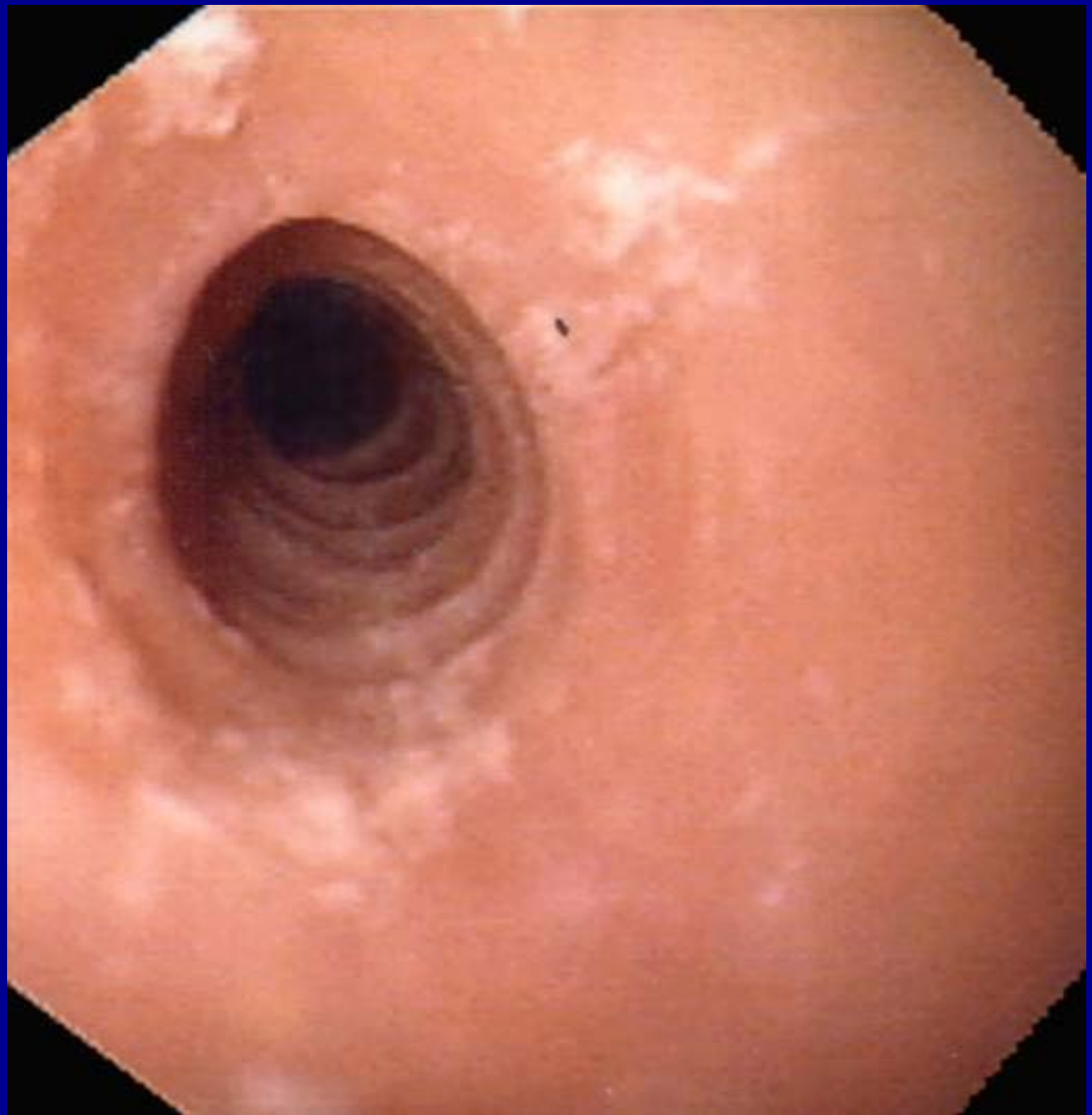
OBJECTIVES

- To recognize the clinical symptoms of EGID's
- Review pathophysiology and diagnosis
- Review medical treatments
- Review the importance of ELIMINATION DIET, multidisciplinary management with RD, allergist, immunologist, gastroenterologist

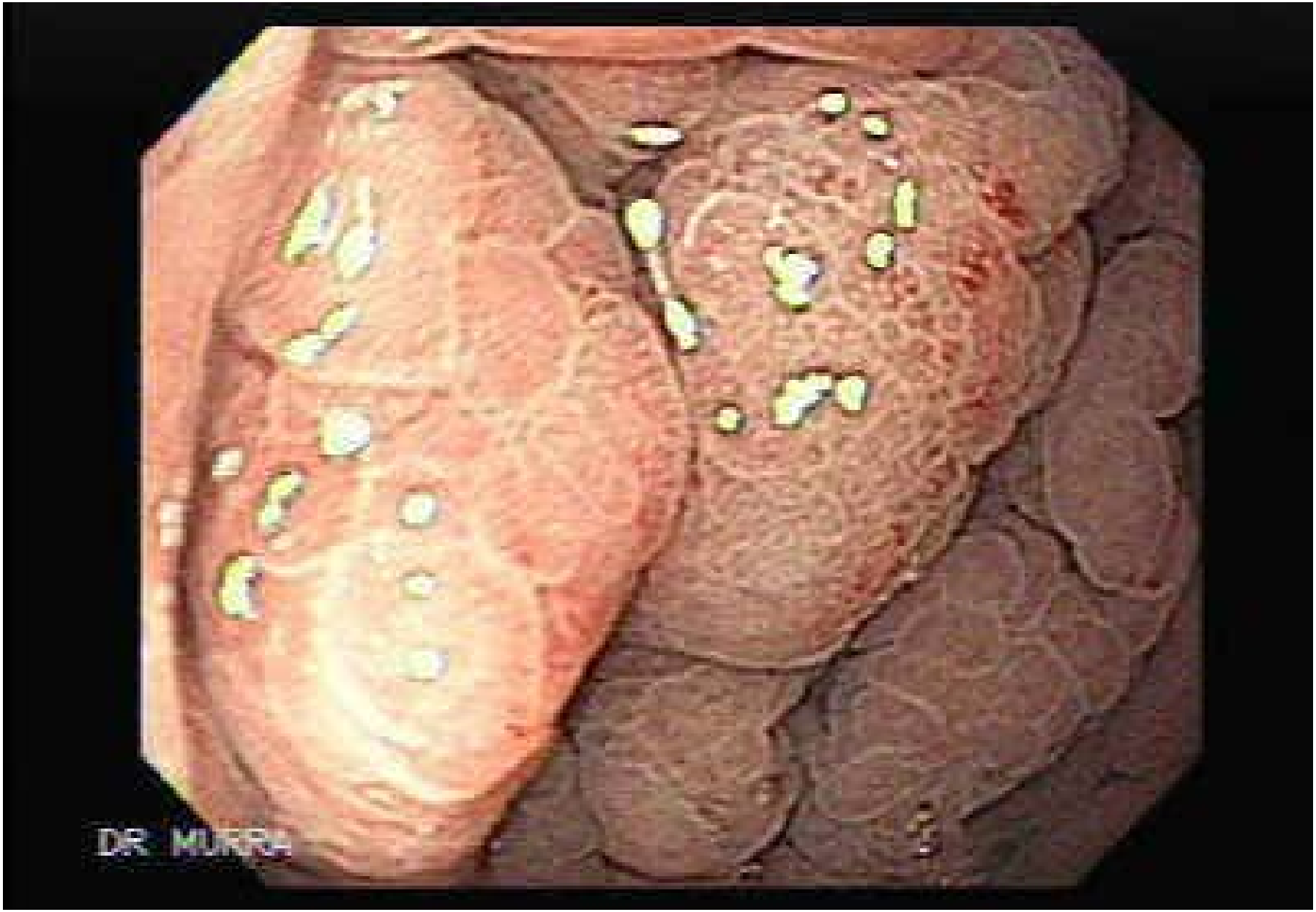
Patient Number One

36 year old self employed tree surgeon with long standing history of intermittent dysphagia and atypical GERD, NOT improved with H2RA's or PPI's. Has been seen and "scoped" by multiple gastroenterologists who tell him he has a "narrow esophagus". Unsure of prior biopsy and no past dilation. Comes to you for second opinion



Patient Number Two

- 58 year old female with epigastric pain, intense nausea, vomiting, albumin 2.3, peripheral eosinophil count greater than 1000, hemoglobin 8.5. She does not take NSAIDS. She takes low dose thryoid replacement, and lisinopril for hypertension. No prior allergy history. Changing her BP med did not improve symptoms.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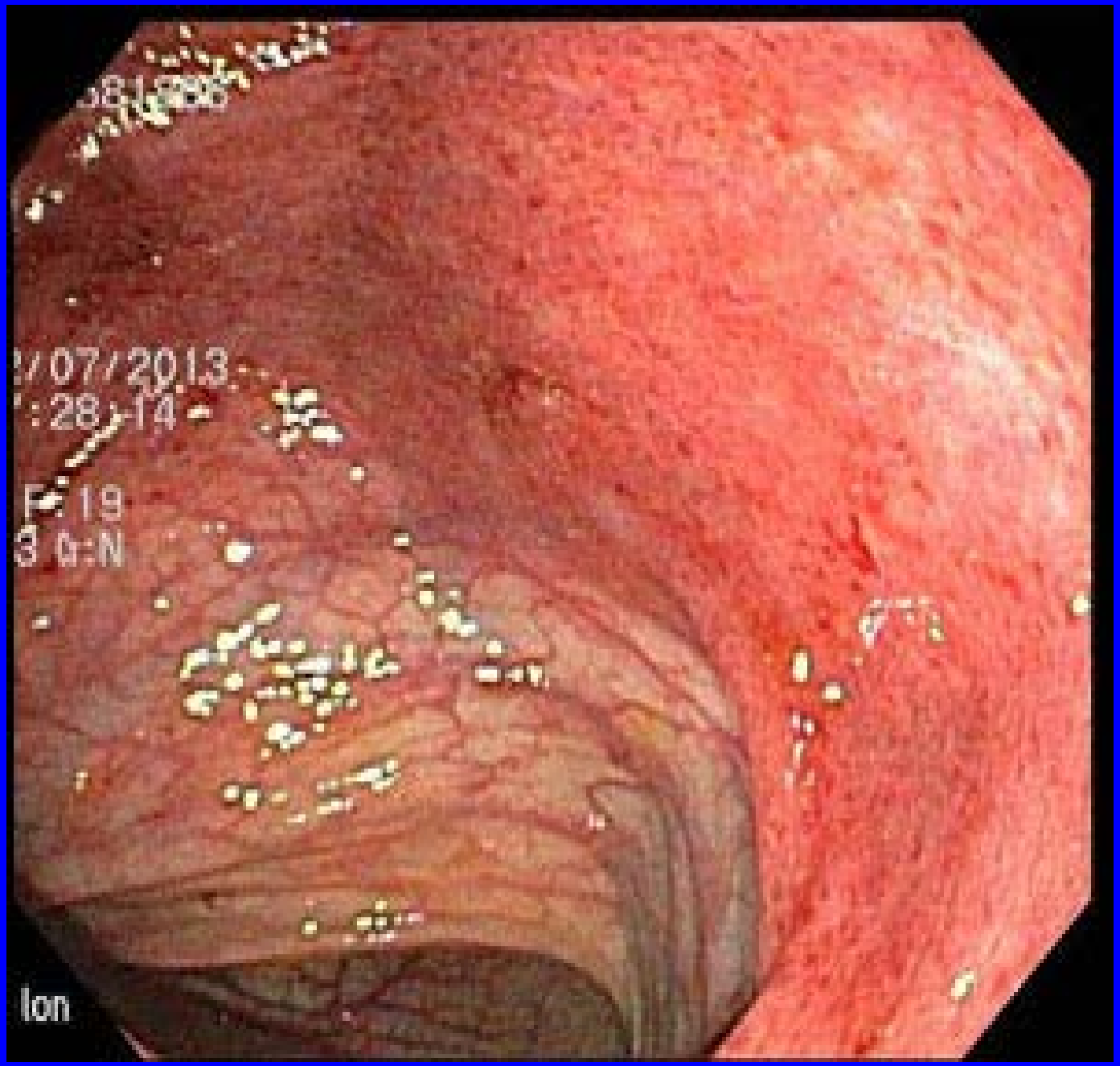
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Patient Number Three

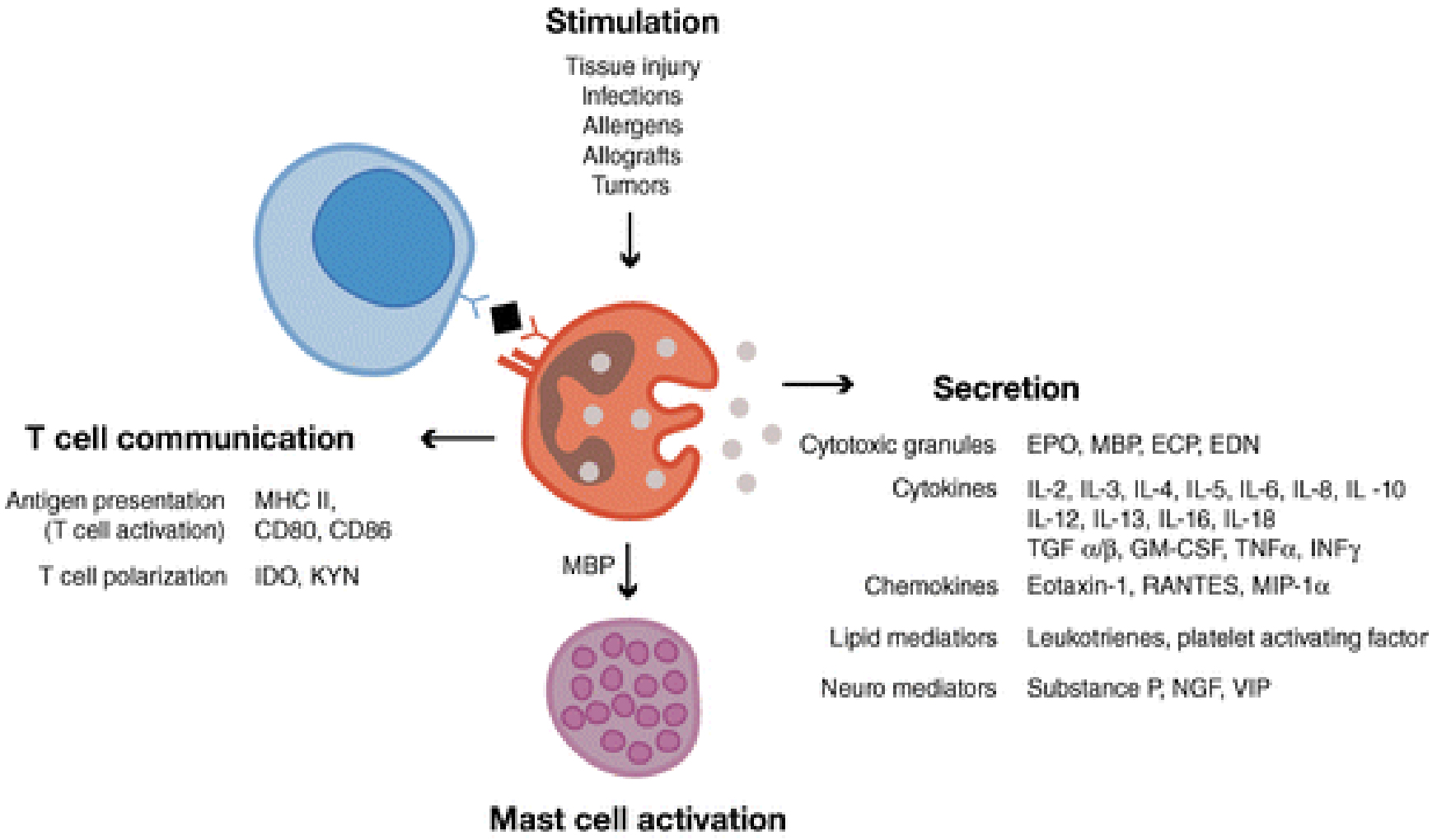
42 year old anesthesiologist with 4-5 loose stools daily for the last year, associated with cramps. History of atopy as a child overseas, has extensively traveled. Reports difficulty keeping weight on. Labs without eosinophilia or anemia. What is your differential diagnosis and how do you proceed?

History and Epidemiology of EGID's

- First described in 1937 by Kaijser; including EOE, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic enteritis, and eosinophilic colitis
- Increasingly recognized world wide: 1% pediatric population and 6% in patients with esophagitis, 10% cases have immediate family member with EGID
- Peak prevalence in peds and then adult males ages 30-50 >females.
- 70% cases with history of atopy or food allergies

EoE Demographics

- Incidence and prevalence are increasing rapidly
- 6-15% children and adults undergoing EGD
- 43-52/100,000, approaching the prevalence of IBD
- Males are 2-4x more likely than Females
- Highest in US and Western Europe, lowest in Japan and China
- Whites> non-Whites but seen in all ethnicities



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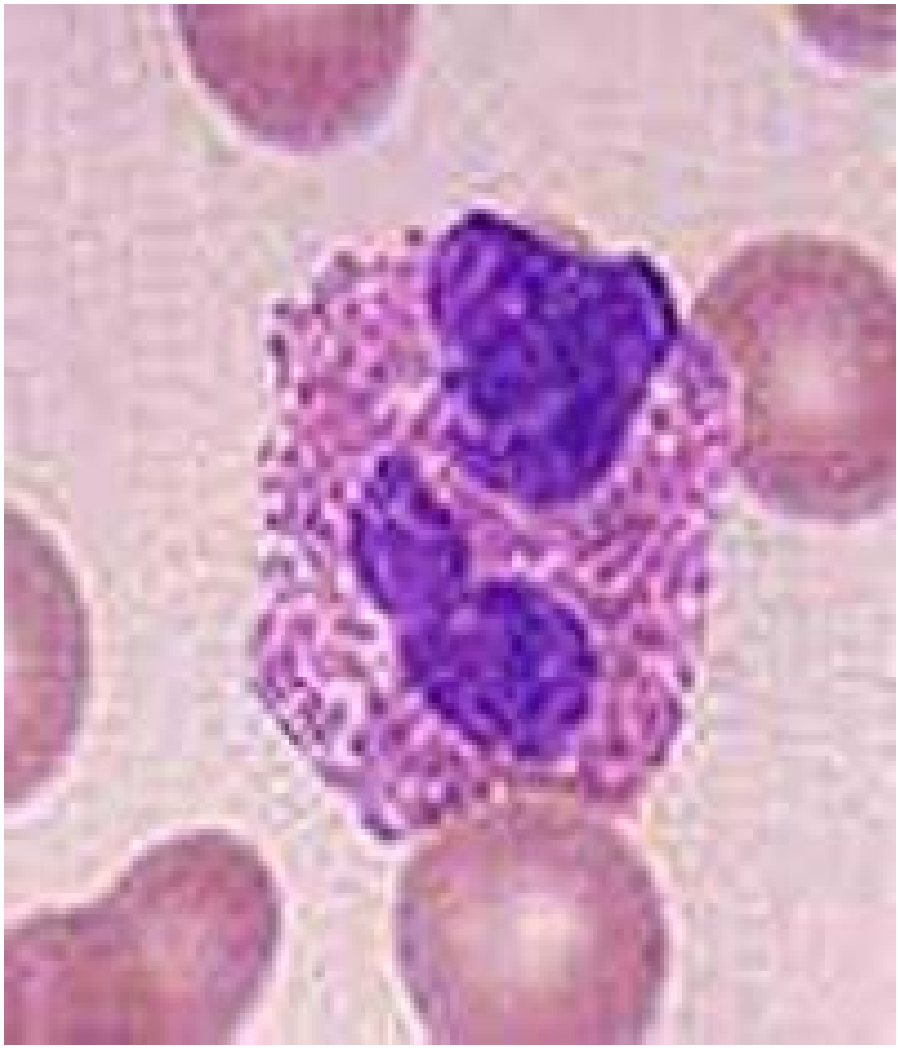
EOSINOPHILS



- 1-3% peripheral blood
- Mature in 8 days in bone marrow under the regulation of transcription factors (GATA-1 and 2, c/EBP, and permissive eosinophil growth factors IL-3, 5, and GM-SCF. **IL-5 felt to be most specific and responsible for expansion.**
- Circulate in peripheral blood 8-12 hours and traffic to specific tissues predominantly the GI tract. Live about one week. Many inflammatory mediators regulate the trafficing, including IL-1,3,4,5, 13, GM-CSF, Chemokines, eotaxin 1,2, and 3., TNF a, PAF, and cysteinyl leukotrientes. **The eotaxins are most critical for tissue recruitment**
- Found normally in the lamina propria of GI tract, spleen, thymus, lymph nodes, but NOT THE ESOPHAGUS.

Pathophysiology

- IgE mediated and non-IgE (cell mediated) hypersensitivity response
- Food and aeroallergens play a critical role in genetically susceptible persons.
- IL-5 (inducer of eosinophil proliferation and activation)
- Cysteine leukotrienes are known eosinophil chemo-attractants
- Eotaxin-3 is over-expressed in GI tract in pts with EOE, eotaxin-1 mRNA found in greater amounts in IBD lesions
- EOE may be a distinctly different disease than EG or EC; with similar immunological triggers to asthma.
- Eosinophil infiltration and subsequent inflammation results in thickening of the bowel wall, which can result in obstruction. Serosal form seen in a minority of patients and is distiguished by exudative ascites with higher peripheral eosinophil counts compared with other forms of EGID's

Differential Diagnosis

- Eosinophilis aggregate in the GI tract for various GI conditions including classic IGE mediated food allergy, EGID's, allergic colitis, and inflammatory bowel disease

- Differential diagnosis for EGID's includes: parasites, drugs (NSAIDS), cancer, certain connective tissue diseases, and IBD

Differential Diagnosis-EOE

- Reflux esophagitis
- Infectious esophagitis (fungal, viral, parasitic)
- Graft vs. host
- Crohn's disease
- Hypereosinophilia syndrome
- PPI responsive esophageal eosinophilia

GERD and PPI responsive EoE

- Substantial overlap in symptoms and histology
- One third of patients with EoE respond to PPI (distinct clinical entity vs. subtype of GERD, or a phenotype of EoE?)
- Most authorities agree that if a trial of 20-40mg twice daily of PPI leads to symptom control and resolution of esophageal eosinophils, then PPI-REE is the dx; if persistent symptoms or eosinophils , then EoE is the dx.

Clinical Presentation EOE Infants and Toddlers

- Failure to thrive, poor growth
- Feeding intolerance
- Abd pain, nausea, vomiting
- Regurgitation, food aversion
- *up to 80% children diagnosed with EoE have atopy, supporting allergic etiology

Clinical Presentation EOE in Adults

- Most often before age 40
- White Males comprise the majority
- Oftentimes with decades of symptoms
- **Most** (70%)have concomitant history of environmental allergies, allergic rhinitis, asthma, and/or food allergies
- Symptoms include food impaction (40%) dysphagia (predominant symptom) heartburn, chest pain
- Rare to have peripheral eosinophilia
- Symptoms and tissue eosinophil counts may vary with season (worse summer through fall)

Clinical Presentation EG

- About 50% have peripheral eosinophilia
- Adults greater than children
- Incidence less than EOE but also on the rise worldwide
- Symptoms include gastric dysmotility, nausea, vomiting, weight loss, sitophobia, abdominal pain, micoscopic anemia, hypoproteinemia

Clinical presentation EC

- Diarrhea predominant symptom
- Most often have functional type abdominal pain
- May or may not have weight loss and hypoproteinemia
- May or may not have peripheral eosinophilia
- May or may not have frank rectal bleeding, iron deficiency anemia or occult positive
- Probably rarer than eosinophilic disorders of the upper GI tract

Diagnosis-Endoscopy is Key

- For EOE: Obtain 4 bx about 6cm above Gejuntion, and 4 in mid to proximal esophagus
- Endoscopic findings
  - Linear furrows
  - Concentric rings
  - White spots or exudates (can be confused with candidiasis
  - Crepe-paper mucosa (manifestation of mucosal fragility)

Endoscopy in EG and EC:

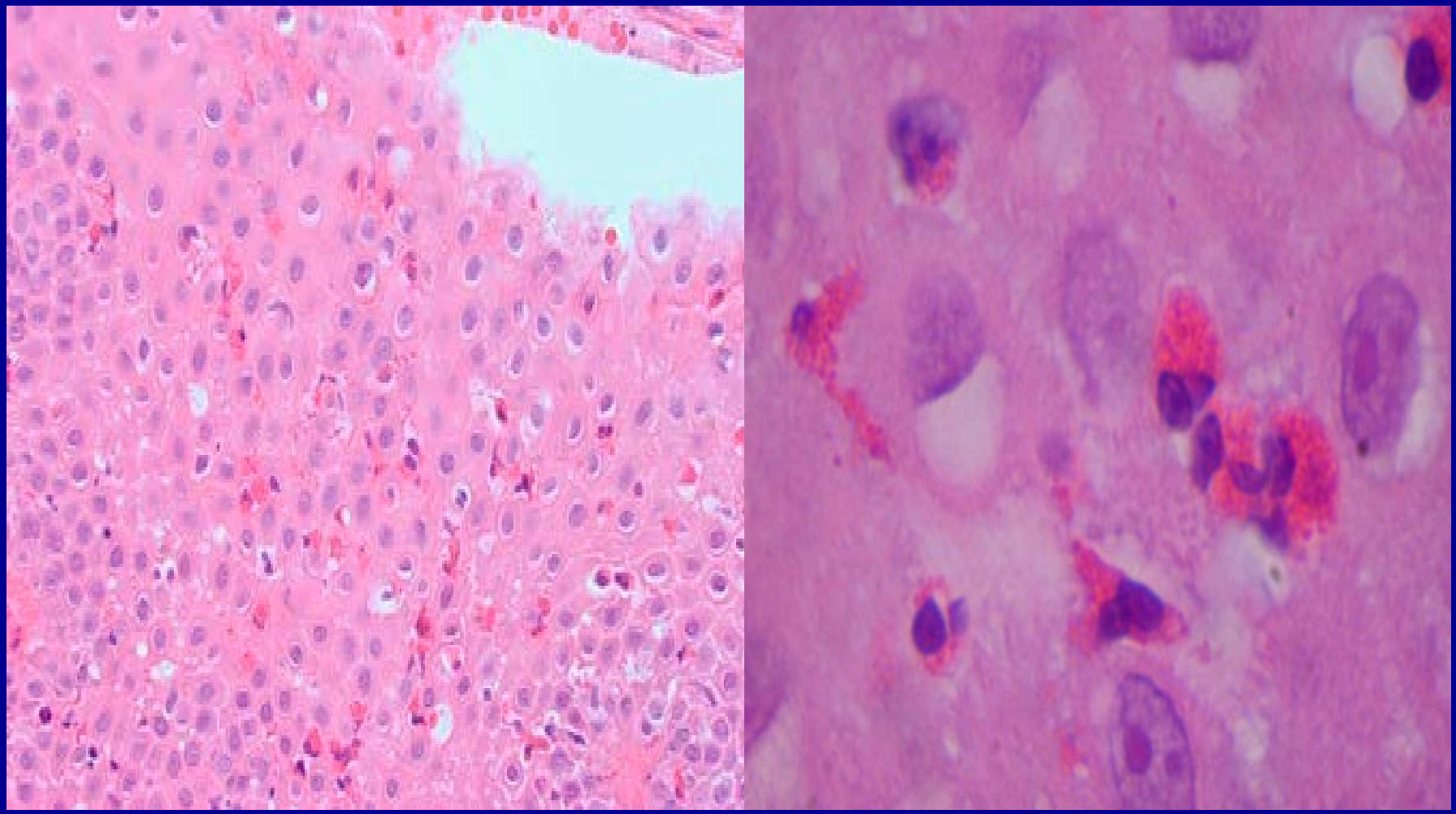
- All EGID's can be patchy, so multiple bx's are needed. Macroscopic findings can be subtle.
- For EG, most often rugae are hypertrophic. Biopsy any red spots, and any nodules (micro abscesses)
- For EC, rectum is most often involved, with nodularity. However, biopsy multiple areas to increase diagnostic yield.

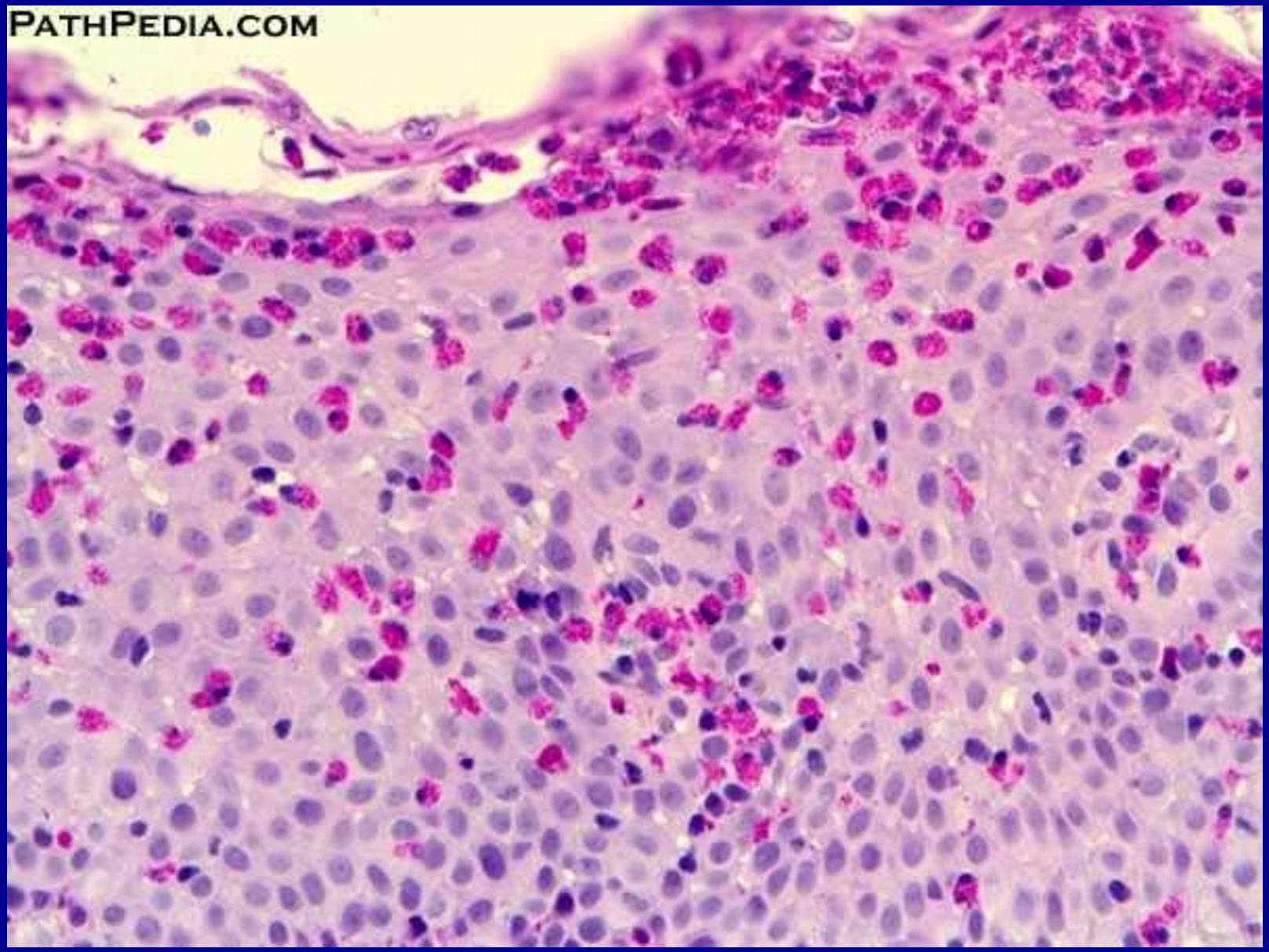
Histopathology

- In GERD, up to 7 eos/HPF may be seen, up to 20 may indicate GERD plus food allergy, more than 20 is characteristic of EOE
- In Small bowel involvement, biopsies show extracellular deposition of eosinophil granule constituents, with immunohistochemically detectable increased major basic protein and eosinophilic cationic protein

Additional Histologic Features in EOE

- Eosinophilic micro abscesses
- Extracellular granular proteins
- Fibrosis in the lamina propria
- Basal layer hypertrophy and Rete PEG elongation

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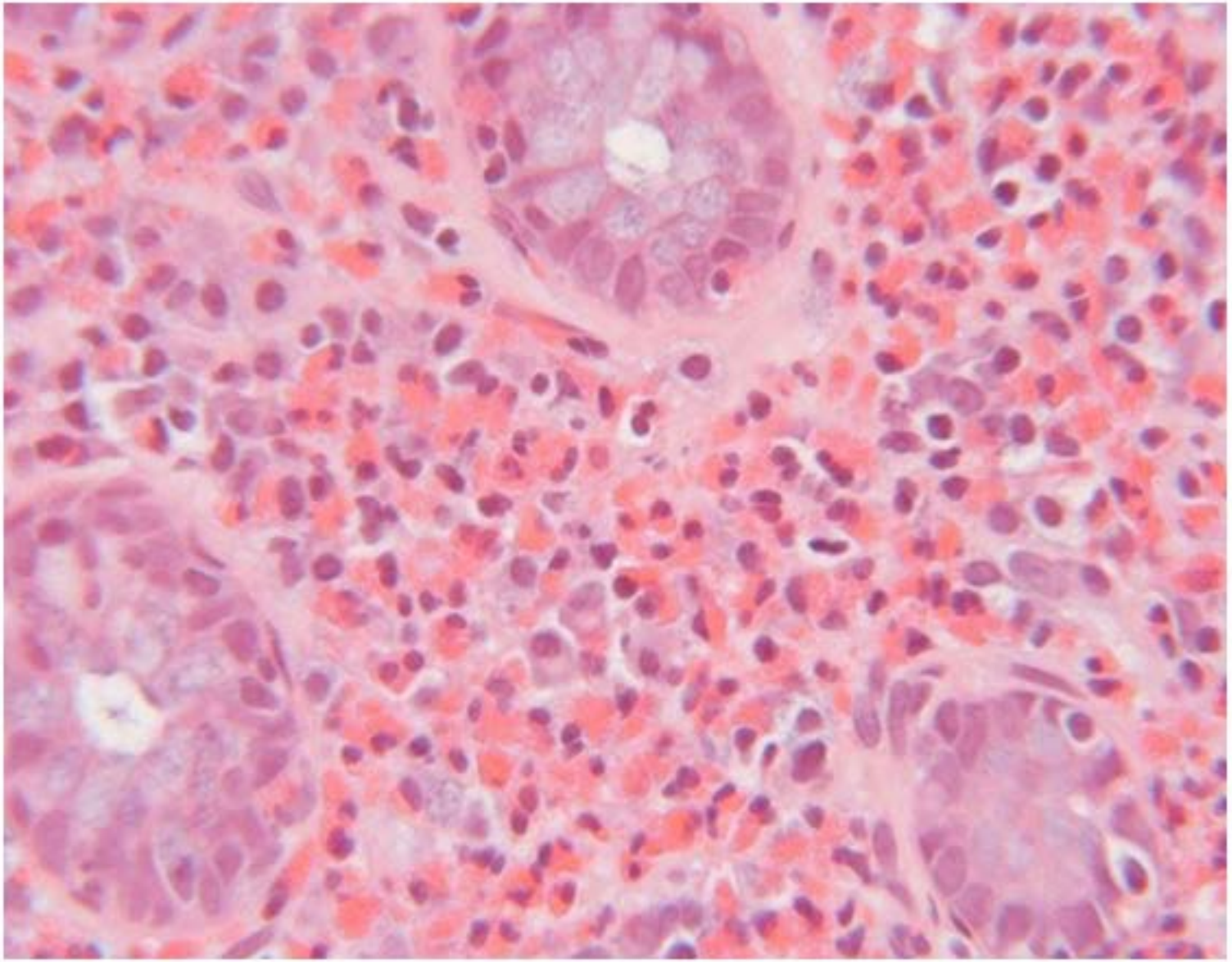

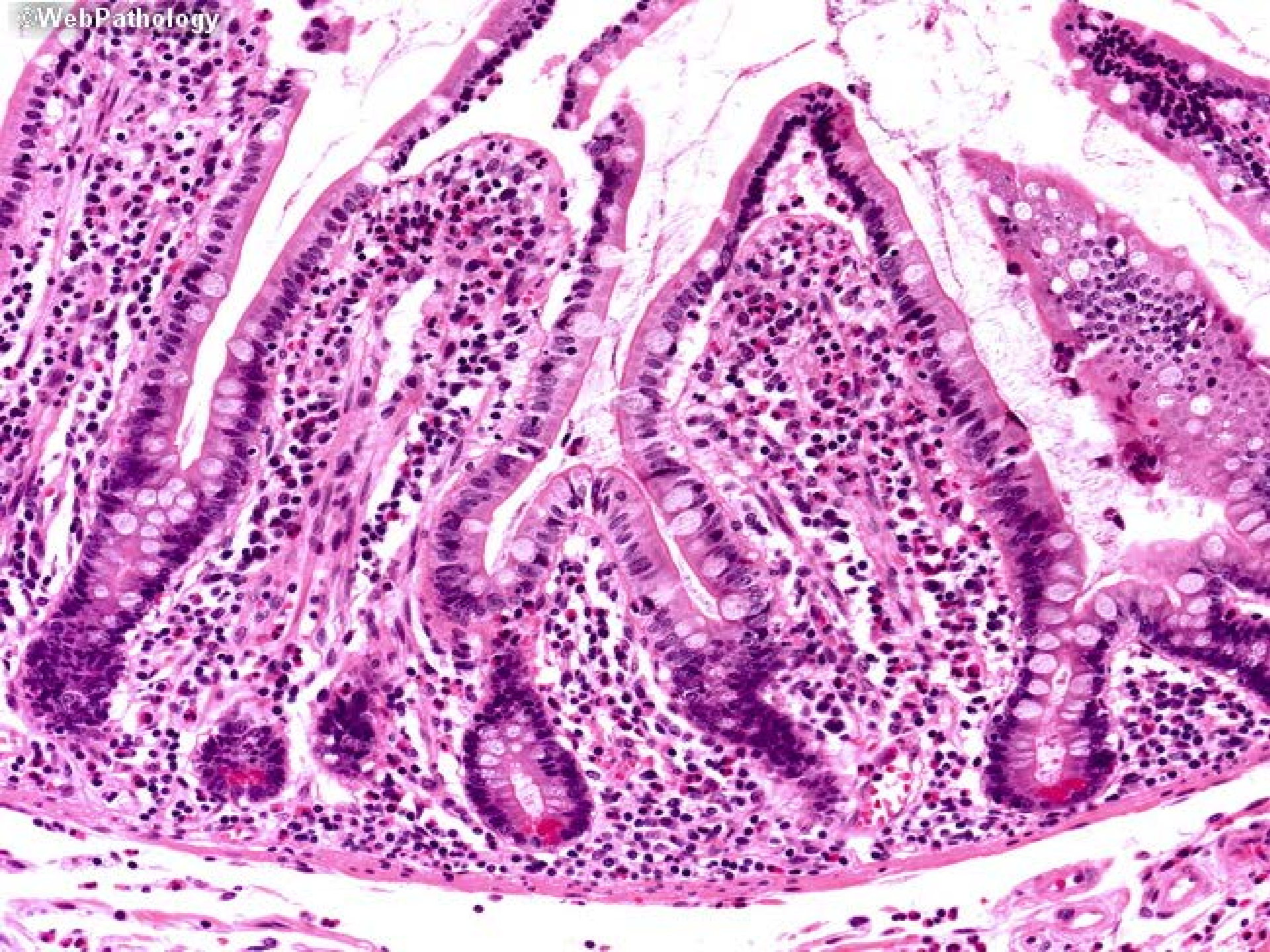
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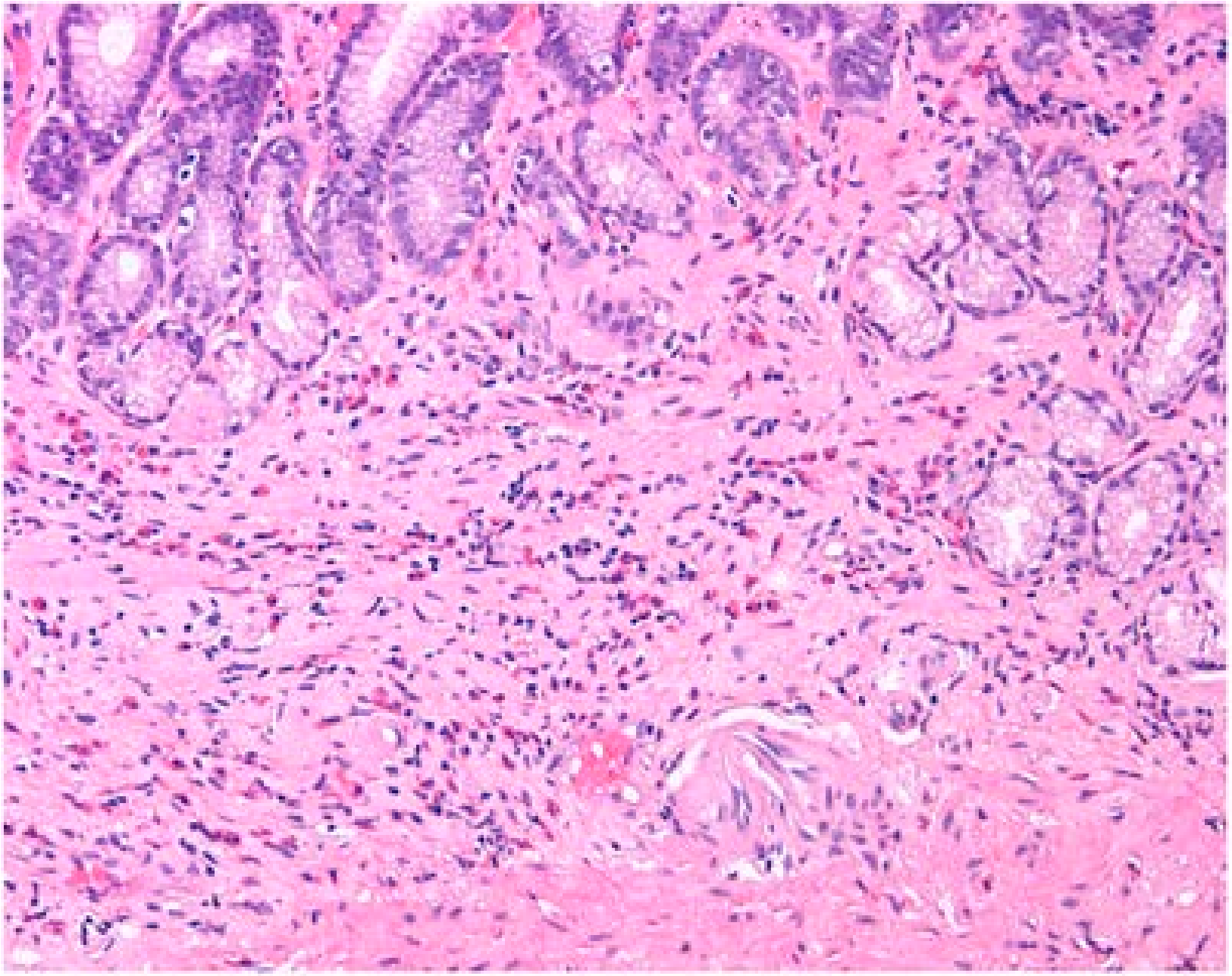

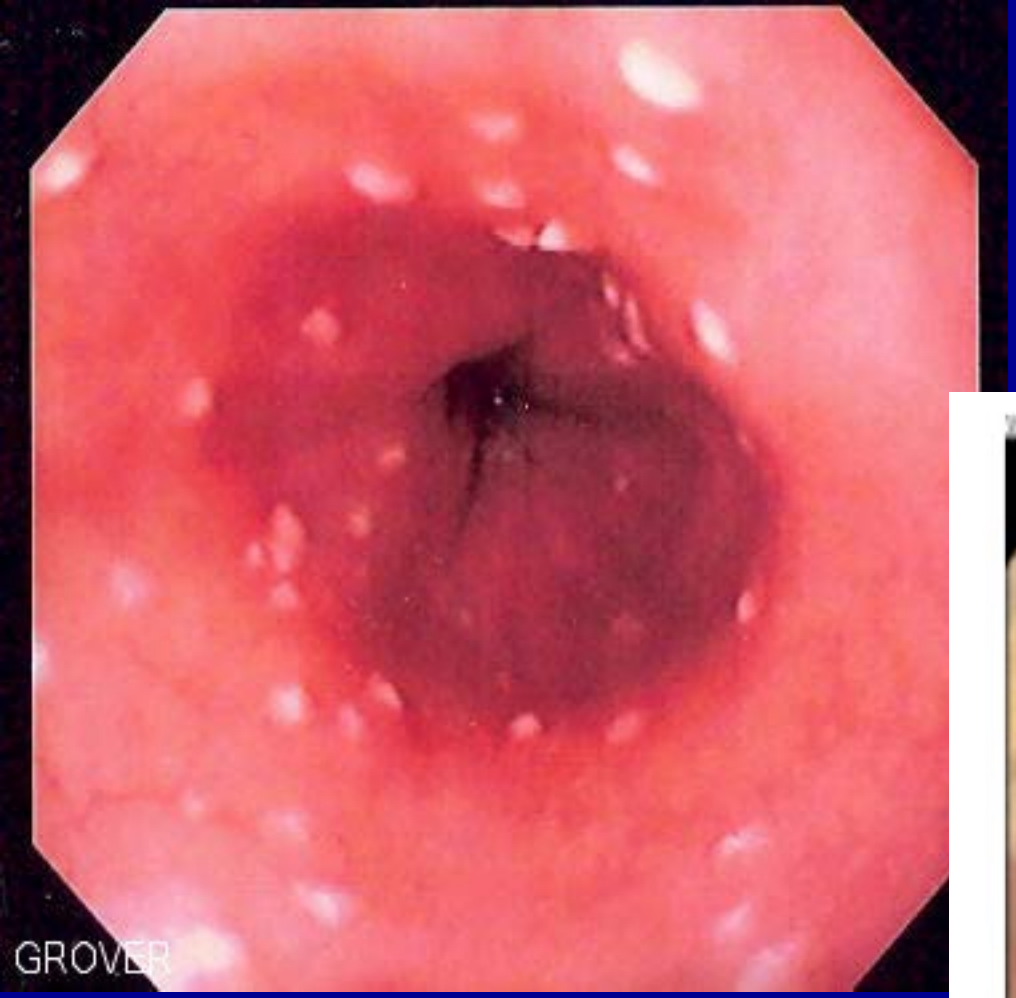

Candida Esophagitis

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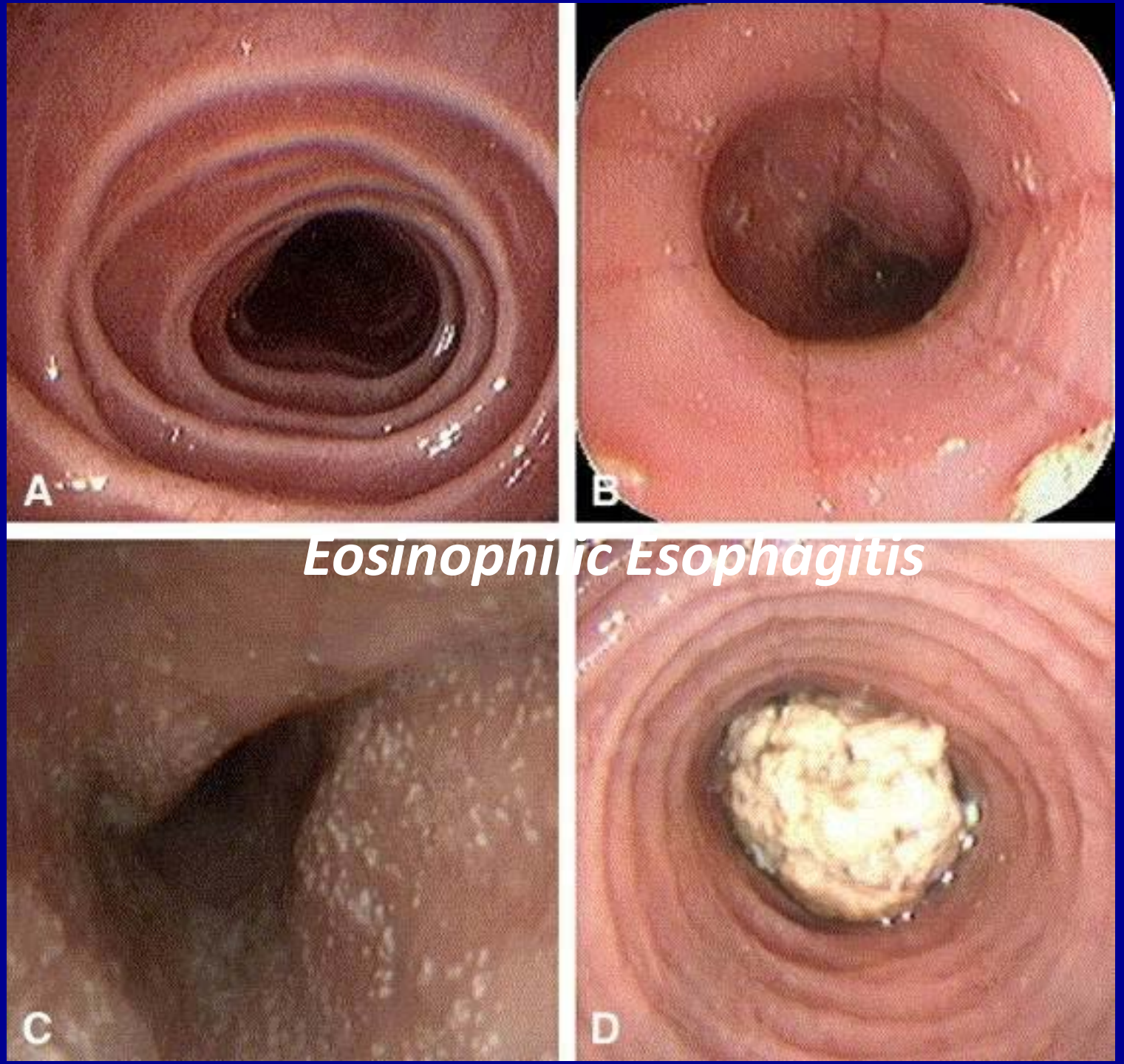
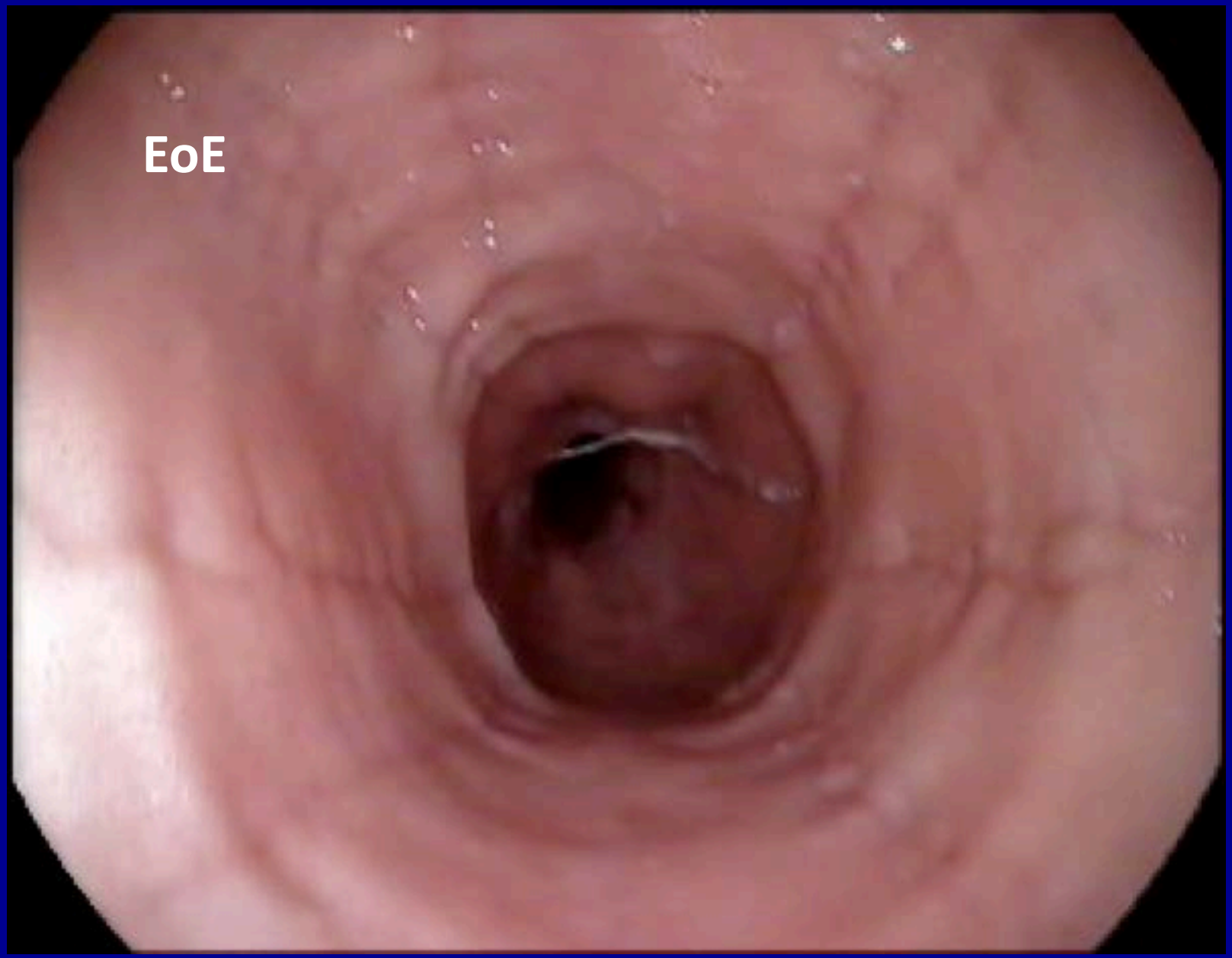


Eosinophilic Esophagitis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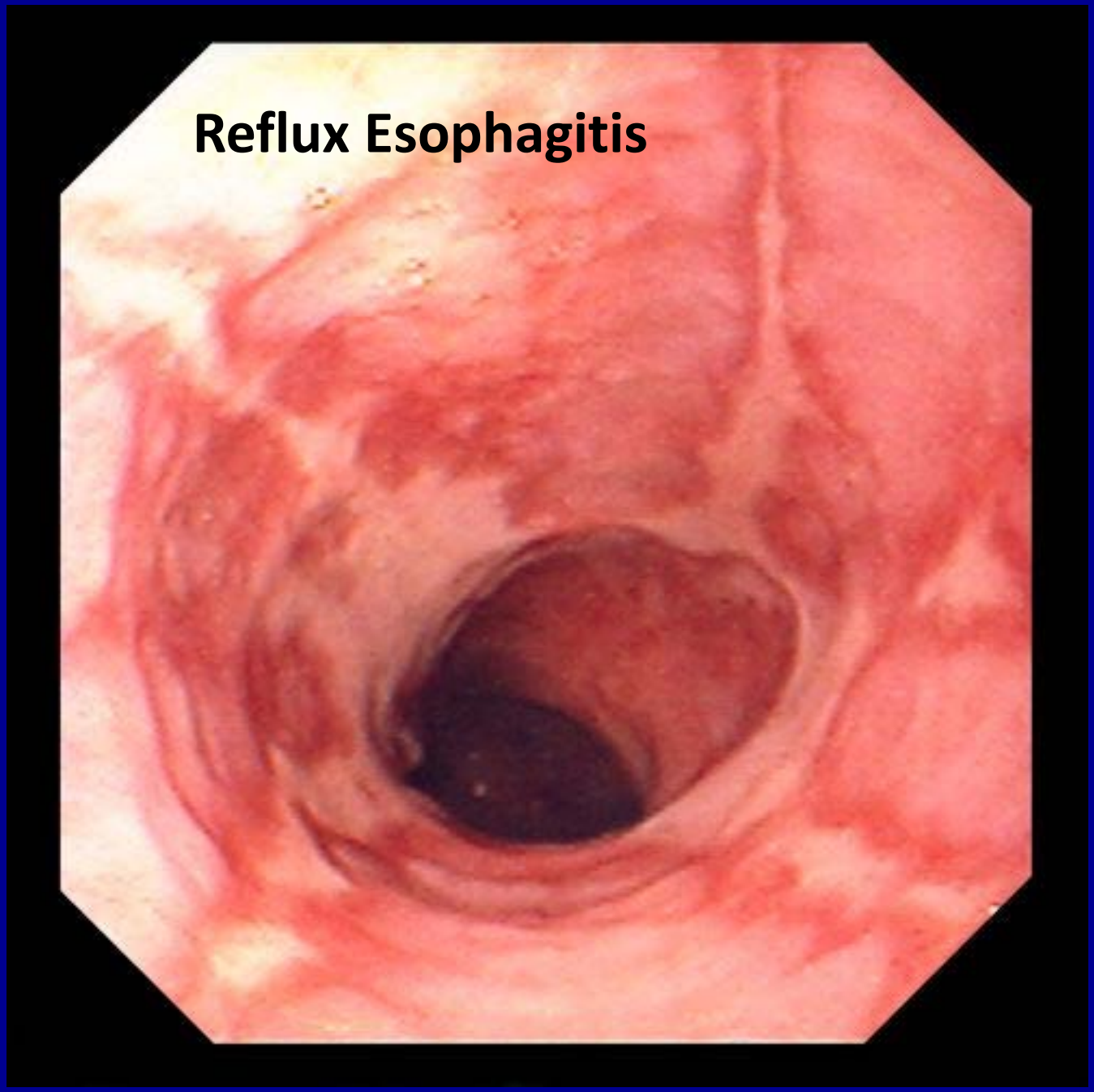
Reflux Esophagitis

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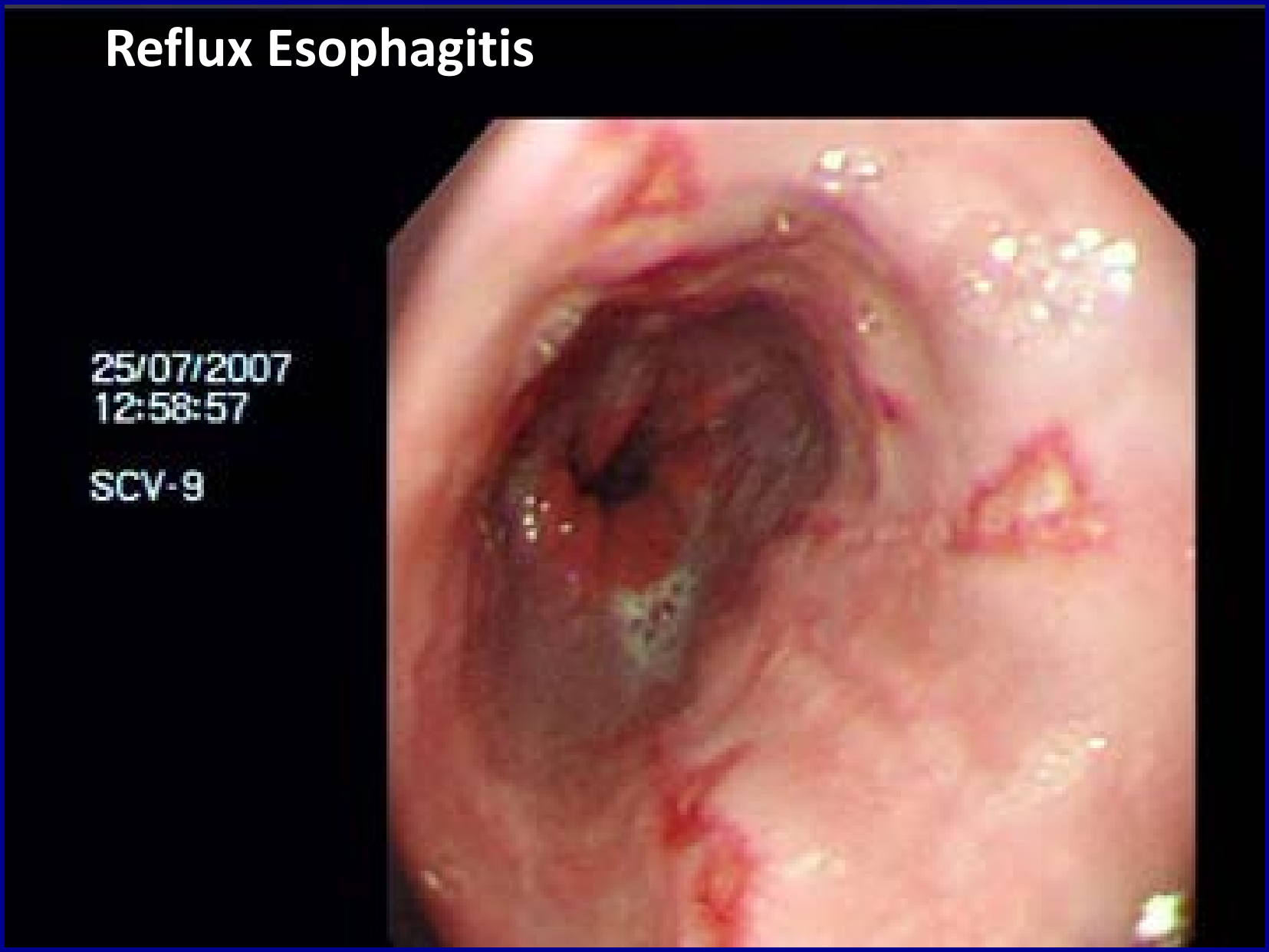
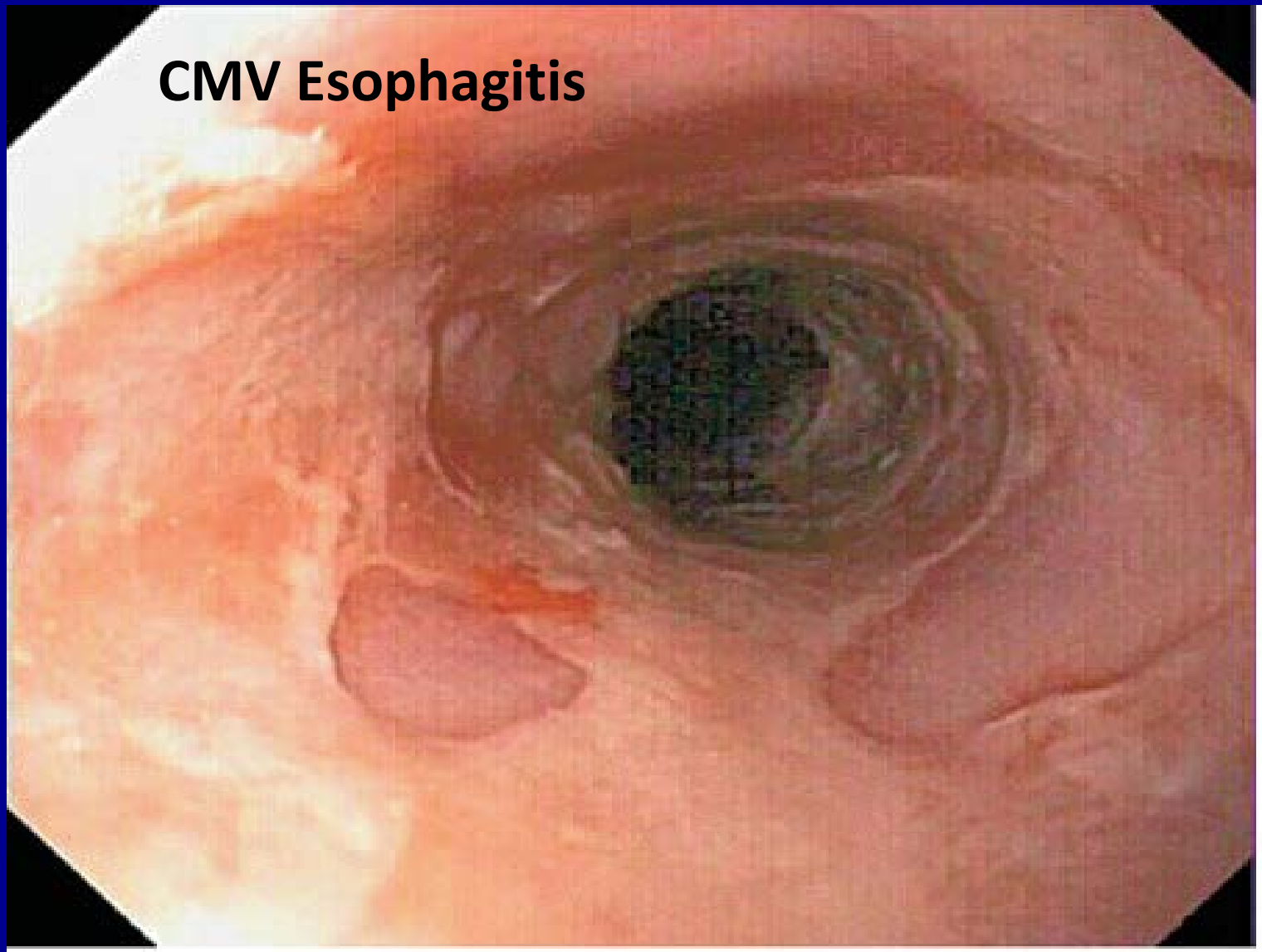


CMV Esophagitis



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Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J:
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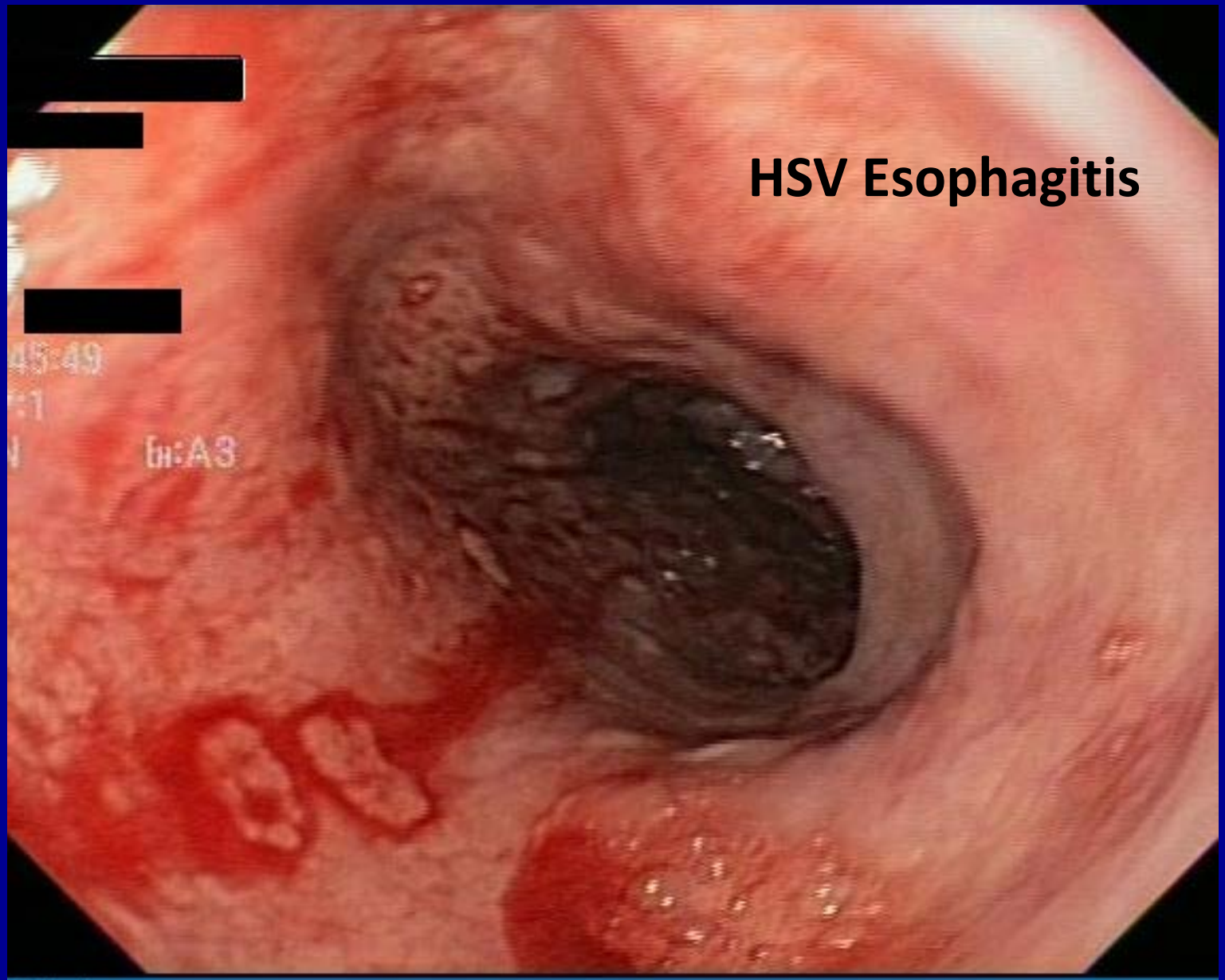
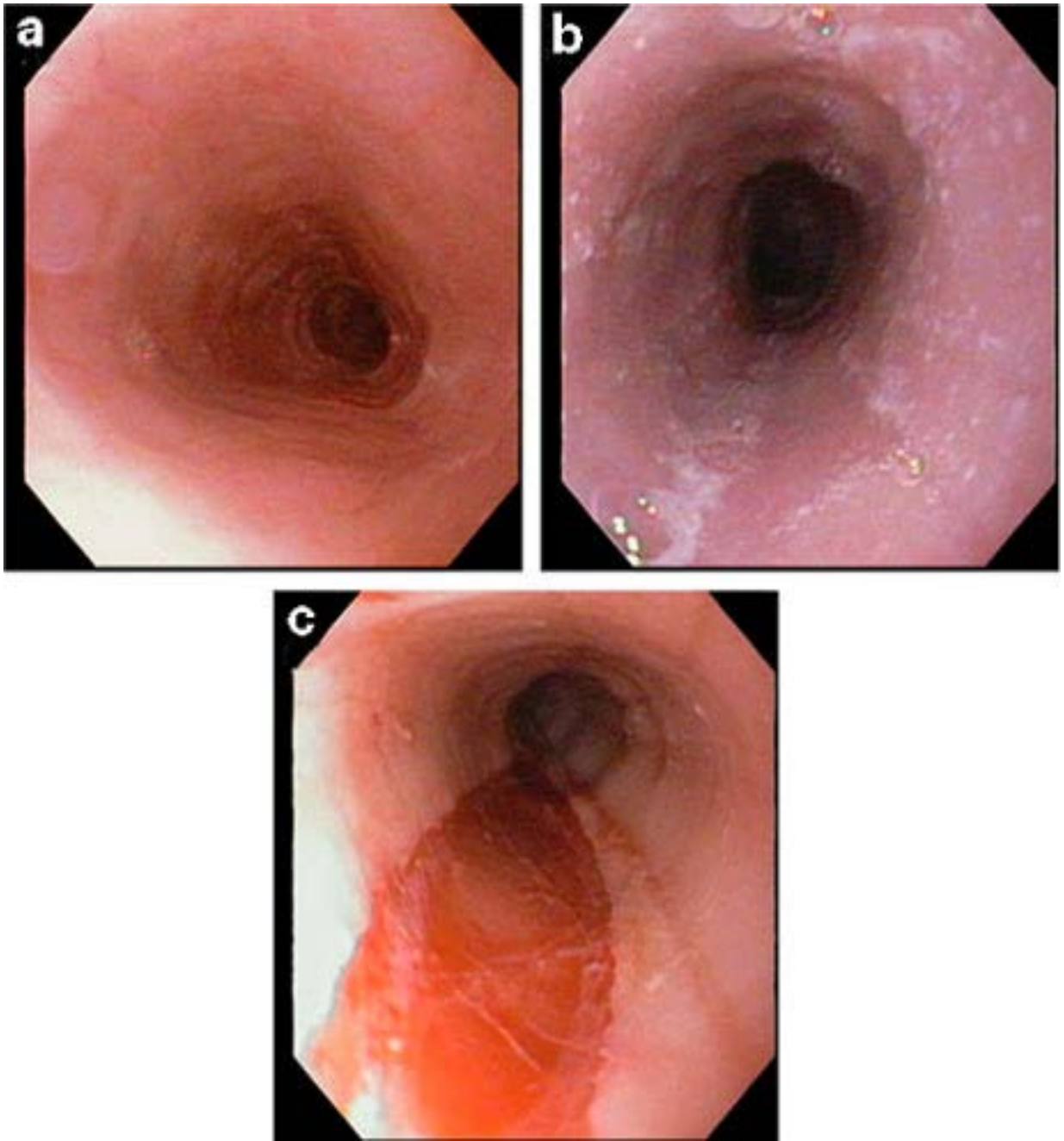

HSV Esophagitis
Medscape



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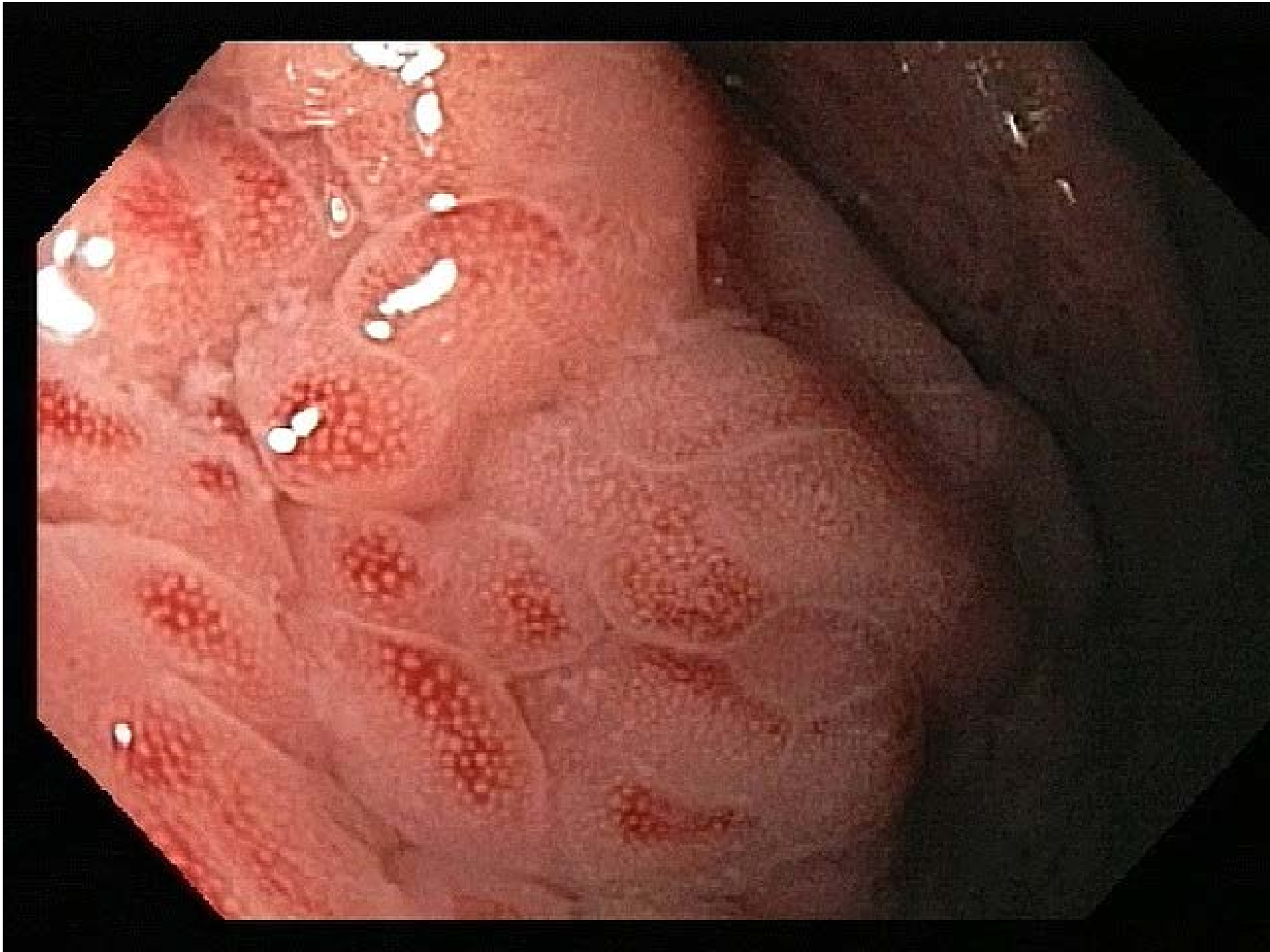
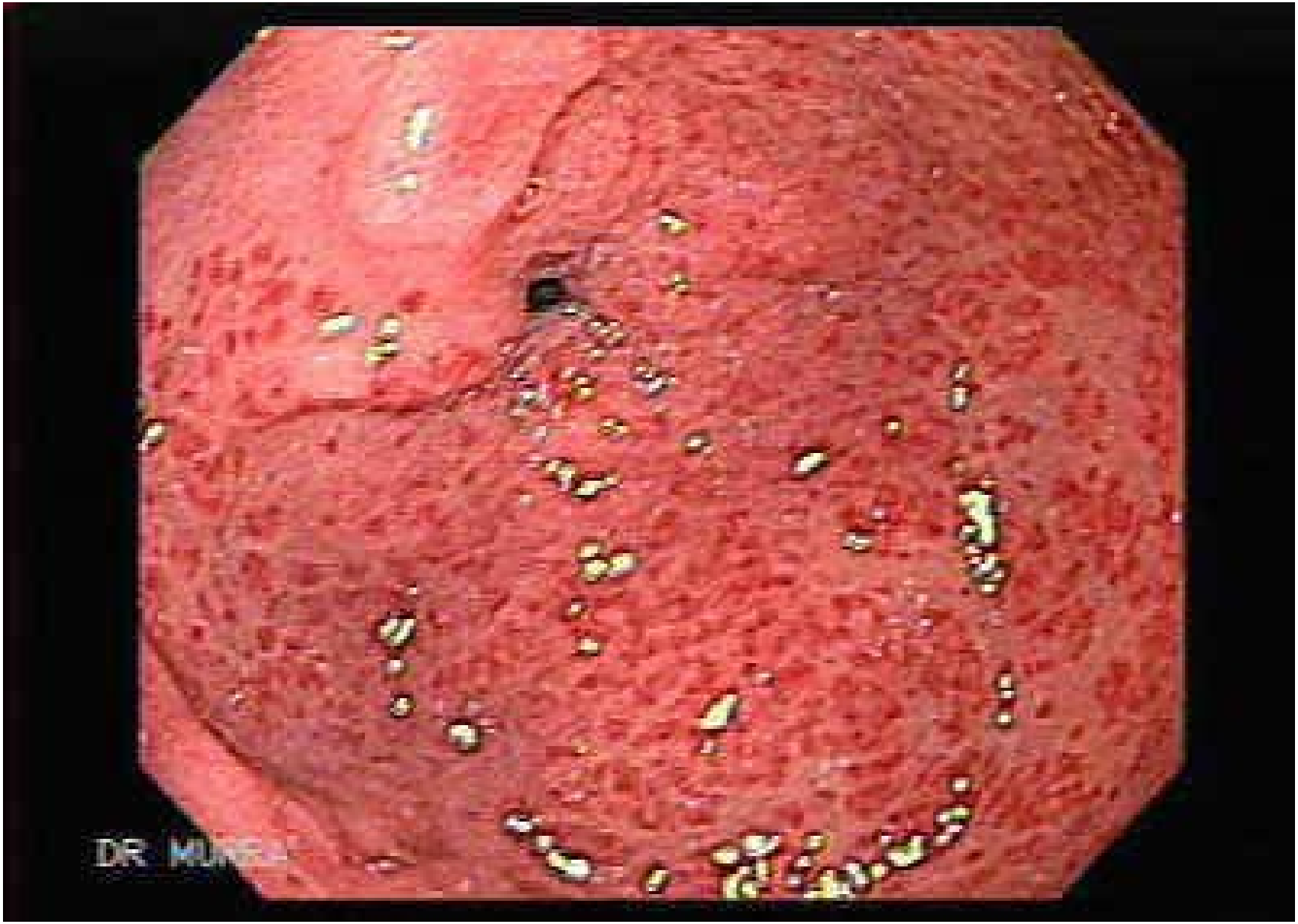
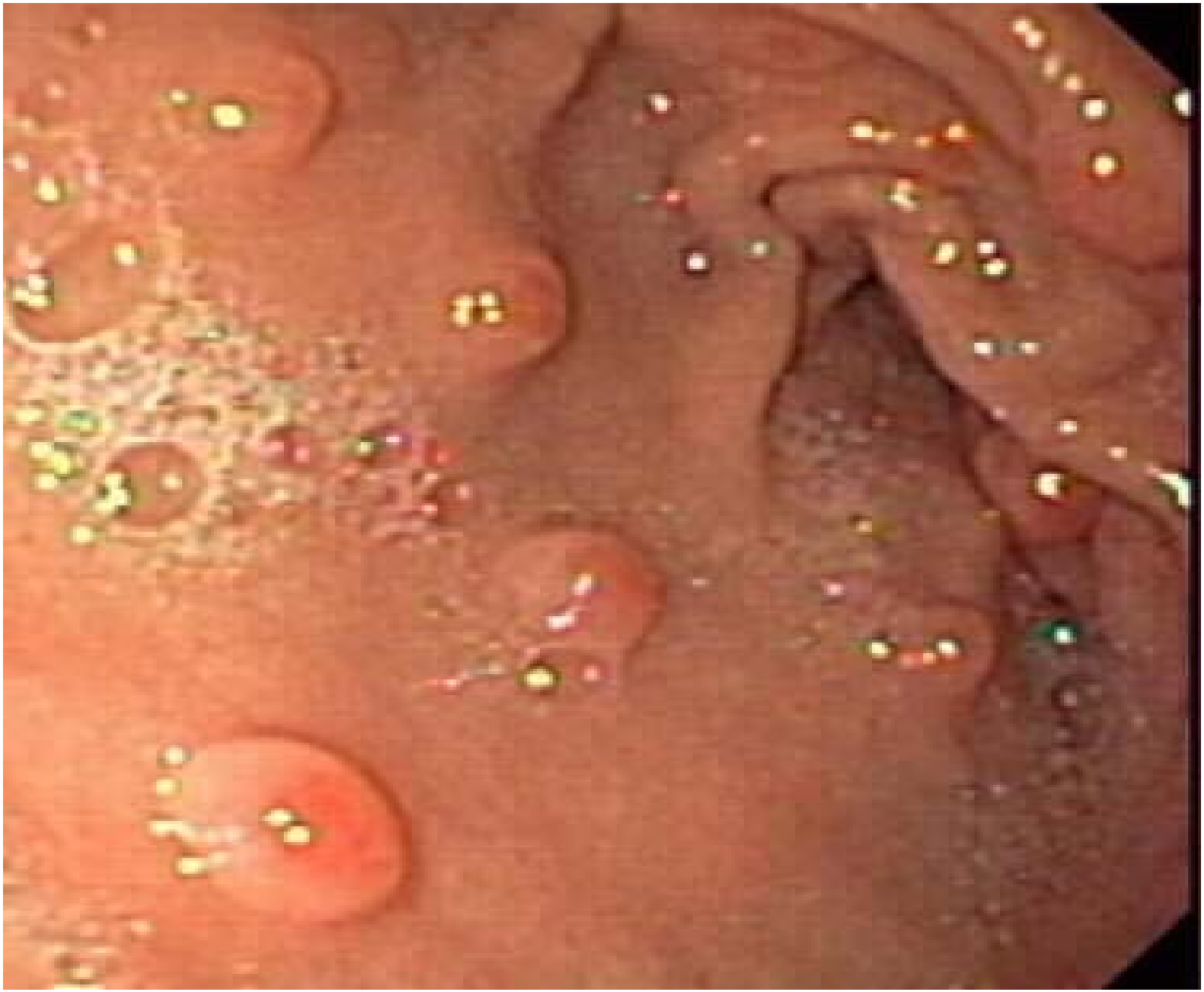





DR. MURRA



Treatment Options-Pharmacologic

- No-FDA approved treatments (off label)
- BID PPI (for EOE) How long, with or without other agents?
- Fluticasone, beclomethasone compared to prednisone (some randomized controlled trials) showed equivalence, so topical treatments are favored
- Budesonide 2-6mg daily usually given as a slurry mixed with sucralose, or fluticasone 880 to 1760 microgram/d show marked histologic response compared to no response with placebo

Biologic Agents- disappointing

- Mepolizumad and reslizumab (monoclonal anti-interleukin-5 antibodies), studies in 3 RCTs (1 adult, 2 children) showed mild to moderate improvement in eosinophil counts, but symptoms did not improve except in one adult with EOE who had dramatic improvement but then relapsed.
- Infliximab –2 patients with mild improvement of symptoms, one got worse. Also, no decrease in eosinophil counts.
- Omalizumab (monoclonal ab against IgE, studies in 30 adults with EoE, resulted in increased tissue eosinophils and no improvement of symptoms, whereas in 9 subjects with allergic eosinophilic gastroenteritis peripheral blood and tissue esoinophils decreased by 30-70%.

Other Agents for EGID's

- Montelukast (selectively blocks the D4 receptor of cysteinyl leukotrienes present in eosinophils.-). Important in asthma pathophysiology, and most useful in EOE. Actions of leukotrienes include eosinophil attraction and migration, smooth muscle constiction, mucosous secretion. 20-40mg-effective in some cases, ineffective in others. High side effects (nausea and vomiting)
- Cromolyn sodium (mast cell stabilizer) may help some
- Ketotifen (antihistamine with anti-mast cell properties) potential but no data
- Immunomodulators (immuran and 6-mp) limited data, not recommended
- Antiinterleukin 13 and anti-eotaxin-3 antibodies as well as prostaglandin D2 receptor antagonists are being investigated as treatment options

Non-Pharmacologic Treatments

- Elimination Diet
- Elemental diet (children and infants)
- For EOE: Esophageal dilation (reduces symptoms but does not reduce inflammation)

Dietary Treatment Outcomes

- In 51 children with EoE elemental diet, **96%** had near complete resolution of esophageal eosinophilia and symptoms within 2 weeks

- Fewer studies but overall 70% improvement in children with EG or eosinophilic enteritis using elemental diet

- Downside: expensive, unpalatable, may require delivery through gastrostomy, dietary endpoint unclear (tolerance)

6 Food Elimination Diet for Adults

- Stop the most highly allergenic foods: dairy, egg, wheat, soy, nuts (tree nuts and peanuts), seafood (fish and shellfish)
- **¾ had resolution of esophageal eosinophilia and almost all had improved symptoms**
- *Can add back food items every two weeks until symptoms recur in order to define specific triggers

Food Allergy Testing

- Avoid foods that were demonstrated on reactive skin or serum testing, response rate less favorable compared to elimination diet.

- Overall response rate in children 50-75%, lower in adults, depending on center and method of testing

Endoscopic Dilation

- Initially felt to have higher perforation rate but now similar to other reasons for dilation without EoE (0.3%)
- No consensus on superior benefit of balloon or bougie; use judgment
- Less experience and reports of dilations for pyloris, small bowel and colon but case reports of imporved symptoms

Back to Patient Number One over the last ten years:

- He has intermittently required dilation
- He has taken budesonide and fluticasone,
- Has had negative food allergy testing but has not tried elimination diet
- Has multiple “aeroallergens”, but continues to work outdoors
- He is compliant with histamine 1 and 2 blockers (Zantac and Zyrtec), which he believes help the most
- I am also treating him with 1-2 T/day of…….

Patient Two-EG- also over last 10yrs

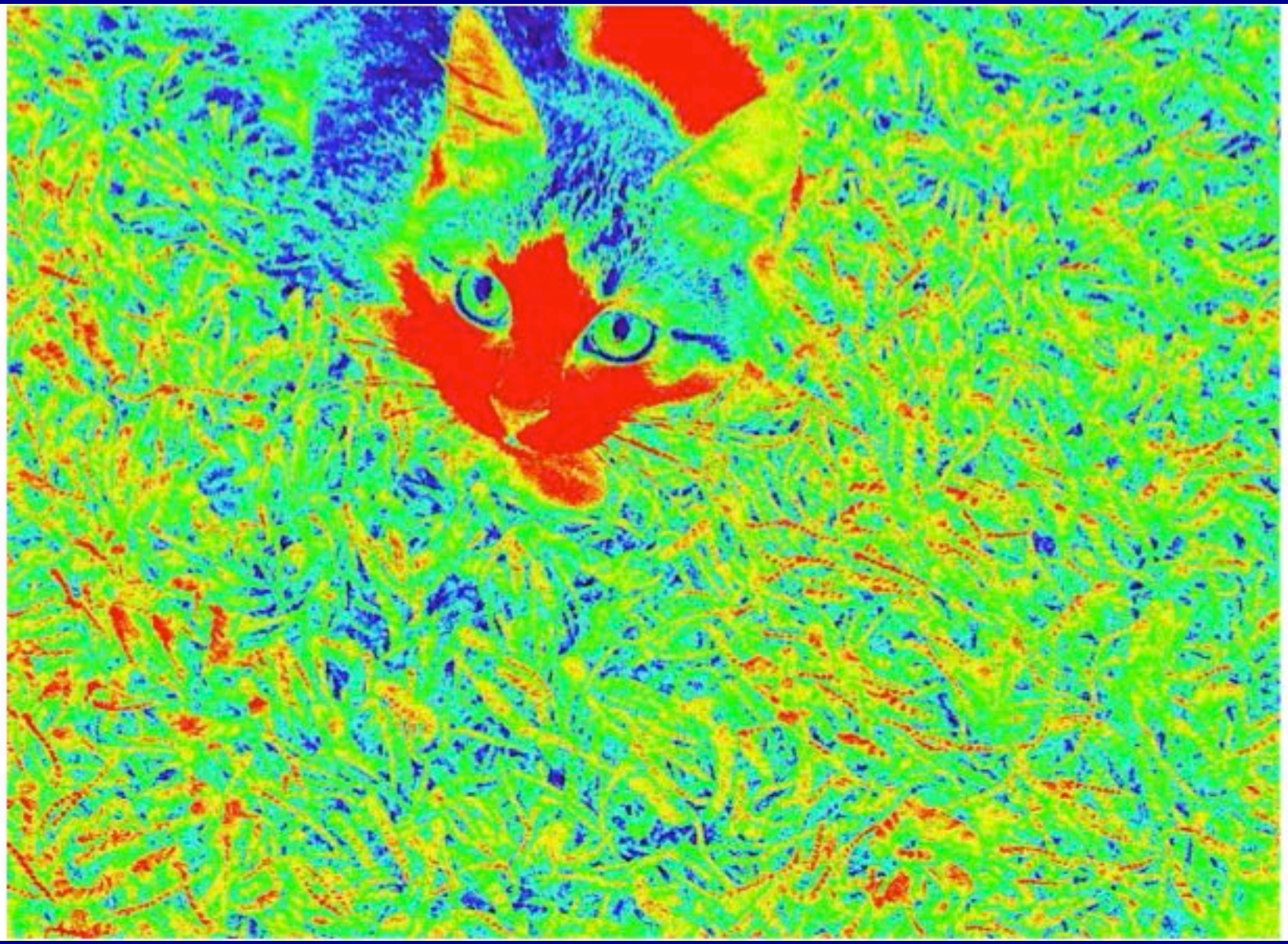
- Corticosteroids were successful. She became adrenally suppressed on systemic corticosteroids, now with minimal symptoms on oral budesonide initially 9 now 6mg daily, and also on zantac and zyrtec. Elimination diet was not successful.
- Her peripheral eosinophil count (initially over 1000, hovers around 300)

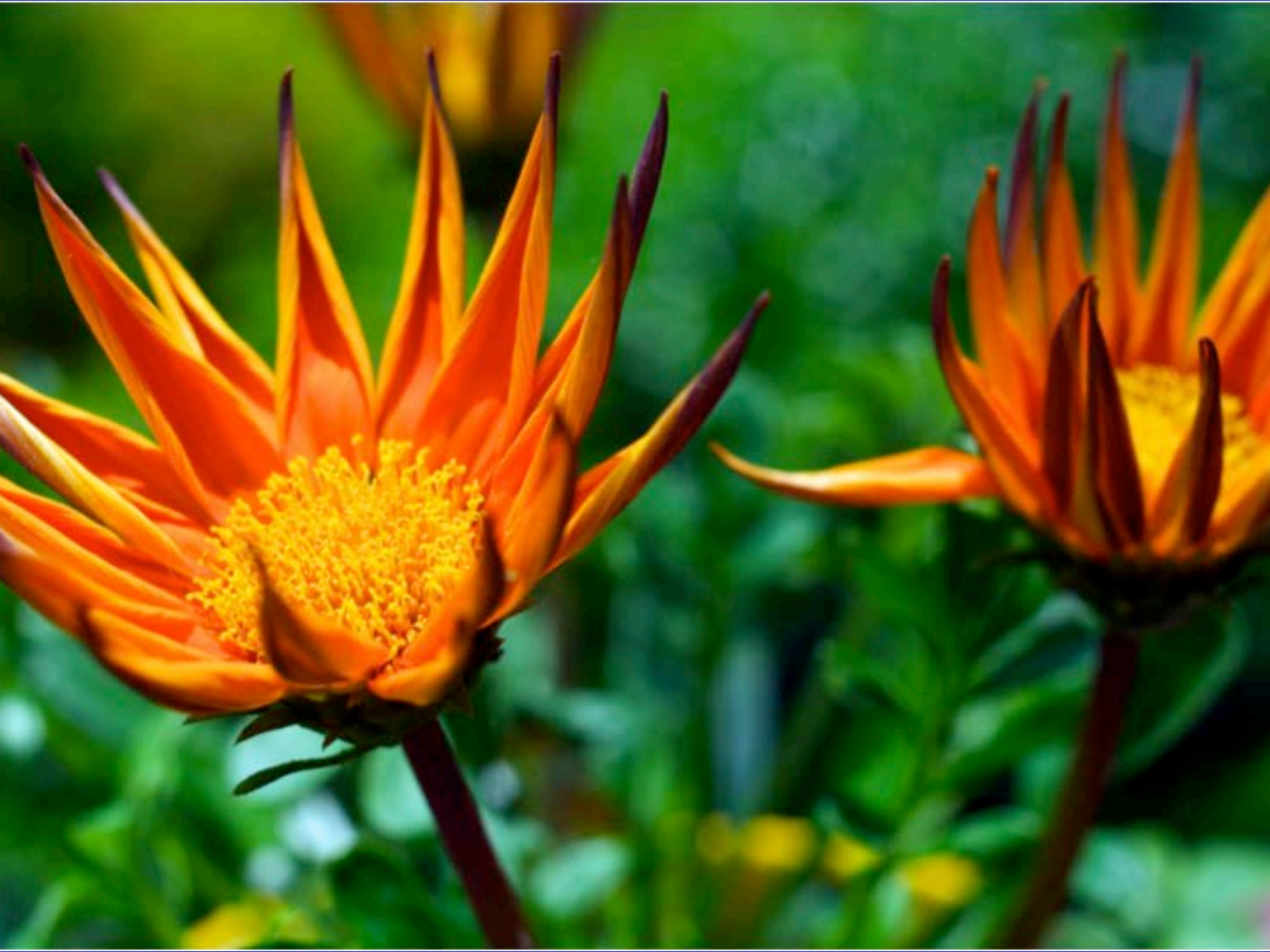
Patient 3-EC

- Ova and parasites were negative x 3
- Treated with oral budesonide with resolution of symptoms
- Eventually stopped budesonide and tried elimination diet, symptoms abated with avoidance of milk and soy

Summary EGD's

- Chronic immuno-allergic condition manifest by dysmotility, functional symptoms, and tissue eosinophilia. TAKE BIOPSIES of any red spot, and any nodules.
- Most patients will have resolution of symptoms and histologic improvement with elimination diet, systemic or topical corticosteroids
- Further understanding of the underlying pathophysiology of the activated or trafficing eosinophil will lead to better selection of medicaitons for the eosinophilic GI disorder subtypes
- PPI responsive EOE in 20-40%; need trial of BID PPI to distinguish these individuals from those with allergic EOE
- Most successful outcomes with multidisciplinary are involving dietician, allergist, immunologist, and gastroenterologist





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