The Flat Duodenal Biopsy
It's Not Sprue So Now What?

Rhonda K. Yantiss, M.D.
Professor of Pathology and Laboratory Medicine
Department of Pathology and Laboratory Medicine
Weill Cornell Medicine, New York, New York, USA

Who Gets a Duodenal Biopsy?

- Diarrhea
  - With or without malabsorption
- Abdominal pain or bloating
- Family history of celiac disease and/or positive serologies (TTG or similar)
- Immunodeficiency
  - HIV, bone marrow/solid organ transplant, others
- Inflammatory bowel disease
- Iron deficiency anemia
- GI hemorrhage

Support for duodenal biopsy in these settings

- Anyone getting upper endoscopy
  - Reflux, gastritis, pain, dyspepsia, Barrett esophagus

Low-yield without great data

Why Would You Biopsy A Normal Duodenum When There is No Clinical Concern to Justify It?

- Nobody wants to miss celiac disease
  - Might make sense in a population with high prevalence of celiac disease
  - Waste of resources in populations at low-risk for celiac disease
- Many duodenal biopsy samples obtained in the United States fall into this category

Nelsen, *et al*. *Dig Dis Sci* 2017; 62: 418-423.

Expensive Hunt for the Needle in a Haystack

- 391 esophagogastroduodenoscopies for indications of abdominal pain
  - 263 non-targeted duodenal biopsy samples (58% of all patients)
    - 4 (1.5%) cases of celiac disease
      - One from endoscopically abnormal mucosa
      - Three from normal-appearing mucosa
    - Charges for case of celiac disease diagnosed: $41,344

Nelsen, *et al*. *Dig Dis Sci* 2017; 62: 418-423.

What is the Predictive Value of Lymphocytosis when the Likelihood of Celiac Disease is Low?

- 6337 non-targeted duodenal biopsies (2018-2019)
  - 212 (3%) cases with intraepithelial lymphocytosis
    - Excluded cases
      - Family or personal history of celiac disease
      - Positive serologic studies
      - Symptoms suggestive of celiac disease (diarrhea, weight loss, iron deficiency anemia)
    - 115 remaining cases unaccompanied by a clinical question celiac disease
      - Pain, dyspepsia, GERD, IBD, Barrett surveillance
      - Only one patient had occult celiac disease

What is the Value of a Duodenal Biopsy When Clinical Suspicion for Celiac Disease is Low?

- Extremely low-yield of duodenal biopsy for patients with dyspepsia and/or abdominal pain
- Extremely low likelihood that sprue-like histologic changes reflect celiac disease when supportive clinical and laboratory data are lacking
- American Gastroenterological Association recommends against biopsy of the normal-appearing duodenum when patients undergo endoscopy for dyspepsia as the sole indication (*i.e.* absence of signs or symptoms associated with an increased risk of celiac disease)

Yang, *et al. Gastroenterology* 2015; 149(4): 1082-1087

Where Do We Biopsy…and How Many Samples Do We Need?

- Most studies suggest at least 4 samples
  - 5 is probably better with 1 of the duodenal bulb
- 10% of patients with celiac disease have involvement of bulb only
- 10% of patients with celiac disease have normal duodenal bulb biopsies and diagnostic changes more distally
- Probably best to biopsy bulb and more distal duodenum, and submit samples in different containers

Robert, *et al*. *Am J Surg Pathol* 2018; 42(9): e44-e58.

The Abnormal Duodenal Biopsy in the Context of Clinically Suspected Celiac Disease

Celiac Disease

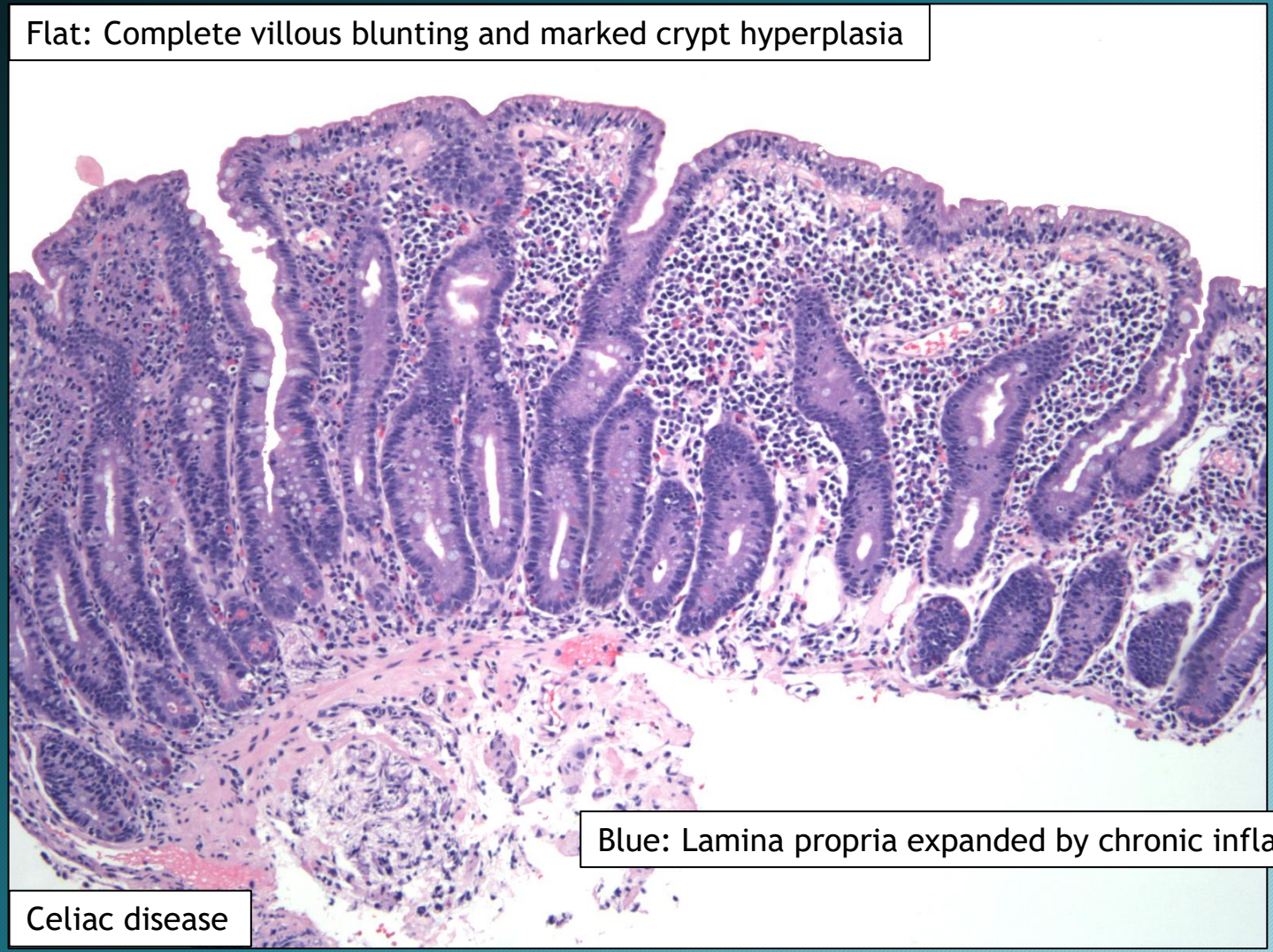
- Genetic factors
  - Familial clustering
  - 70% concordance between identical twins
  - HLA associations (DQ2, DQ8) in almost all patients
    - Corollary: celiac disease unlikely in patients without one of these HLA types
- Environmental factors
  - Dietary gluten
  - Probably triggered by viral exposure (adenovirus type 12)
  - Emerging evidence for reovirus as a stimulus

Serologic Markers of Celiac Disease

Marker	Sensitivity	Specificity
Anti-gliadin	31-100%	85-100%
Anti-reticulin	42-100%	95-100%
Anti-endomysium	60-100%	95-100%
Anti-tissue transglutaminase	85-100%	92-97%

- Serologic tests need to be done in patients who are not on gluten restriction
- Sensitivities for all markers decrease among patients with mild/no symptoms (can be normal in patients with Marsh 1 lesions)
- None are entirely specific for celiac disease; can be spuriously elevated in other immune-mediated disorders

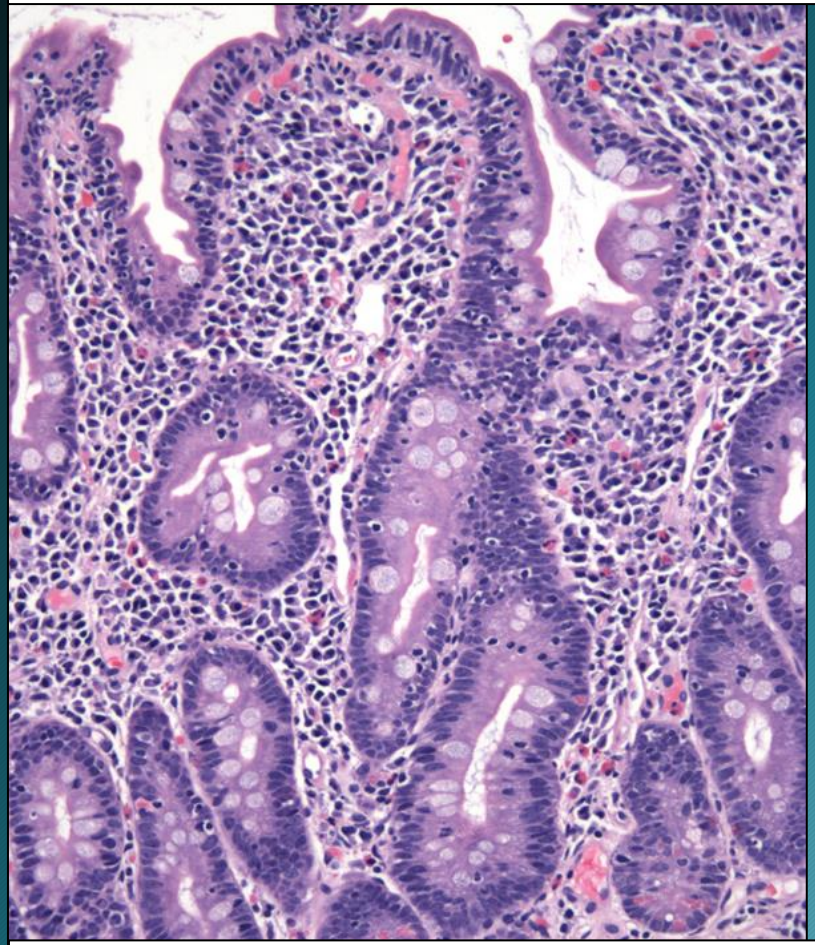
Flat: Complete villous blunting and marked crypt hyperplasia

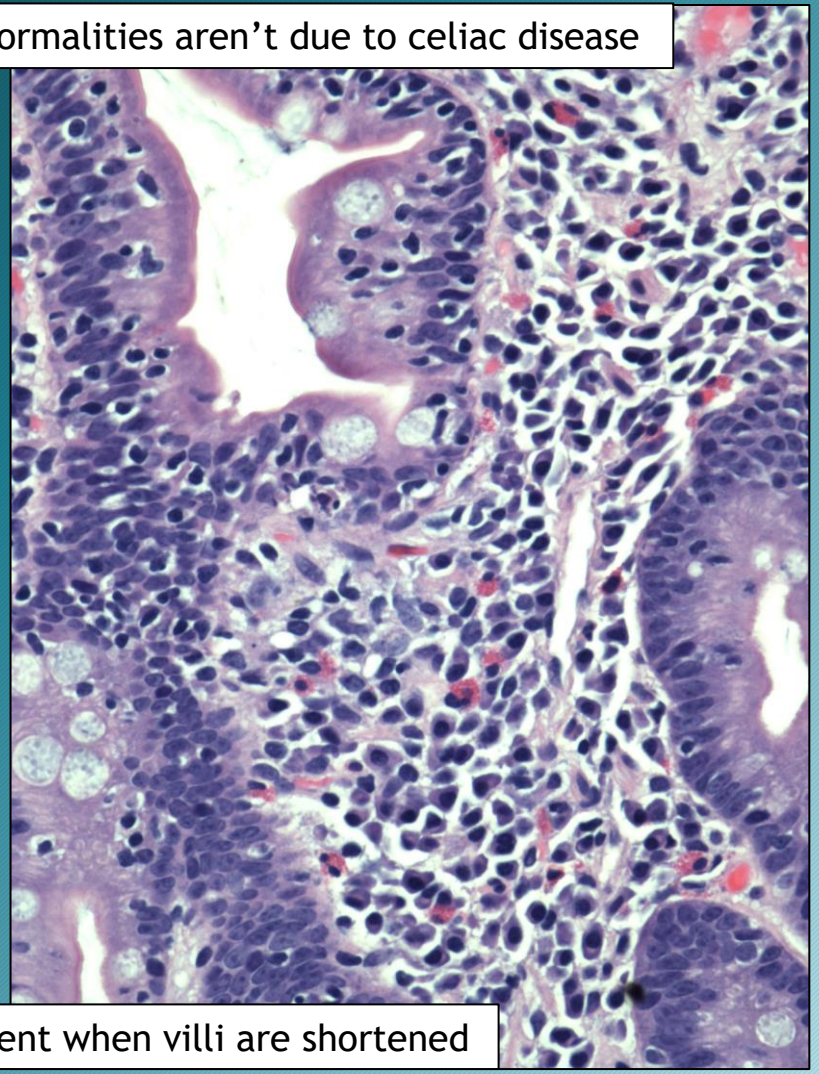


Blue: Lamina propria expanded by chronic inflammation

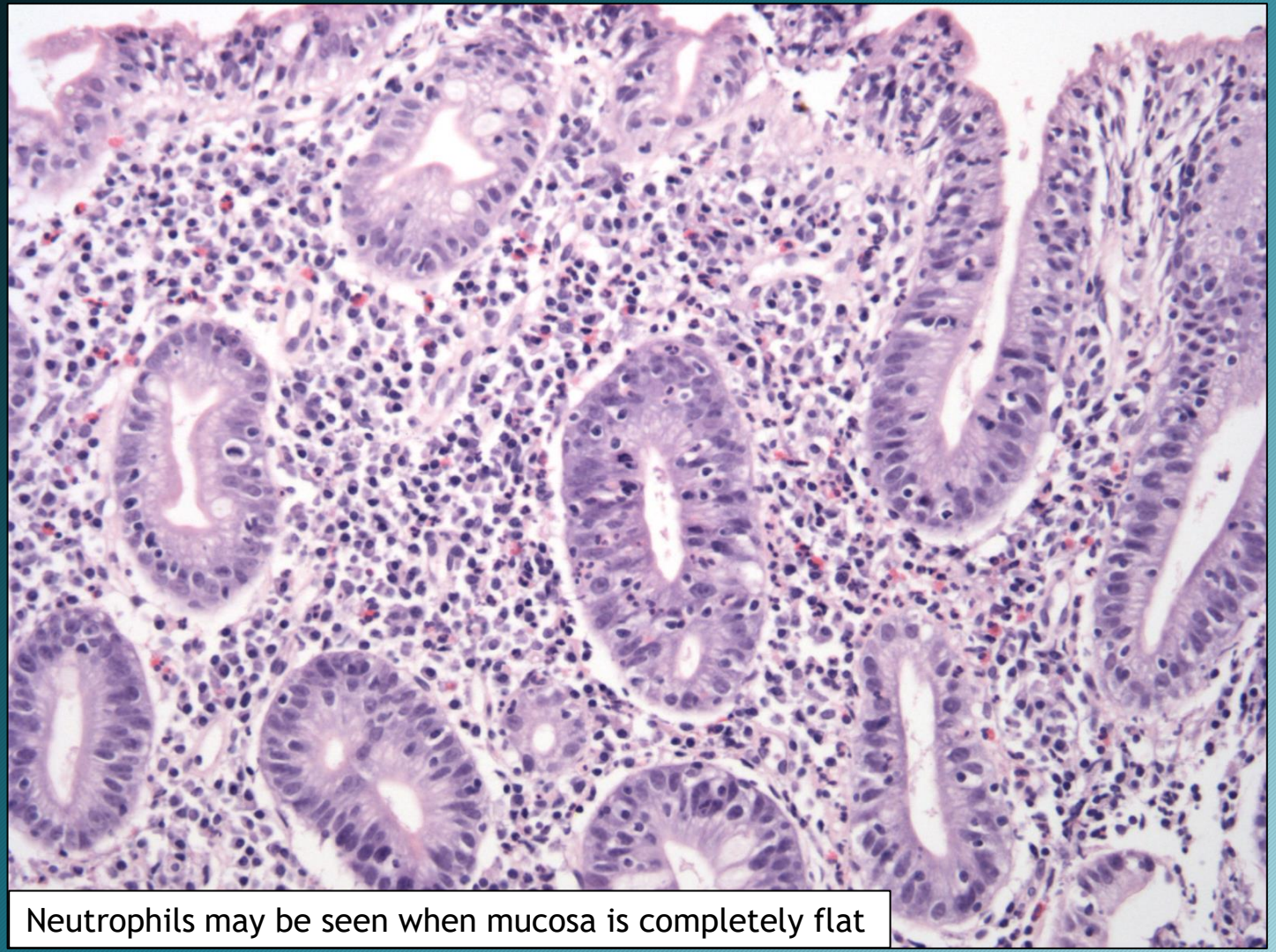
Celiac disease

Tip: If there aren't lots of IELs, then villous abnormalities aren't due to celiac disease





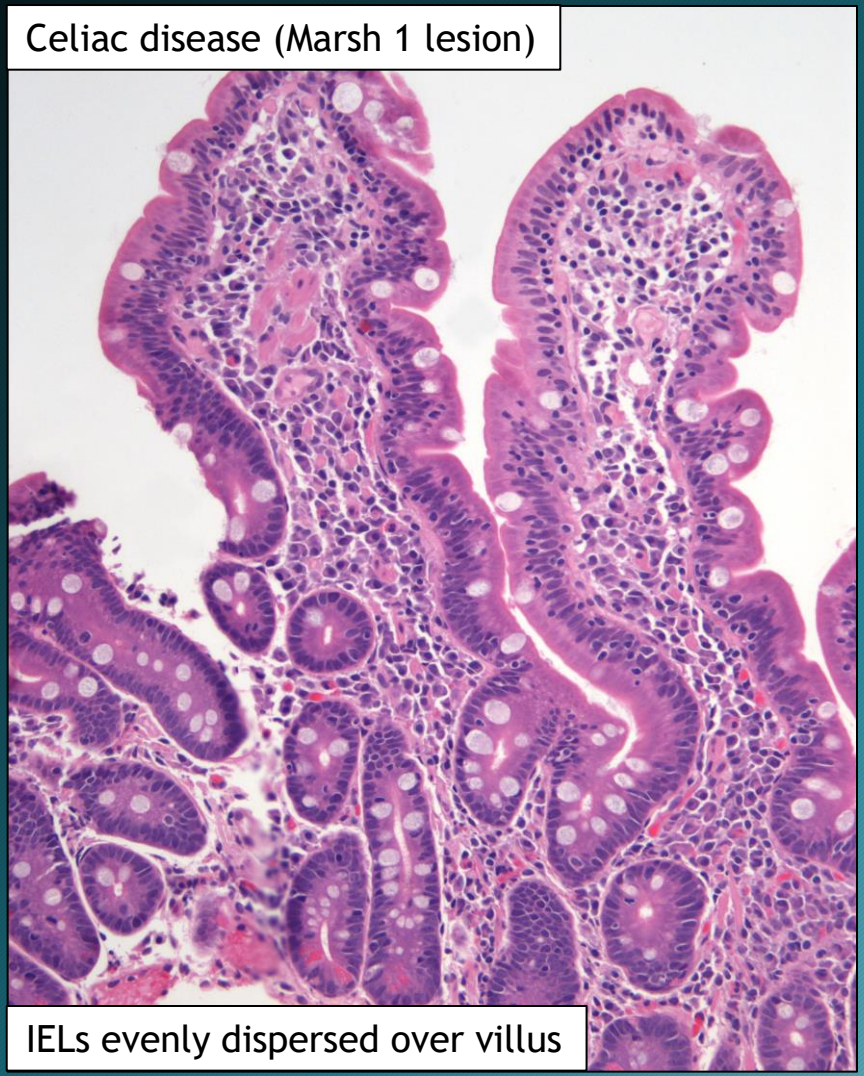
Intraepithelial lymphocytes are universally present when villi are shortened

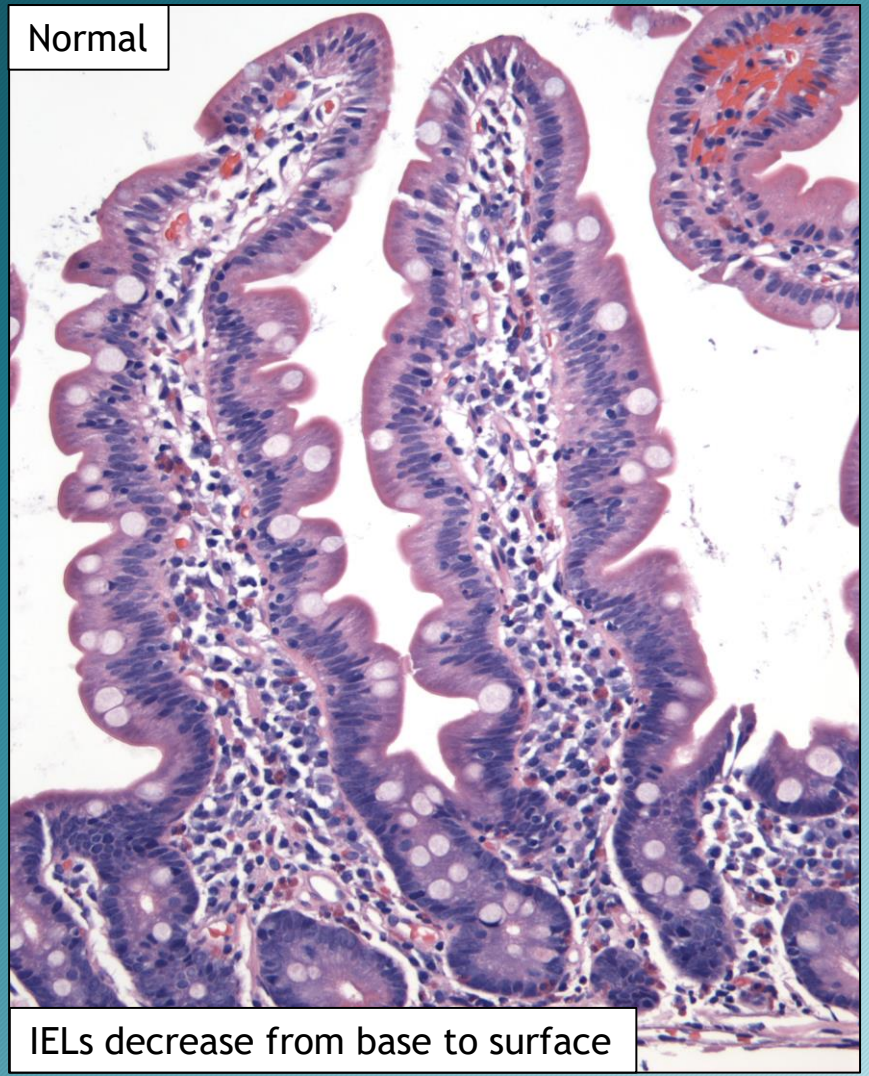


Neutrophils may be seen when mucosa is completely flat

Celiac Disease
Summary of Features

- Intraepithelial lymphocytosis always present
- Variable villous abnormalities, crypt hyperplasia
- Lymphocytes and plasma cells predominate in lamina propria
  - Eosinophils and neutrophils present in small numbers
- Neutrophilic/eosinophilic cryptitis is not prominent
- May be associated with generalized gastrointestinal lymphocytosis


Celiac disease (Marsh 1 lesion)
IELs evenly dispersed over villus


Normal
IELs decrease from base to surface

The Significance of Intraepithelial Lymphocytosis Affecting Normal Villi

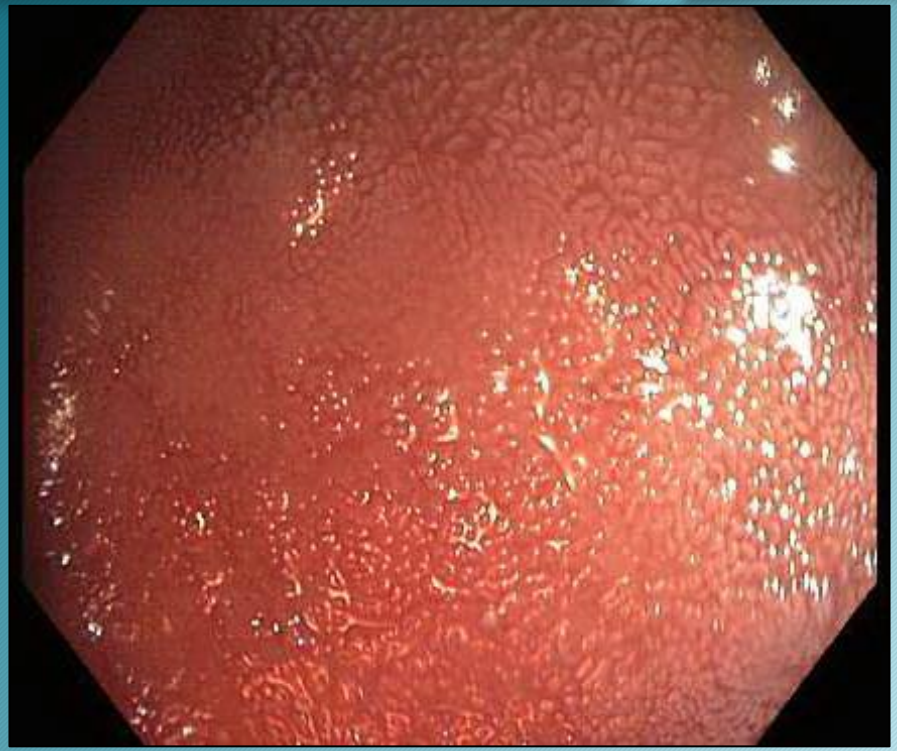
- 1-3% of duodenal biopsy samples will show increased intraepithelial lymphocytosis with normal villous architecture
- Up to 30% of these prove to be related to gluten depending on the population studied
  - Once patients with high pre-test probability of celiac disease are excluded, the number is probably less than 5%

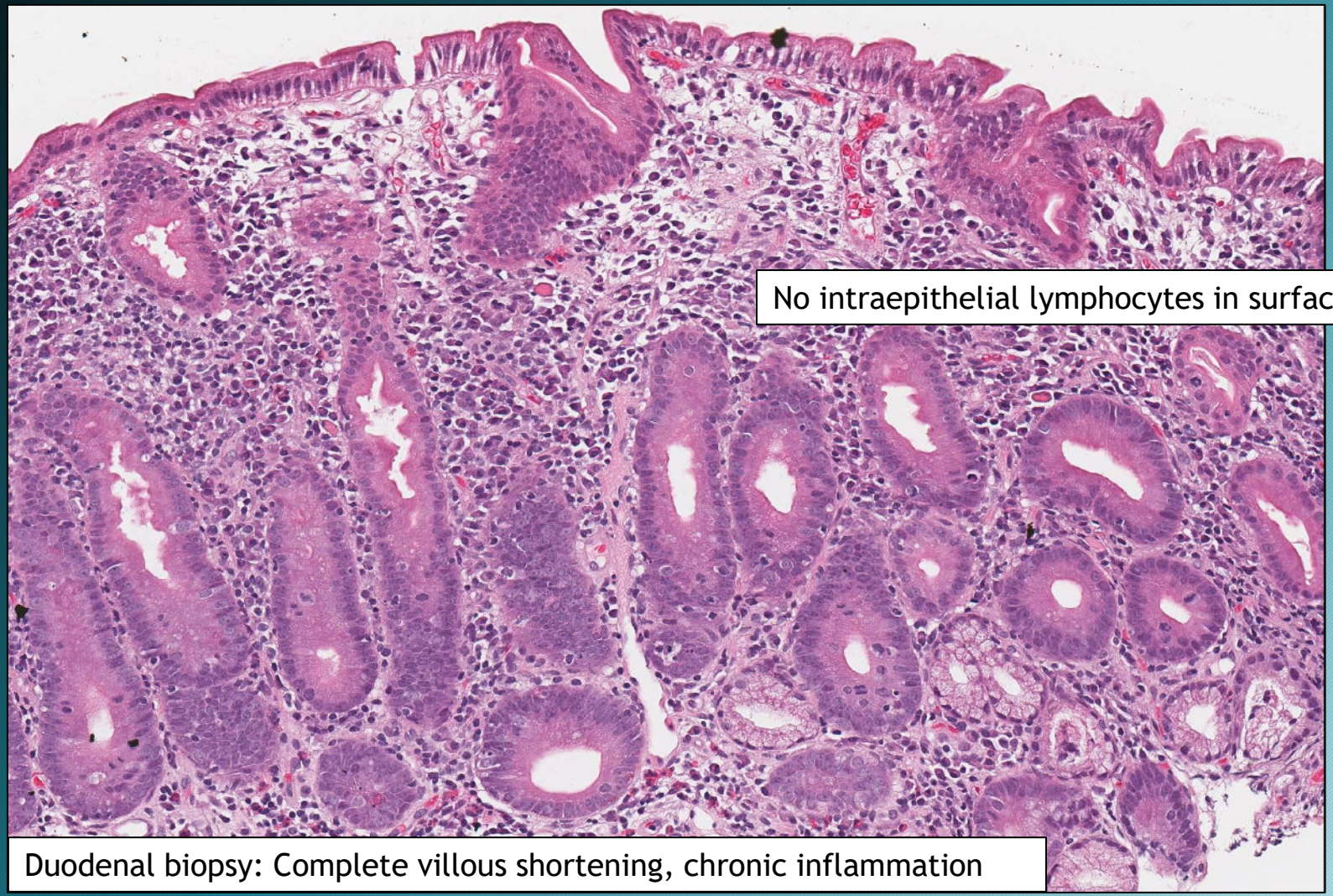
The Differential Diagnosis for the Malabsorptive Pattern in Duodenal Biopsies

- Peptic duodenitis — Peptic Injury
- Celiac disease
- Protein intolerance (non-gluten)
- Food allergies (cereals, eggs, milk, etc)
- Autoimmune enteropathy — Altered Immunity
- Common variable immunodeficiency
- Inflammatory bowel disease
- Eosinophilic gastroenteritis
- Targeted biologic agents (often immunomodulators for cancer) — Medications
- Olmesartan (and related agents)
- Bacterial overgrowth
- Tropical sprue — Infection
- Infection (viruses, coccidians, protozoa)

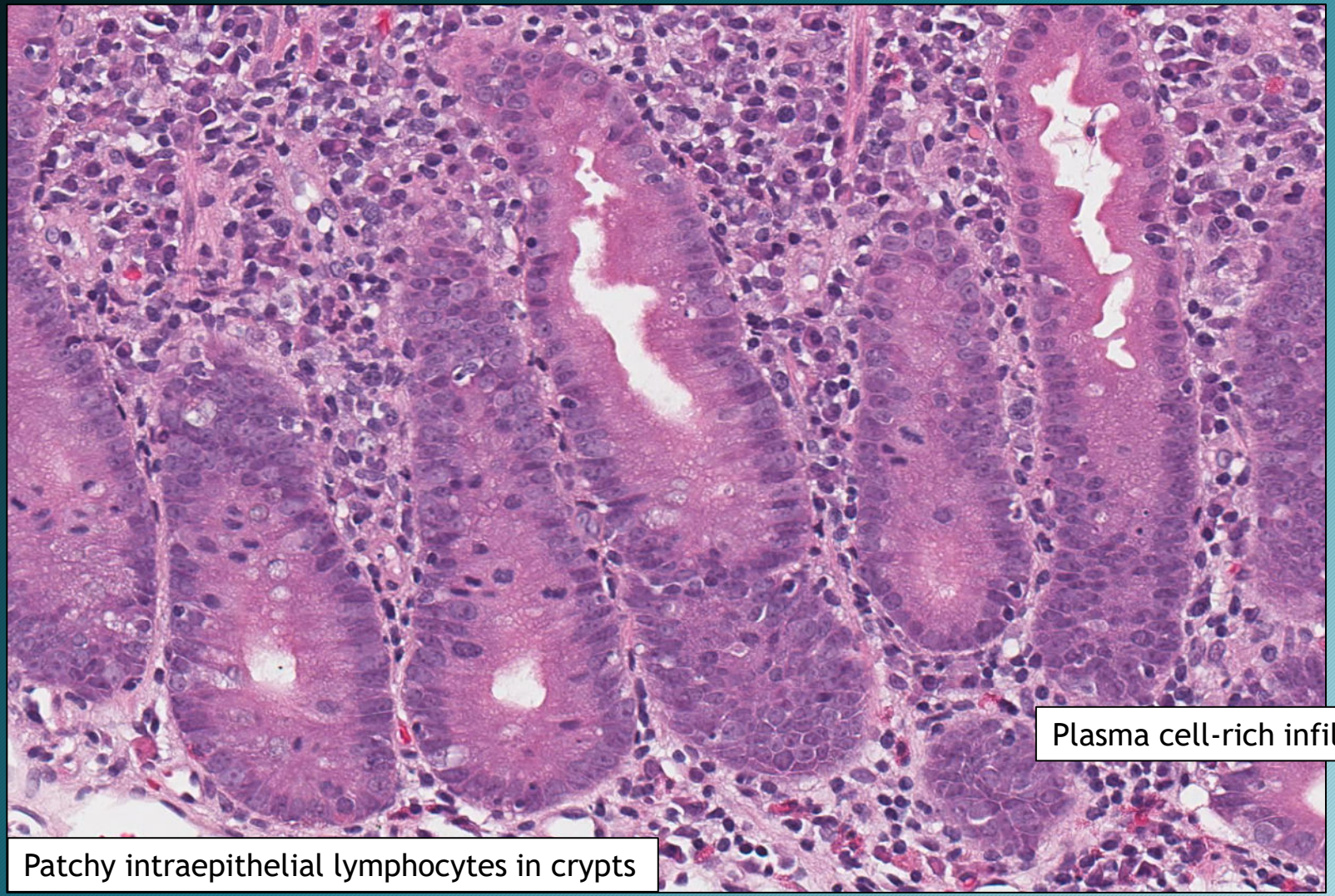
Case 1

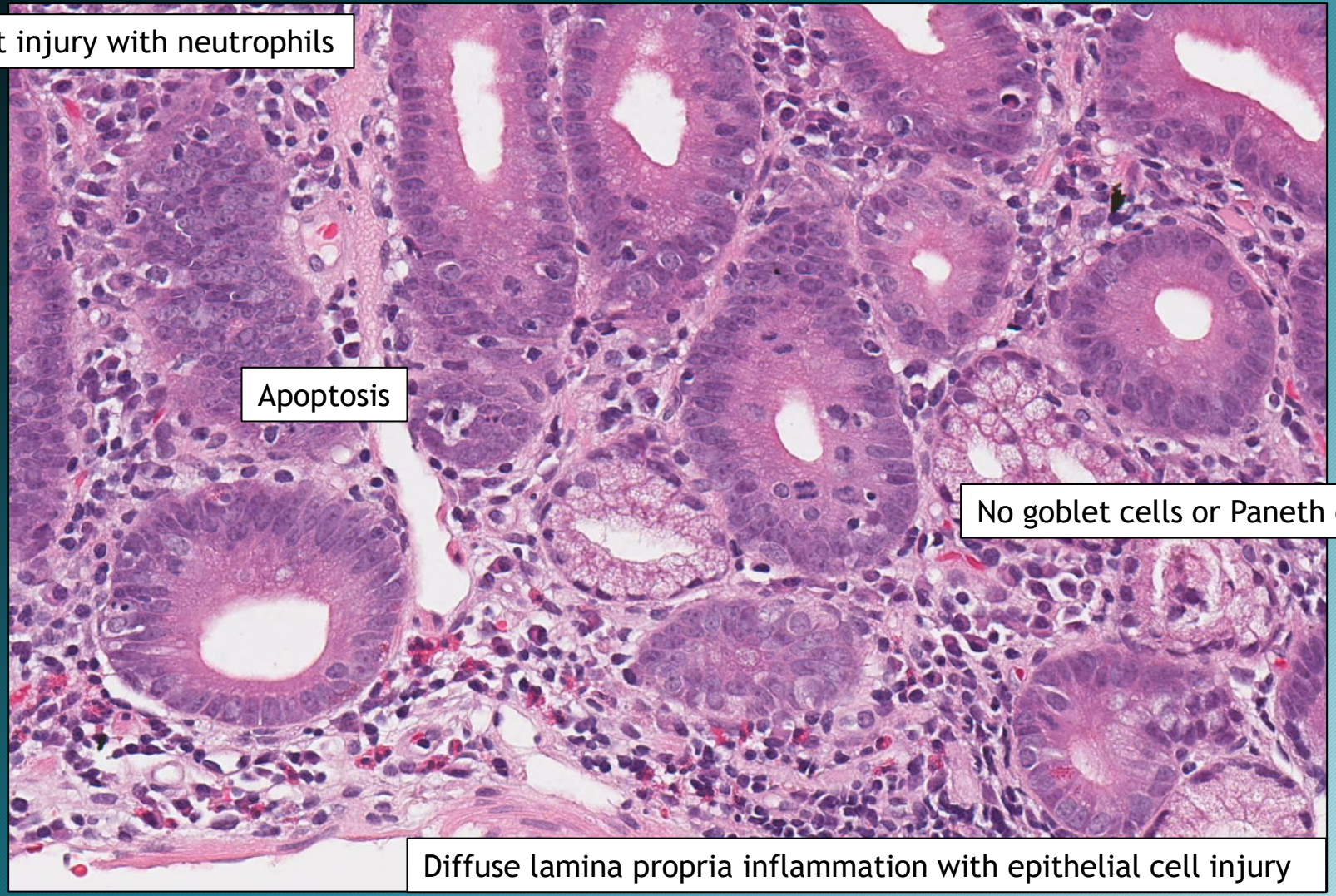
- 3-year-old male with severe diarrhea and failure to thrive admitted to hospital
- Laboratory studies
  - Polyclonal hypergammaglobulinemia
  - Elevated celiac markers; negative HLA-DQ2 and HLA-DQ8
- Endoscopy
  - Loss of mucosal folds





Duodenal biopsy: Complete villous shortening, chronic inflammation


Plasma cell-rich infiltrates
Patchy intraepithelial lymphocytes in crypts


Crypt injury with neutrophils
Apoptosis
No goblet cells or Paneth cells
Diffuse lamina propria inflammation with epithelial cell injury

Case 1-Red Flags for Celiac Disease

- 3-year-old male with severe diarrhea and failure to thrive admitted to hospital
- Laboratory studies
  - Polyclonal hypergammaglobulinemia
  - Elevated celiac markers; negative HLA-DQ2 and HLA-DQ8
- Endoscopy
  - Loss of mucosal folds

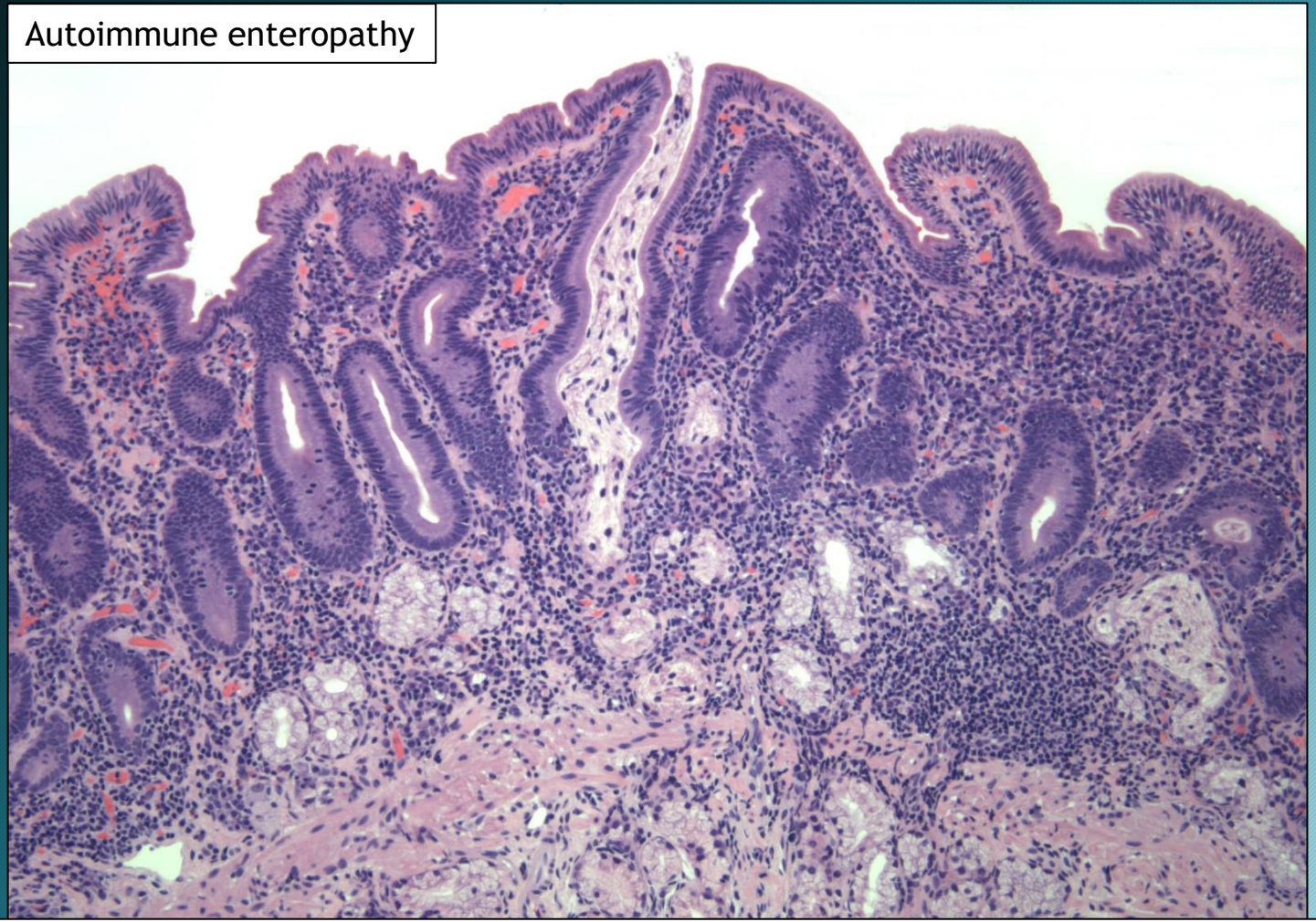
Really unusual for celiac disease to cause symptoms severe enough to warrant hospitalization

HLA data do not support a diagnosis of celiac disease, regardless of serologic data

Autoimmune Enteropathy

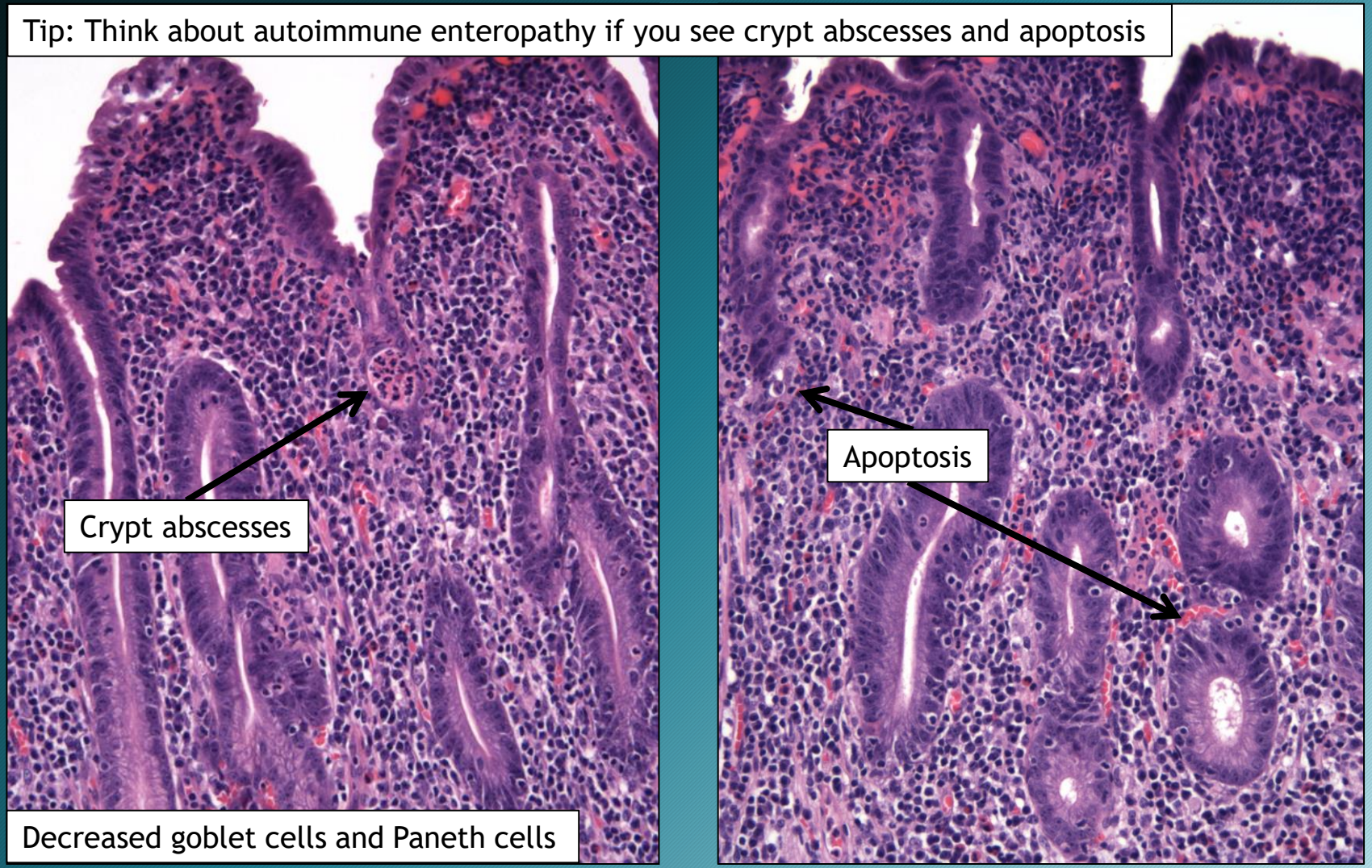
- Severe protracted diarrhea that may result in hospitalization (very unusual for celiac disease)
  - No response to gluten withdrawal
- Extra-intestinal immune-mediated diseases
- Reported associations with thymoma
- Autoantibodies to enterocytes, goblet cells, and others (*e.g.* ANA)
- More common in young children, especially males
- Sporadic
- Immunodysregulation, polyendocrinopathy and enteropathy, X-linked (IPEX) syndrome
- APECED syndrome (mucocutaneous candidiasis, ectodermal dystrophy)

Autoimmune enteropathy

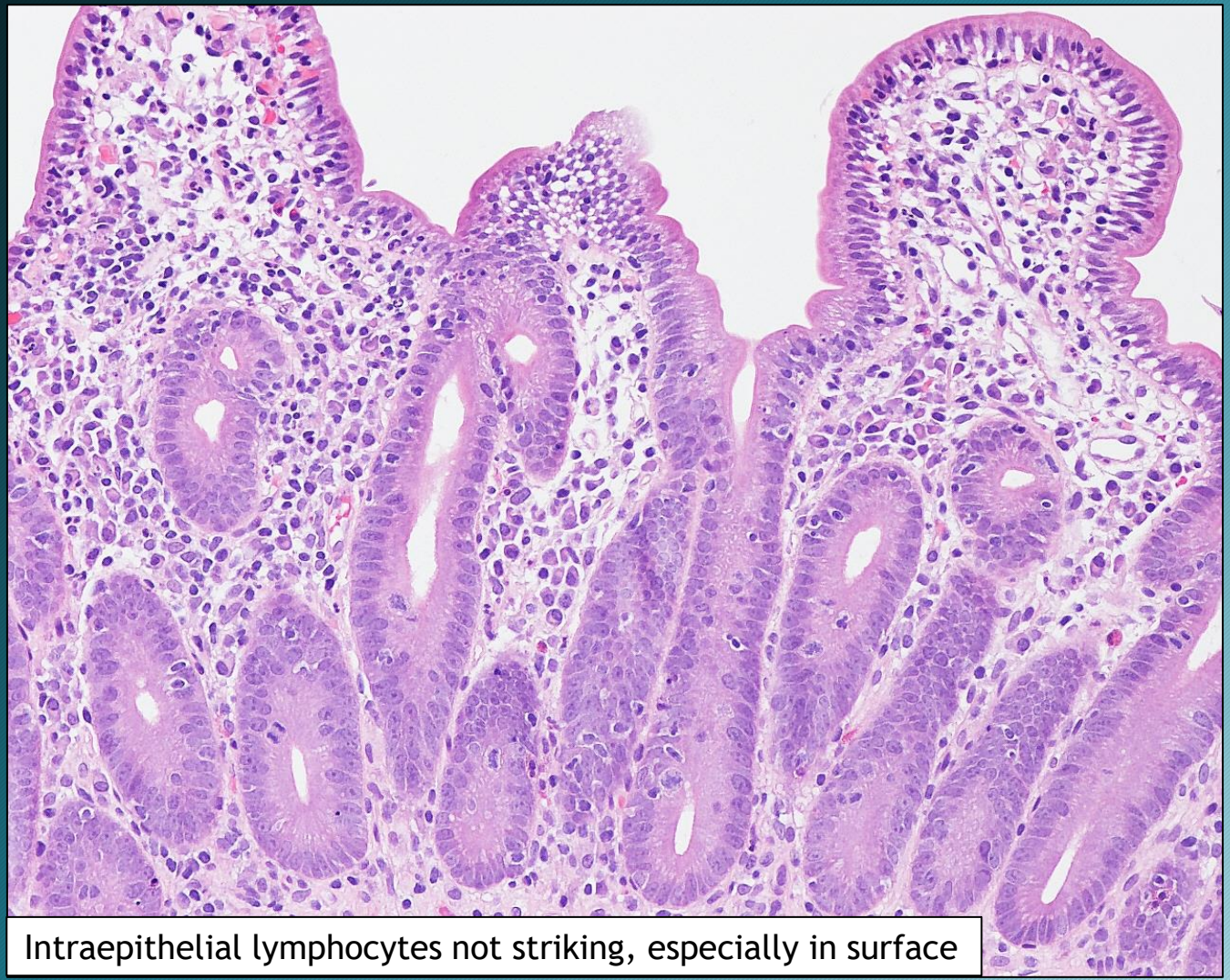


Diffuse, full-thickness plasma cell-rich inflammation with complete villous shortening

Tip: Think about autoimmune enteropathy if you see crypt abscesses and apoptosis



Decreased goblet cells and Paneth cells



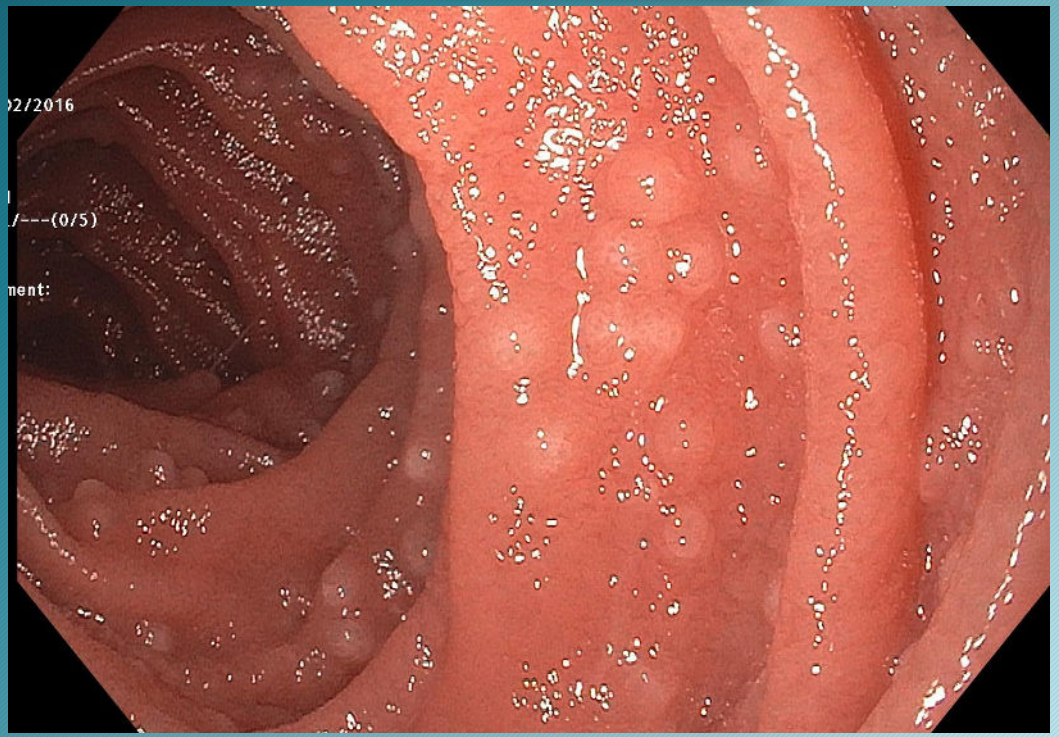
Intraepithelial lymphocytes not striking, especially in surface

Histologic Features

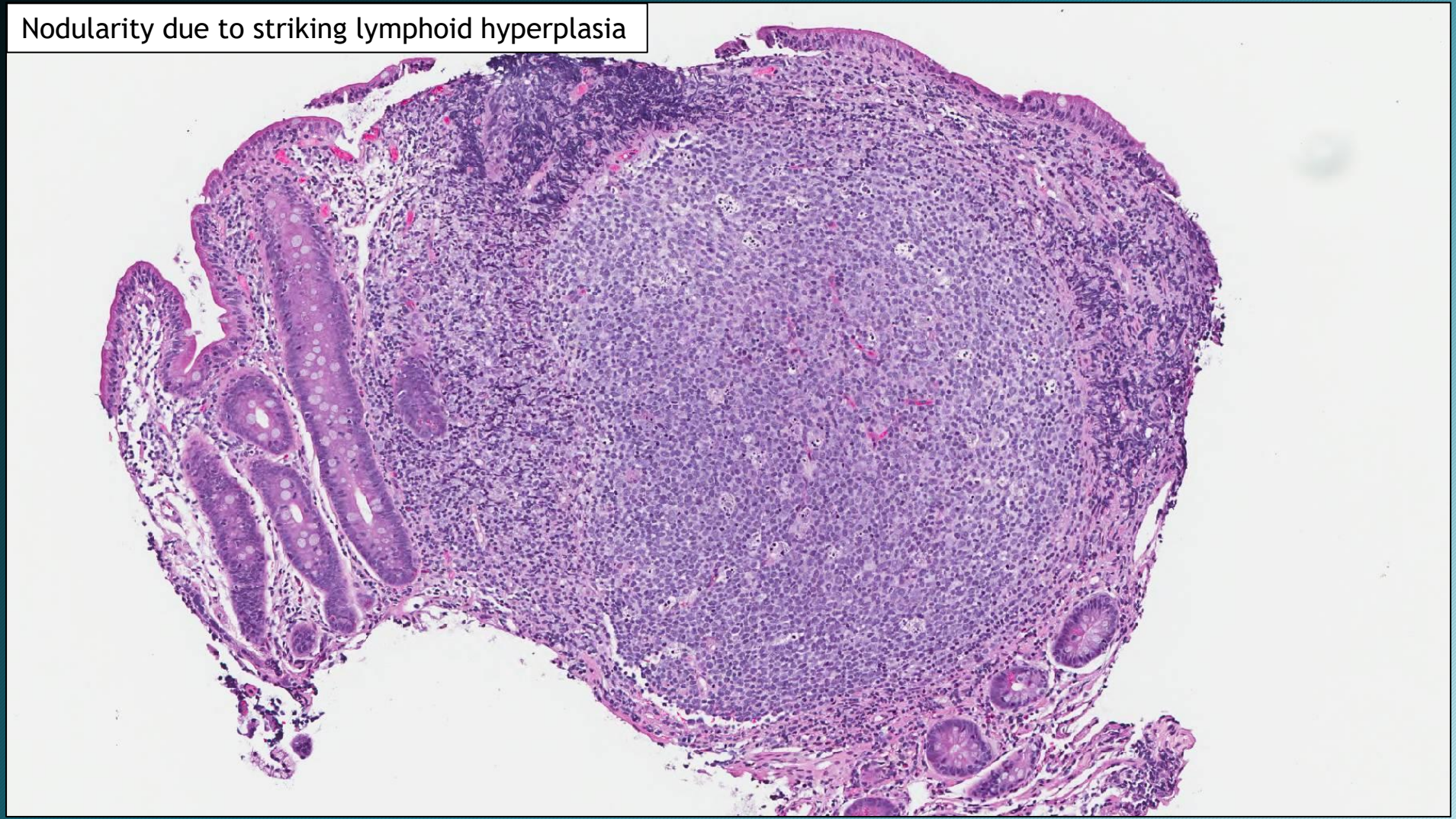
- Celiac disease
  - Surface more than crypt injury
  - IELs uniformly present in surface and crypts
  - Granulocytes are infrequent
    - Crypt abscesses rare
  - Apoptosis uncommon
  - Duodenum and proximal jejunum most severely affected
- Autoimmune enteropathy
  - Severe crypt injury with relative sparing of surface
  - IELs more prominent at crypt bases
  - Neutrophils readily identified
    - Crypt abscesses frequent
  - Apoptotic crypt cells common
  - Stomach and colon often affected

Case 2

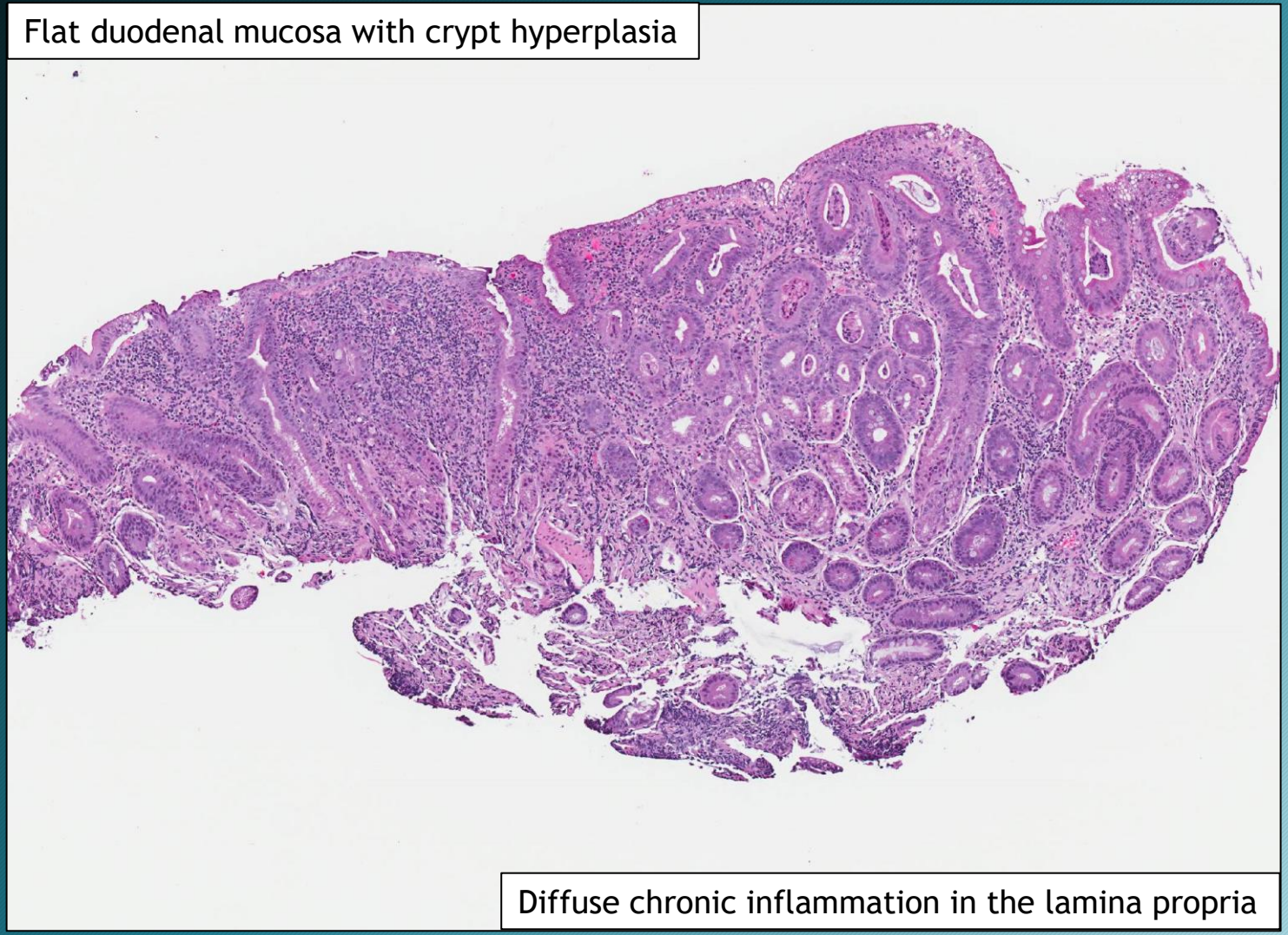
- 34-year-old female with malabsorptive diarrhea
- Negative celiac serologies



Nodularity due to striking lymphoid hyperplasia

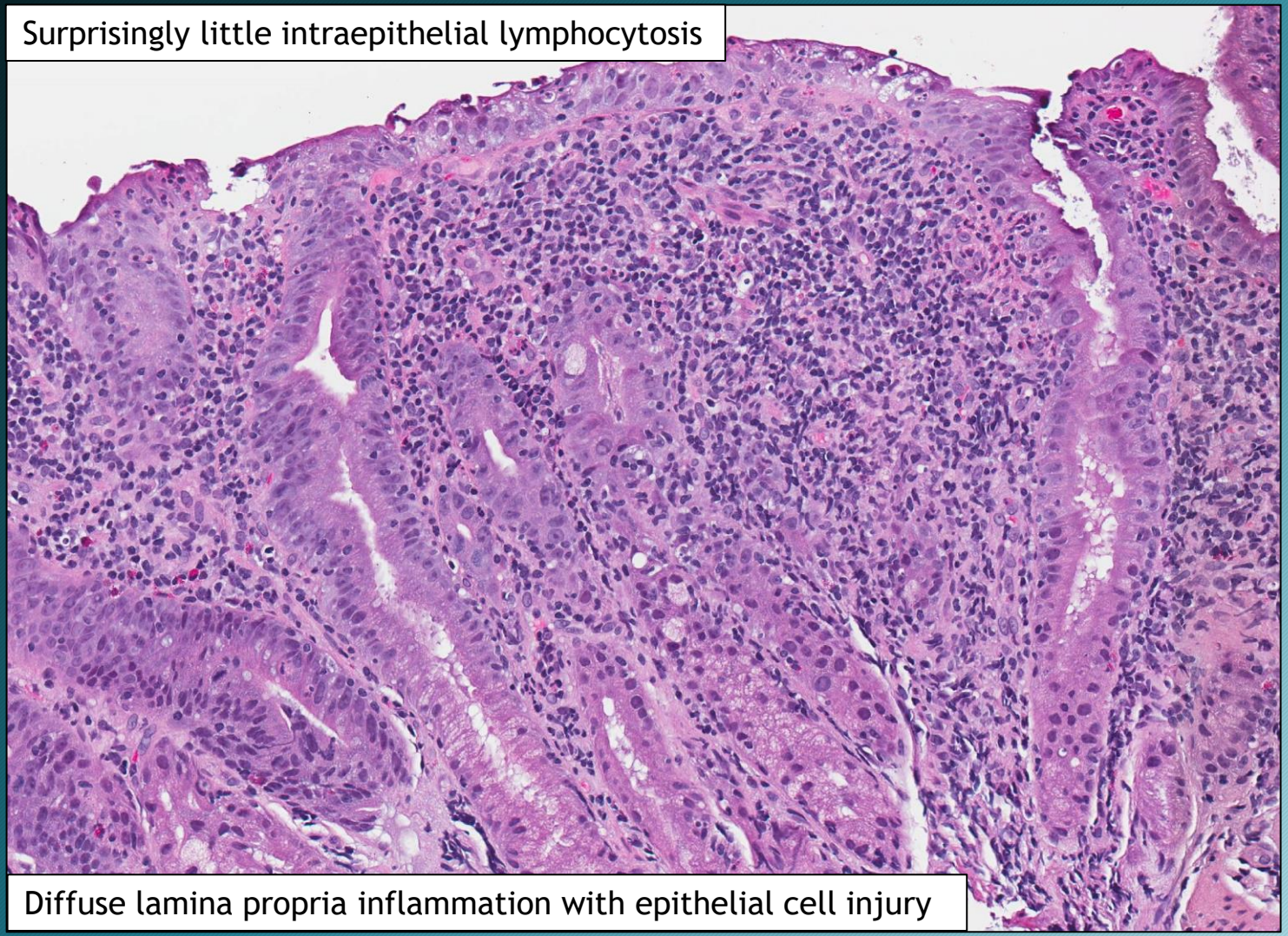


Flat duodenal mucosa with crypt hyperplasia

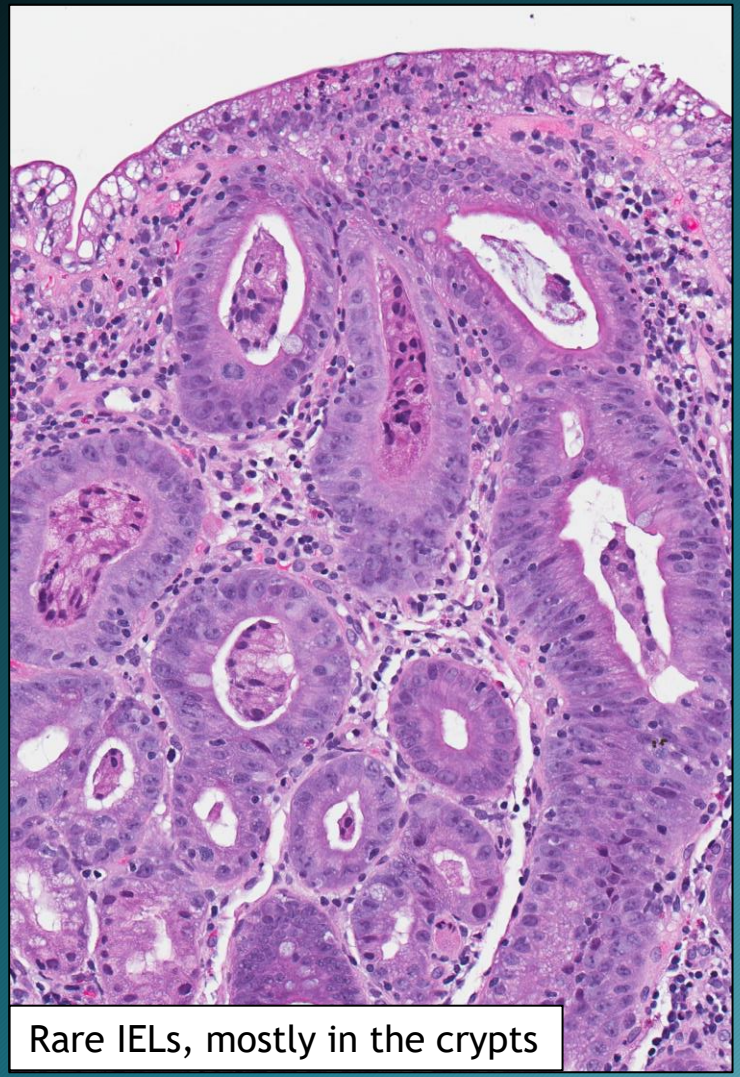


Diffuse chronic inflammation in the lamina propria

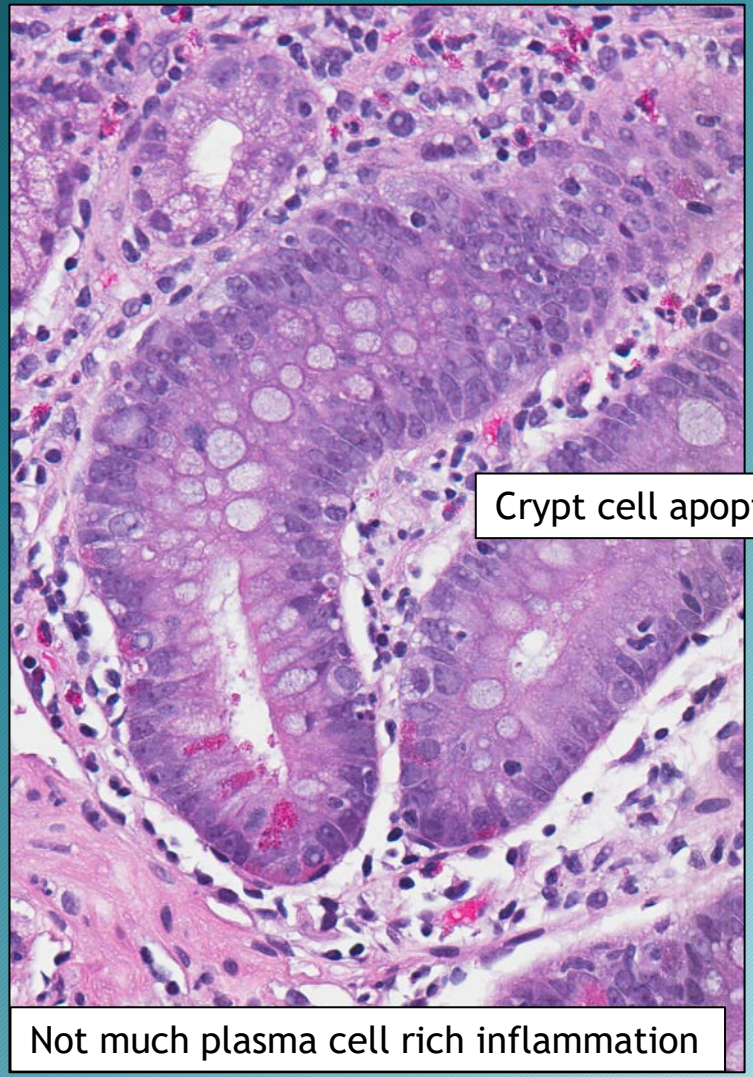
Surprisingly little intraepithelial lymphocytosis



Diffuse lamina propria inflammation with epithelial cell injury



Rare IELs, mostly in the crypts



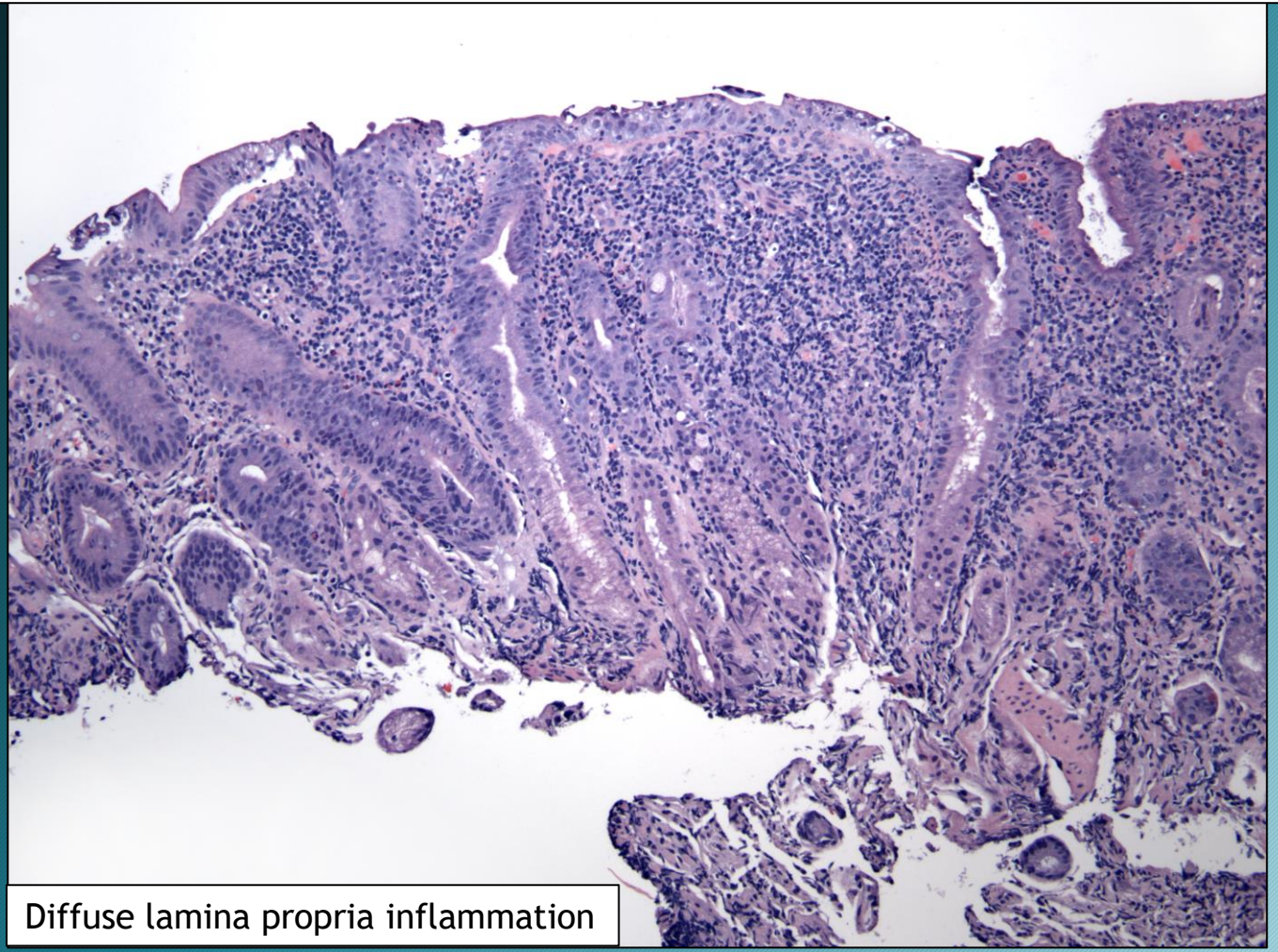
Crypt cell apoptosis

Not much plasma cell rich inflammation

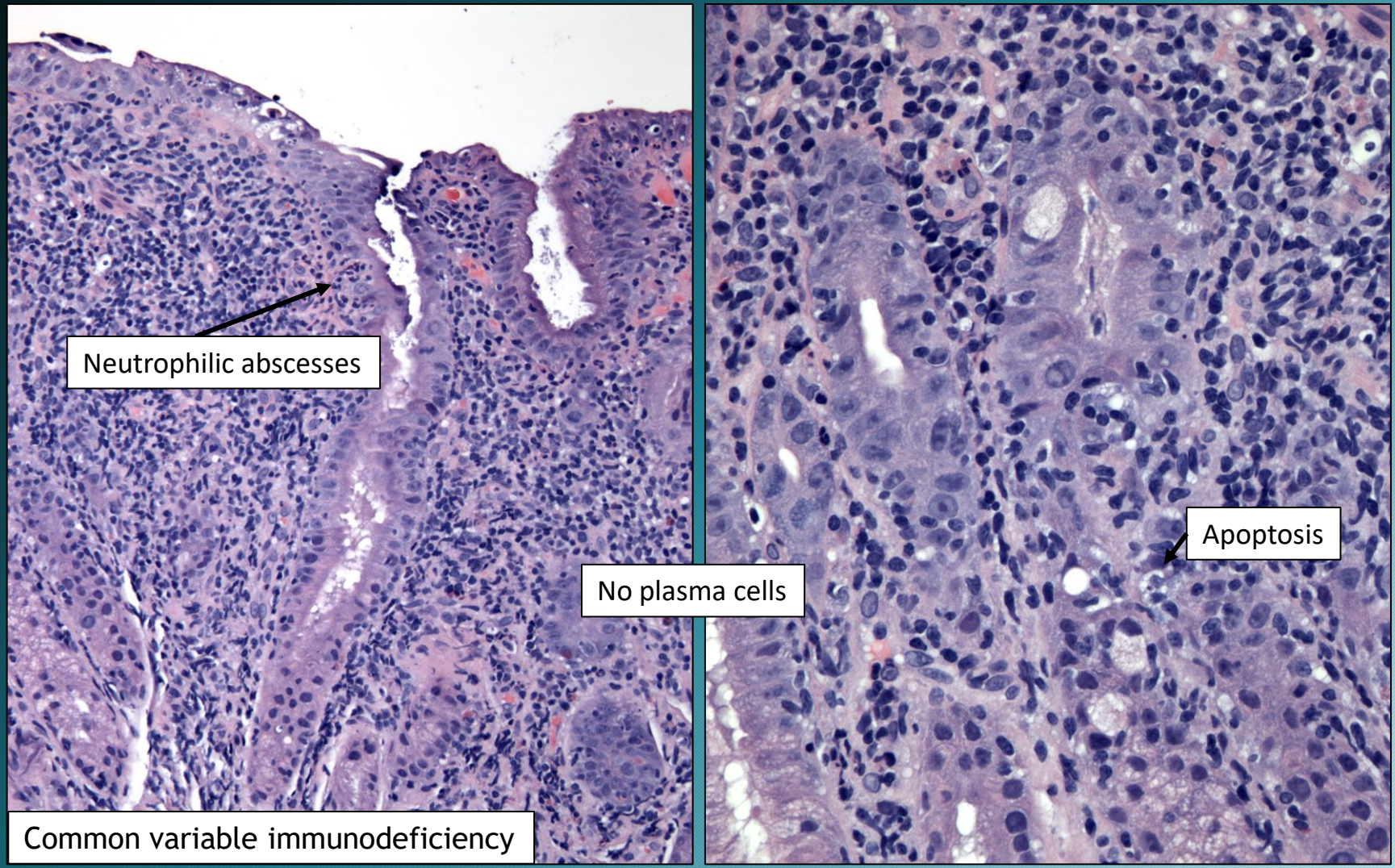
Common Variable Immunodeficiency

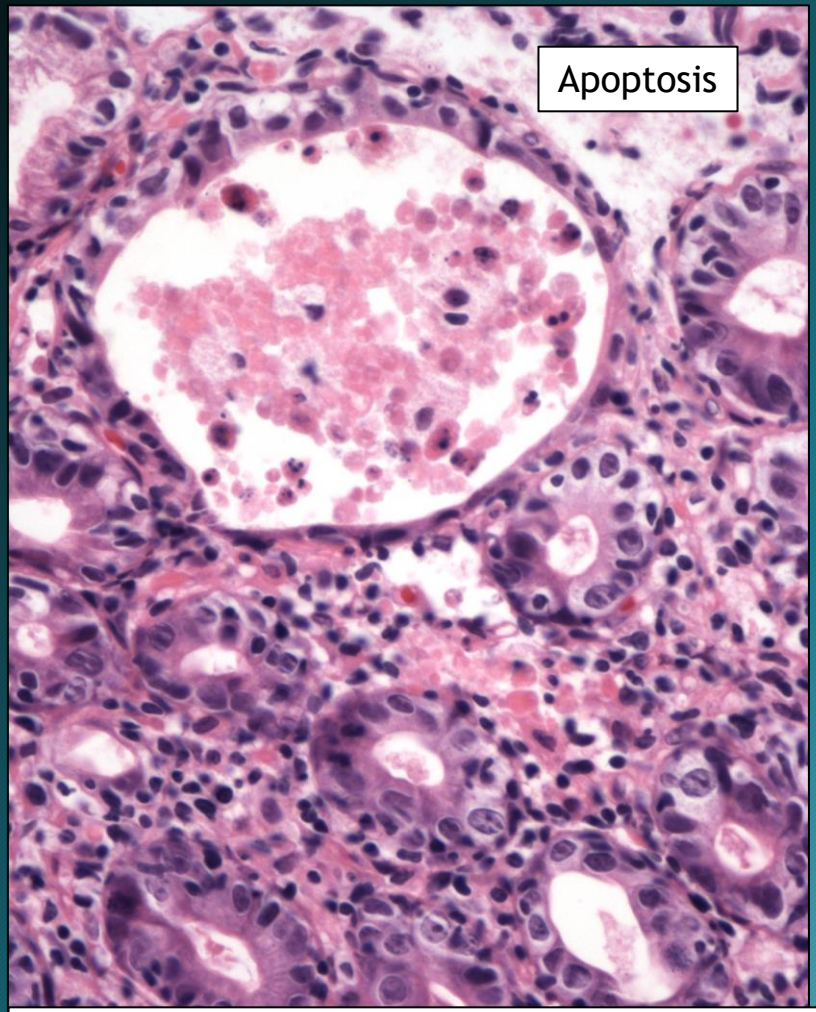
- Immunodeficiency resulting from failed plasma cell maturation
  - Absent, or decreased plasma cells
  - Plasma cells present, but non-functional
- Symptoms of malabsorption
- Chronic giardiasis and CMV
- Strongyloidiasis?

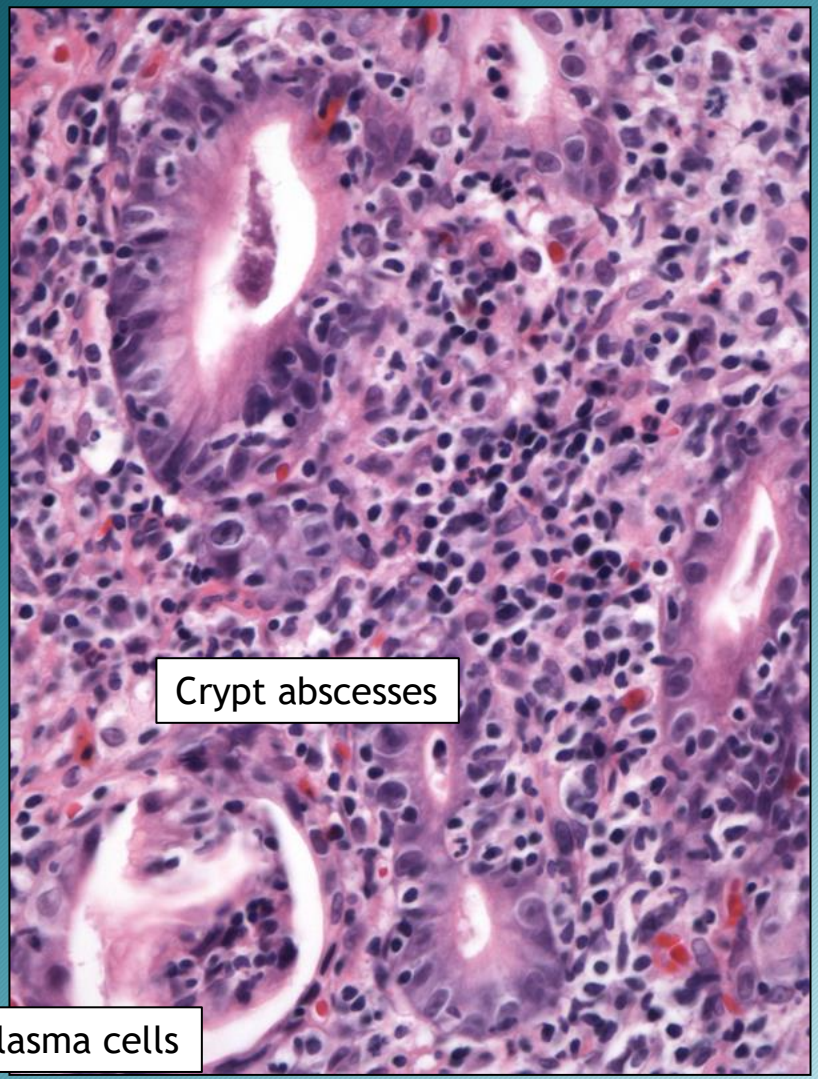
Common variable immunodeficiency: Complete villous shortening, crypt hyperplasia



Diffuse lamina propria inflammation


Neutrophilic abscesses
No plasma cells
Apoptosis
Common variable immunodeficiency





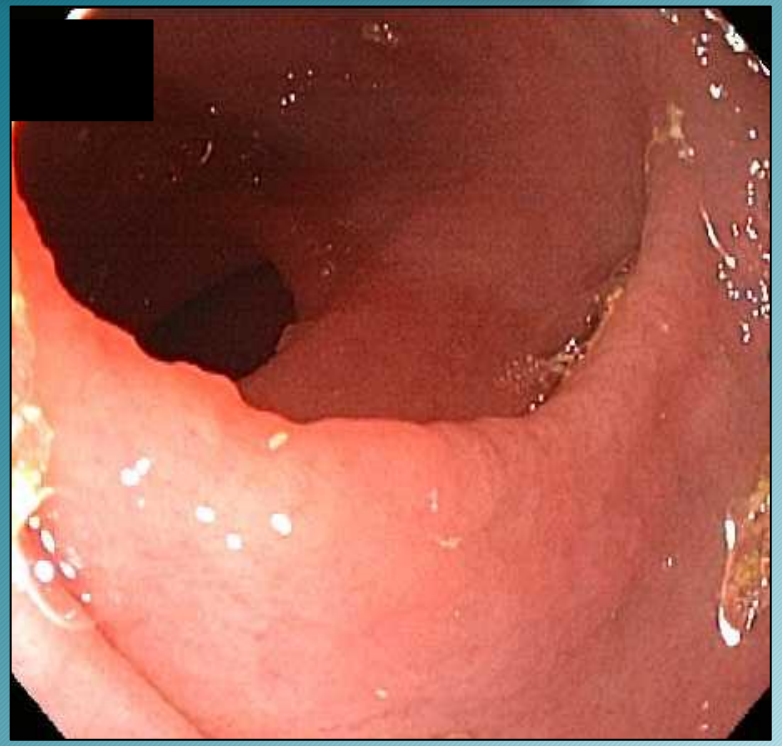
Cellular lamina propria with decreased, or absent, plasma cells

Histologic Features

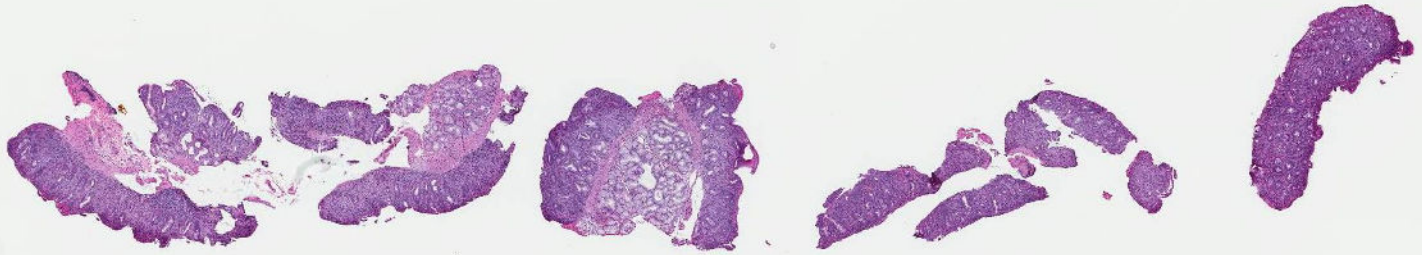
- Celiac disease
  - Surface more than crypt injury
  - IELs uniformly present in surface and crypts
  - Numerous lamina propria plasma cells
  - Granulocytes are infrequent
    - Crypt abscesses rare
  - Apoptosis uncommon
  - Duodenum and proximal jejunum most severely affected
- Common variable immunodeficiency
  - Crypt more than surface injury
  - IELs more prominent in crypts
  - Lamina propria plasma cells are decreased or absent
  - Neutrophils readily identified
    - Crypt abscesses frequent
  - Apoptotic crypt cells common
  - Stomach and colon often affected
  - Lymphoid hyperplasia
  - CMV and/or *Giardia*

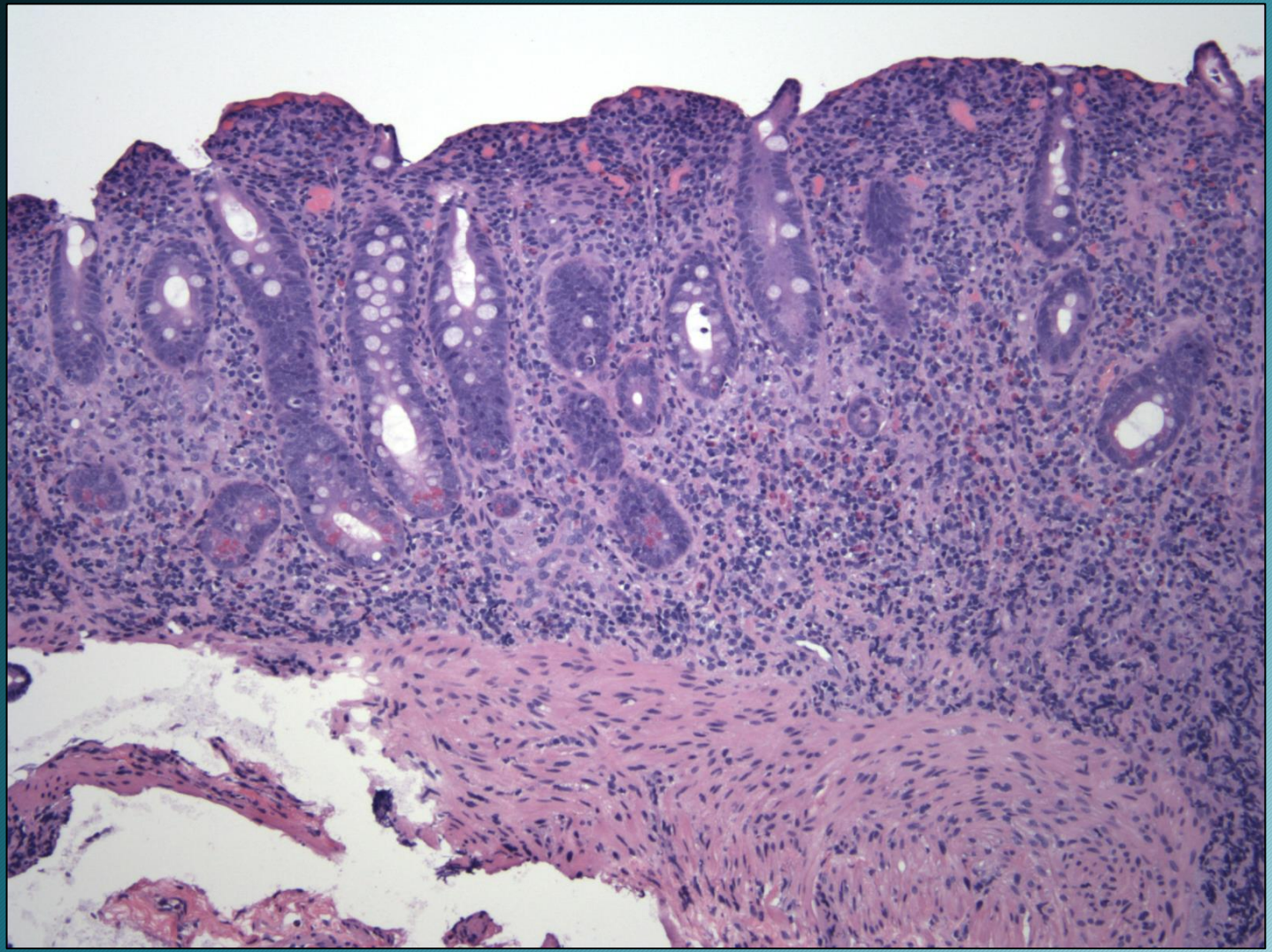
Case 3

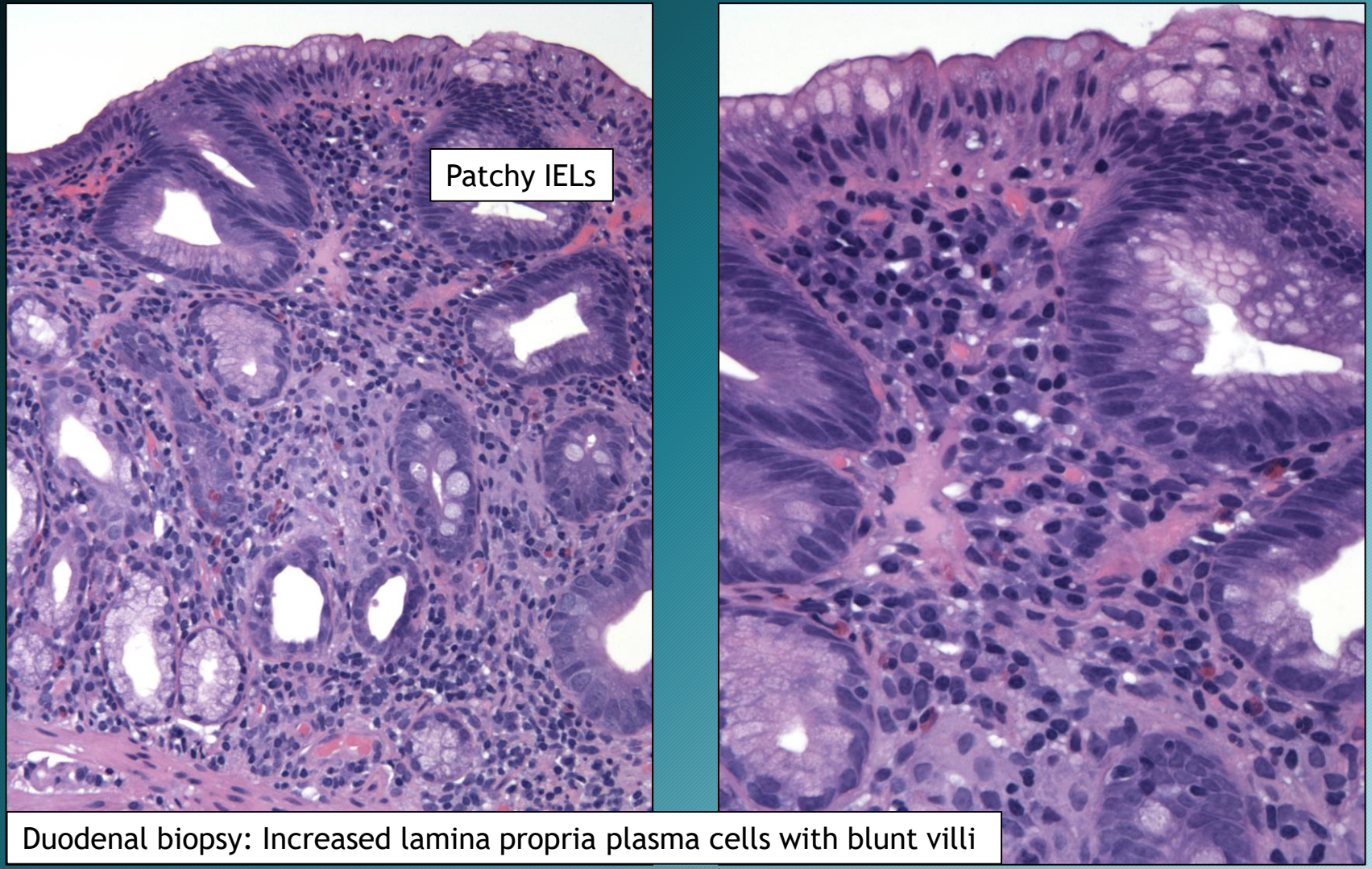
- 60-year-old man with unexplained, severe diarrhea
- Celiac serologies and HLA testing were negative
- Requisition
  - Rule out IBD, microscopic colitis, celiac disease, amyloid, Whipple disease, etc.
- Endoscopic findings
  - Mild congestion of colonic and gastric mucosae
  - Nodular duodenal mucosa with some scalloping of folds throughout



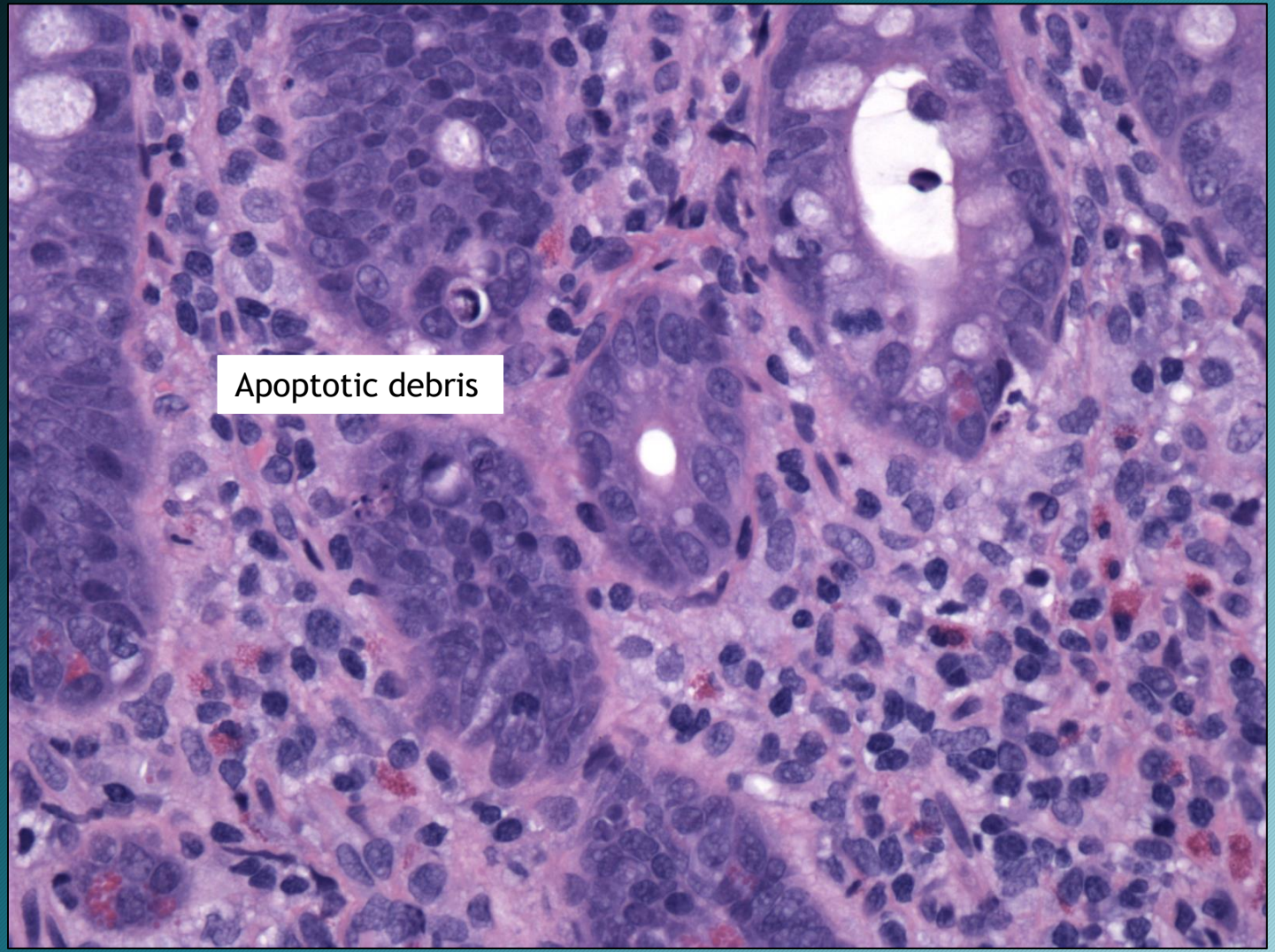
Duodenum is flat and blue







Duodenal biopsy: Increased lamina propria plasma cells with blunt villi


Apoptotic debris

Case 3-Red Flags for Celiac Disease

- 60-year-old man with unexplained, severe diarrhea
- Celiac serologies and HLA testing were negative
- Requisition
  - Rule out IBD, microscopic colitis, celiac disease, amyloid, Whipple disease, etc.
- Endoscopic findings
  - Mild congestion of colonic and gastric mucosae
  - Nodular duodenal mucosa with some scalloping of folds throughout

Really unusual for celiac disease to cause symptoms severe enough to warrant hospitalization

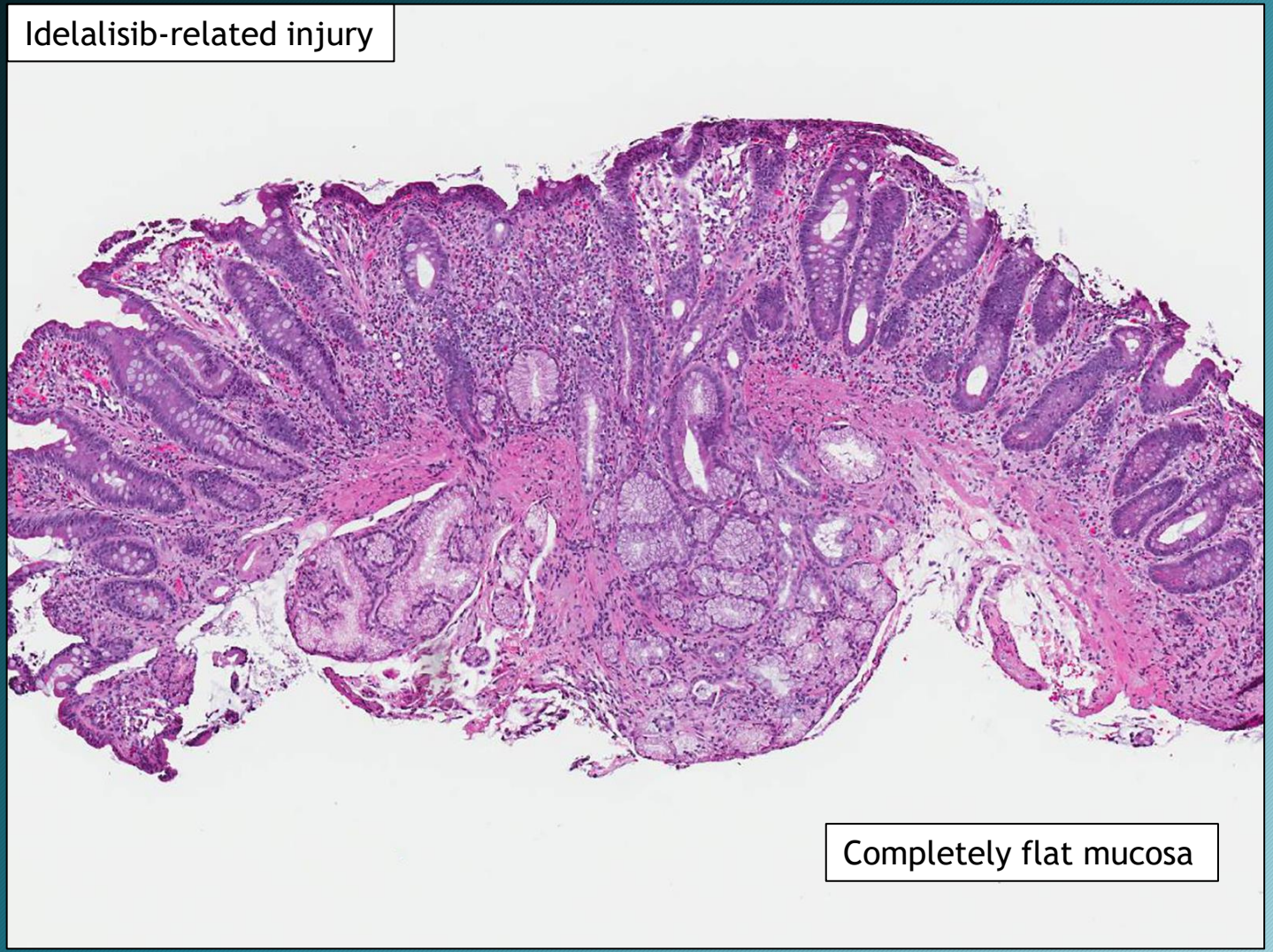
Celiac sprue not supported by laboratory results

Celiac disease may manifest in older adults, but other things are more common

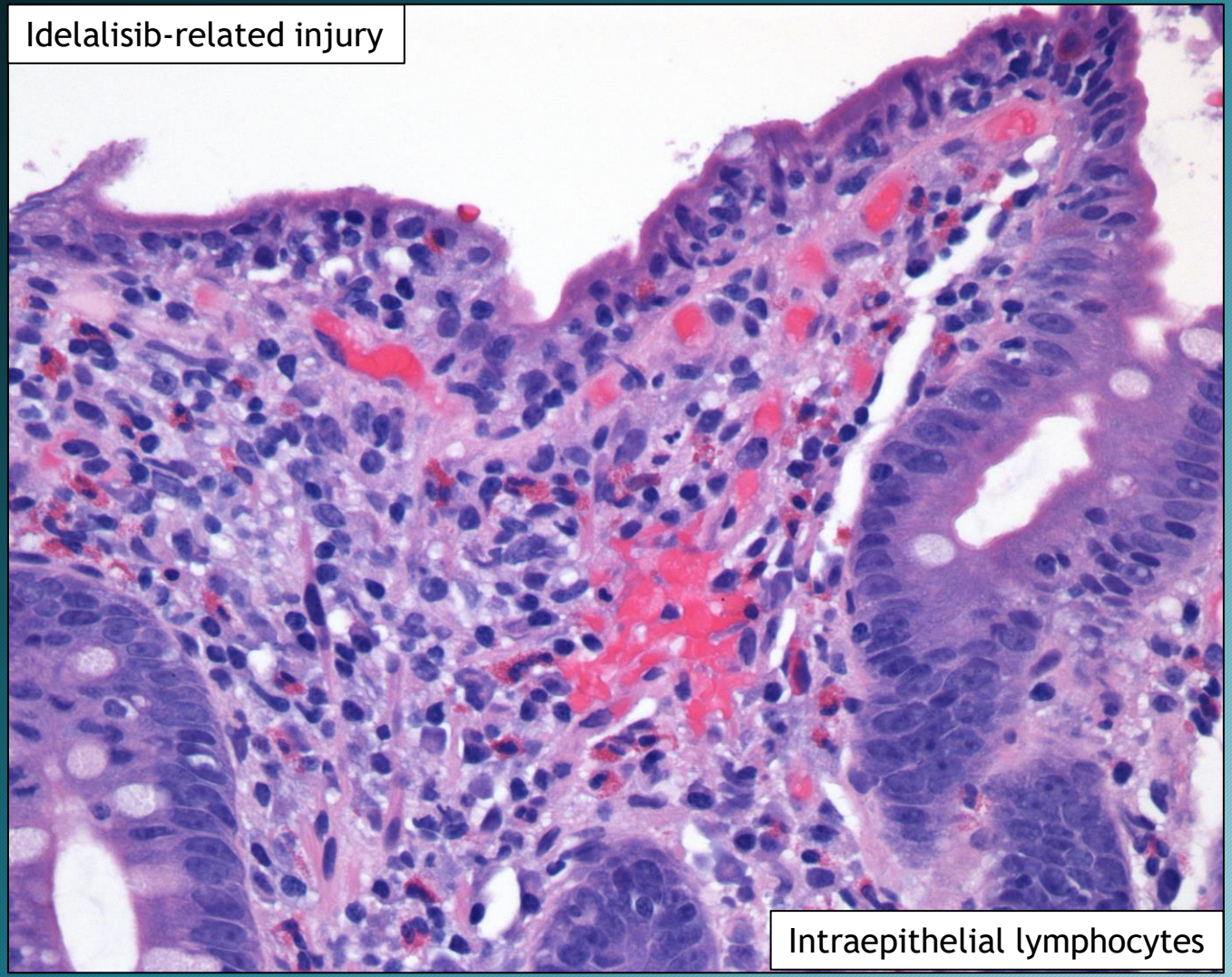
Medications/Treatment-Related Injury

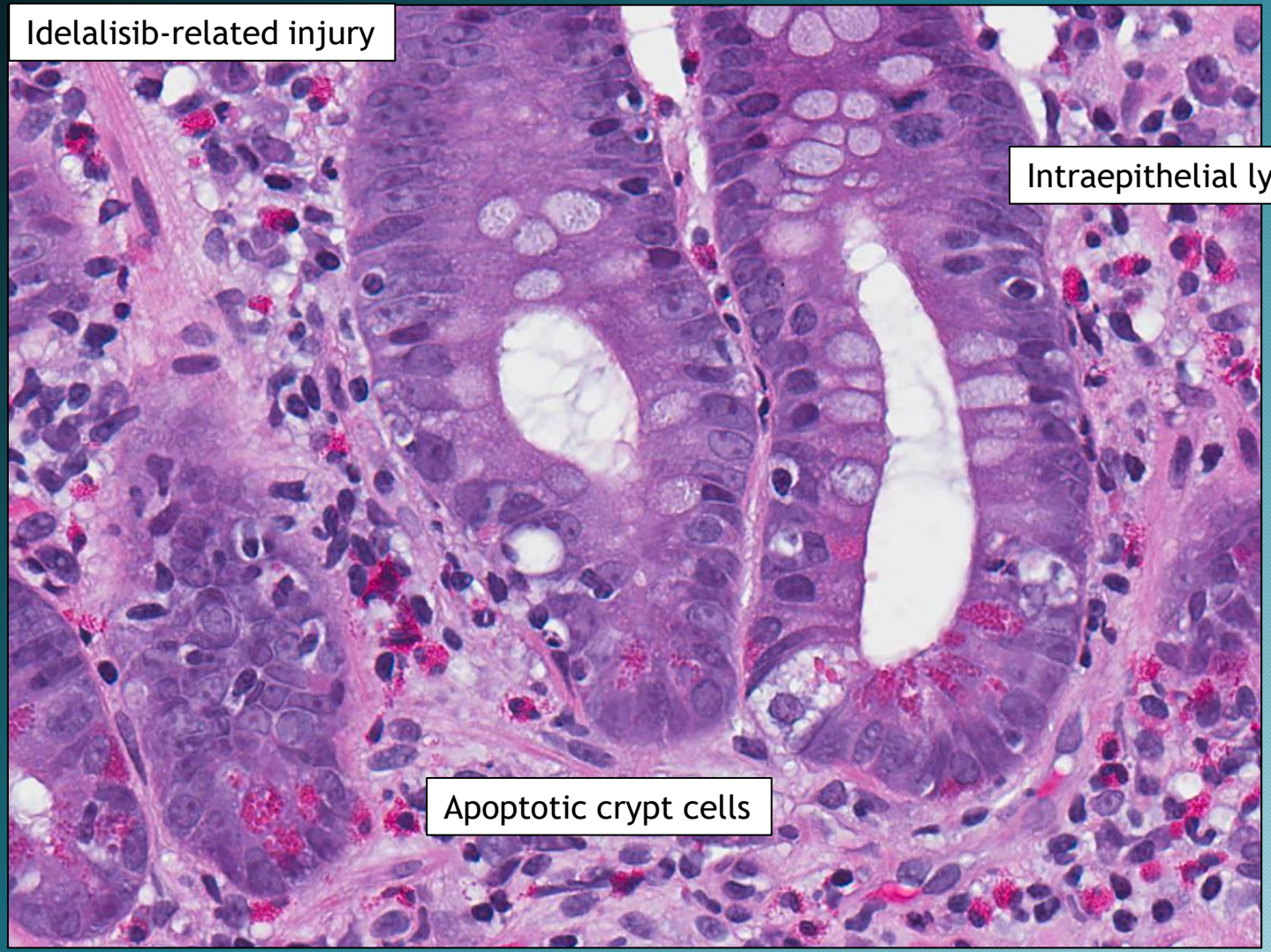
- NSAIDs
- Graft *versus* host disease
- Mycophenolate
- Chemotherapy/Radiation
- Targeted biologic agents (-ib, -ab)
  - Idelalisib (inhibits PI3Kδ-mediated signaling)
  - Ipilimumab (inhibits CTLA-4-mediated immune tolerance)
  - Pembrolizumab (inhibits PD-L1-mediated immune tolerance downstream to CTLA-4)
- Olmesartan (Benicar) and related compounds

Idelalisib-related injury



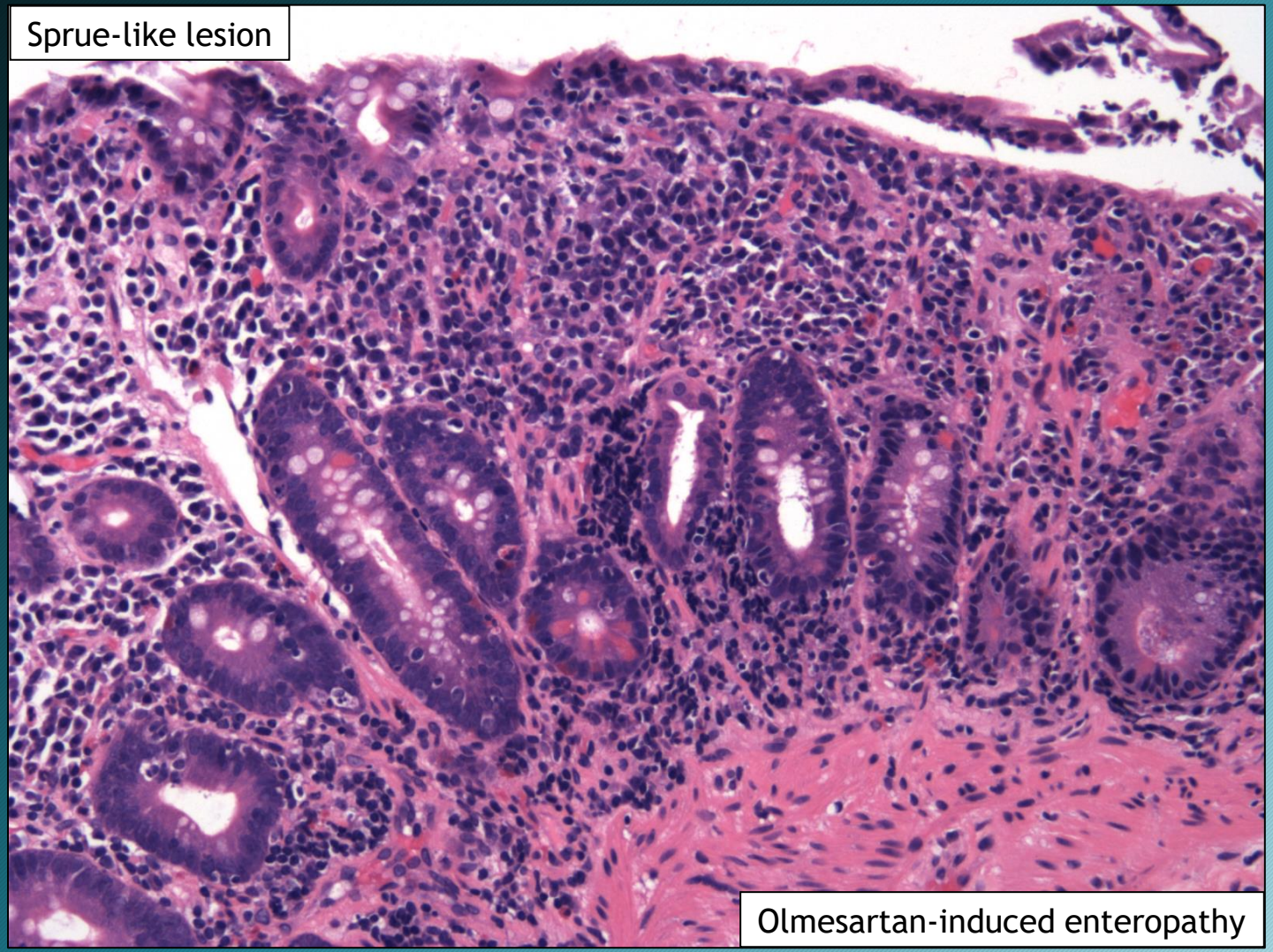
Completely flat mucosa


Idelalisib-related injury
Intraepithelial lymphocytes

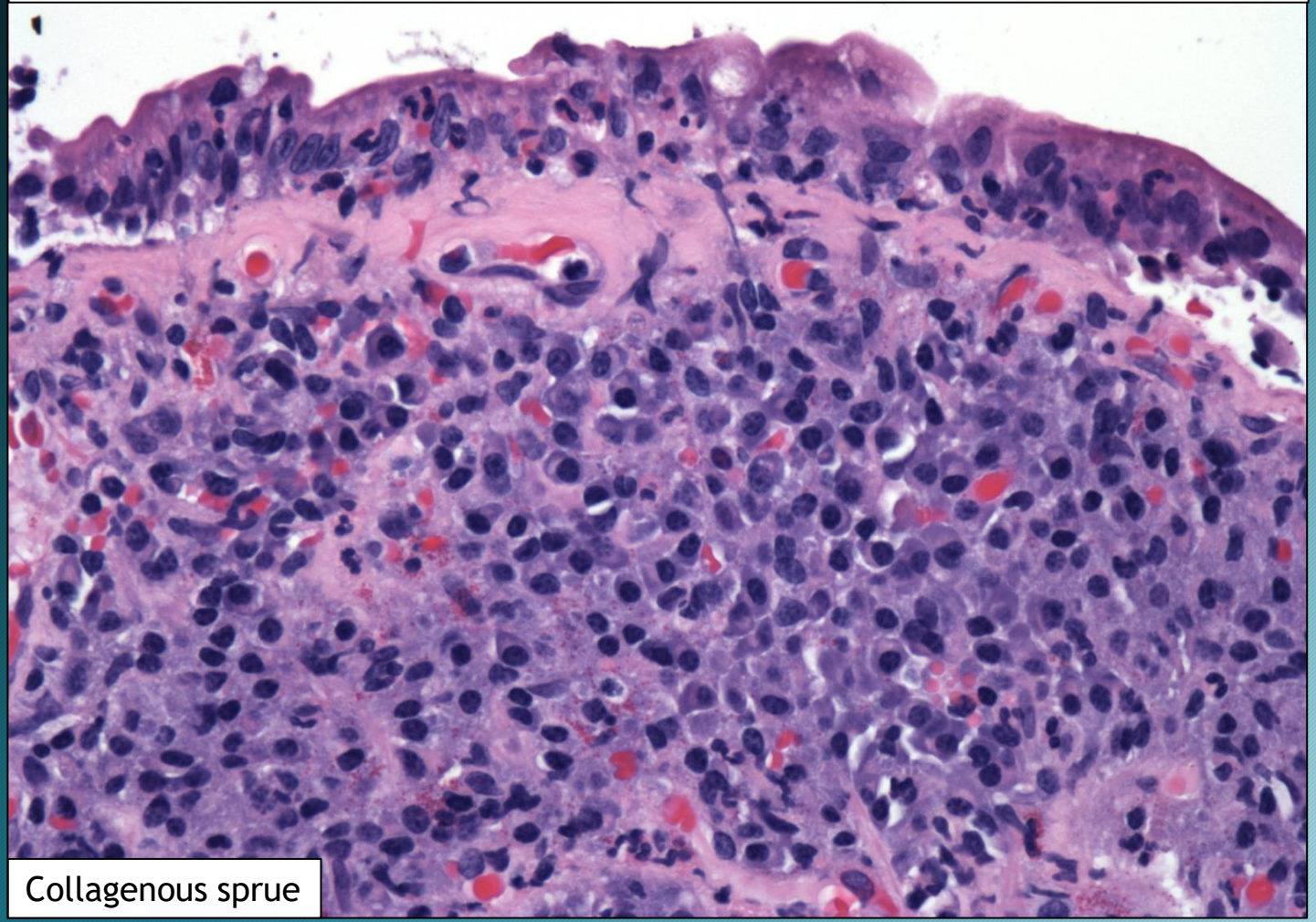

Idelalisib-related injury
Intraepithelial lymphocytes
Apoptotic crypt cells

Olmesartan Enteropathy (culprit in this case)

- Angiotensin II receptor antagonist (anti-hypertensive)
- Severe chronic diarrhea; may require hospitalization
- Serologic studies generally normal
- Mimic of celiac disease and autoimmune enteropathy
  - May affect stomach and colon as well
- Culprit in collagenous “-itis” throughout GI tract


Sprue-like lesion
Olmesartan-induced enteropathy

Tip: Think about olmesartan when you see collagenous “itis” anywhere in GI tract



Collagenous sprue

Histologic Features

- Celiac disease
  - Surface more than crypt injury
  - IELs uniformly present in surface and crypts
  - Granulocytes are infrequent
    - Crypt abscesses rare
  - Apoptosis uncommon
- Medication-related injury
  - Severe crypt injury with relative sparing of surface
  - IELs usually more prominent at crypt bases
  - Neutrophils readily identified
    - Crypt abscesses frequent
  - Apoptotic crypt cells common

The Value of Duodenal Biopsies
Take Home Points

- Low-yield unless there is a clinical question
- Celiac disease
  - The most reliable change is intraepithelial lymphocytosis
  - If IELs are not increased, villous abnormalities are not due to celiac disease
- Autoimmune enteropathy
  - Dense plasma cell-rich inflammation accompanied by cryptitis, and crypt cell apoptosis
  - Often loss of goblet cells, Paneth cells, and endocrine cells
- Common variable immunodeficiency
  - Crypt more than surface injury, apoptosis, cryptitis, decreased or absent plasma cells
  - Giardiasis or CMV infection should raise concern
- Medications mimic immune-mediated disorders—get history
  - Crypt cell apoptosis, neutrophils, and lymphocytes are clues