State of the Art: Celiac Disease

Focus on Non-Responsive CD

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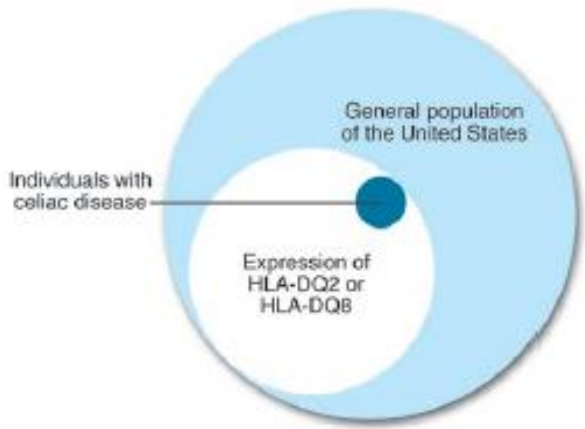
Changing Prevalence of Celiac Disease

- Prevalence of up to ~1:100 in most genetically susceptible populations, 0.71% in NHANES study, M=F serological, F =2-3X Bx
- Estimated that only 15 to 20% of current cases of CD have been diagnosed in the US
- CD is 4 to 4.5 times more prevalent than 50 yrs ago
- Increase in food allergies and autoimmune diseases as well
- Cause of "CD epidemic" unknown
  - Dietary – grains with increased gluten, increased wheat in diets worldwide
  - Other environmental, antimicrobials
  - Microbiota

Fasano et al, Arch Int Med, 163:286, 2003
Rubio-Tapa et al, Gastroenterology, 137: 88, 2009
AGA Technical Review, Gastroenterology, 131:1981, 2006
Virta et al, Scand J Gatroenterol, 44:933, 2009
Rubio-Tapia, Am J Gastroenterol, 2012

Risk Factors: Genes & Grains



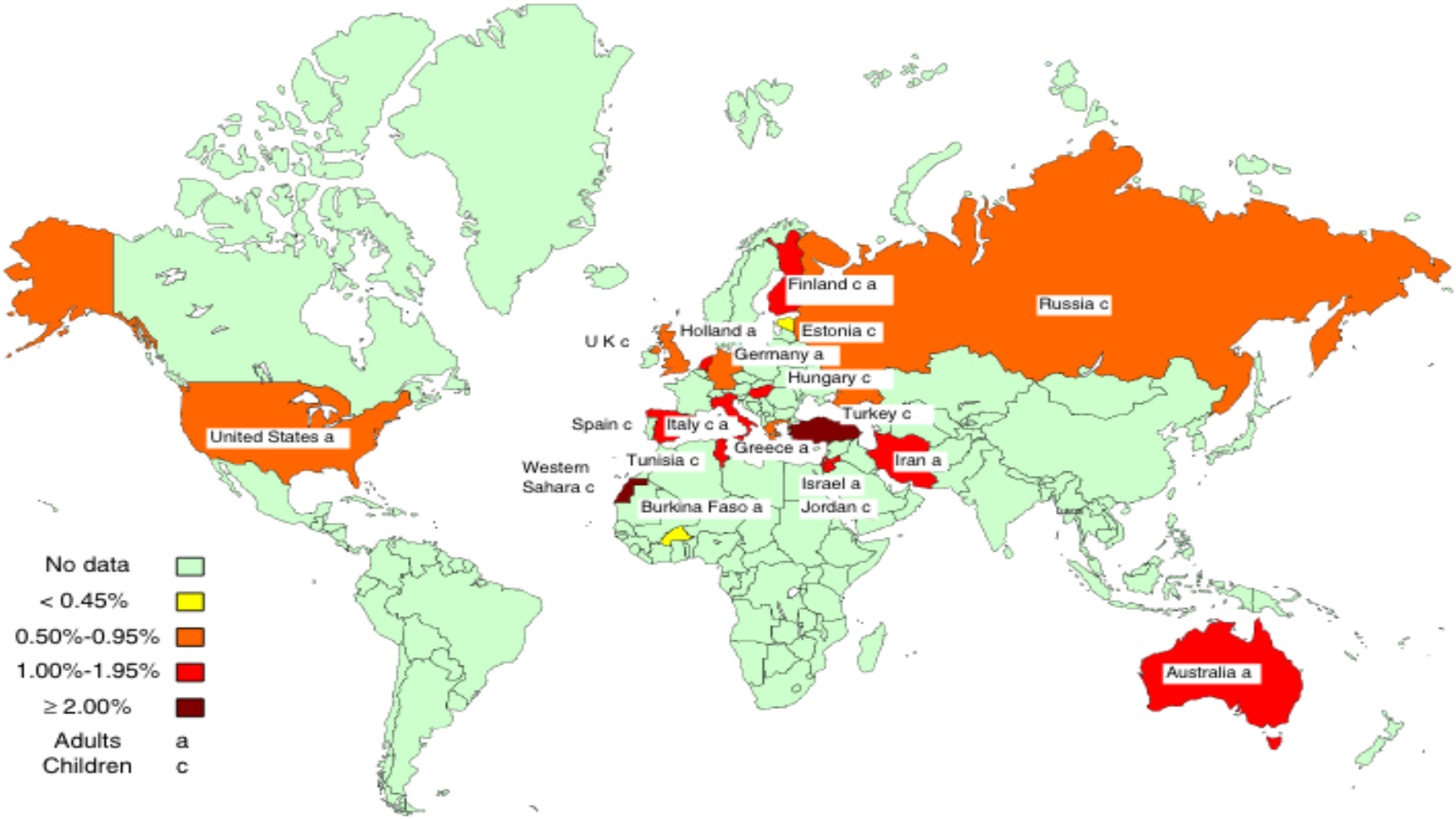
Wheat consumption

US daily consumption of wheat per individual:

moderately high (24% to 32% of diet)

Adapted from Fasano A, Catassi C. Gastroenterology. 2001;120:636-651.

Celiac Disease: Worldwide Prevalence



Kang, et al. Aliment Pharmacol Ther. 2013;38:226-45.

Varying Forms of Celiac Disease

- Classical celiac disease of childhood
- Late onset, non-specific GI symptoms
- Dermatitis herpetiformis
- Extra-intestinal presentations (many)
- Associated conditions (many)
- Silent or asymptomatic celiac disease (relatives)
- Latent or potential celiac disease
- **Nonresponsive or refractory celiac disease**

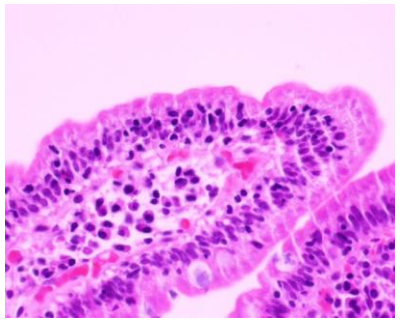
What are the Best Serological Tests for Screening?

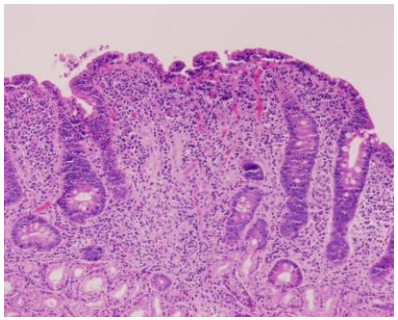
- Depends on prevalence and age of population being examined
- Overall, TTG IgA is the recommended test to screen for disease but sensitivity varies with lower levels (≤90%) reported in routine practice, 1 in 10 false negative rate
- Check total IgA for assays with narrow range of normal
- EMA IgA is helpful when positive
- TTG, EMA less sensitive for milder histologic stages
- Traditional AGA no longer used as a first line antibody test except in young children
- Antibodies to GDP are less sensitive than to TTG*

AGA Technical Review, Gastroenterology, 131:1981, 2006
** Lewis, NR, Aliment Pharmacol Ther, 31: 73, 2010*

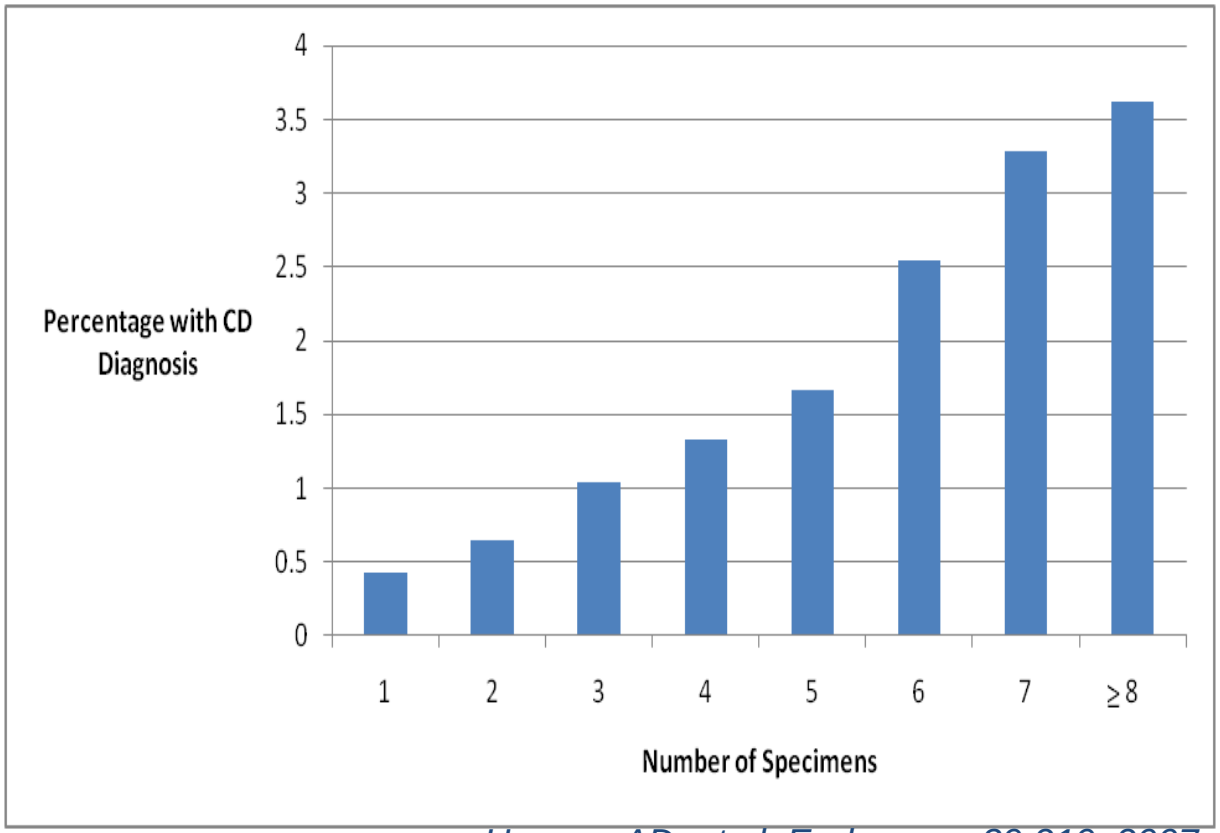
Importance of Taking Biopsies and Reading Histopathology

Marsh II (modified 2





Marsh IV (modified 3c



Enhance detection by taking ≥4-6 biopsies including at least one from duodenal bulb

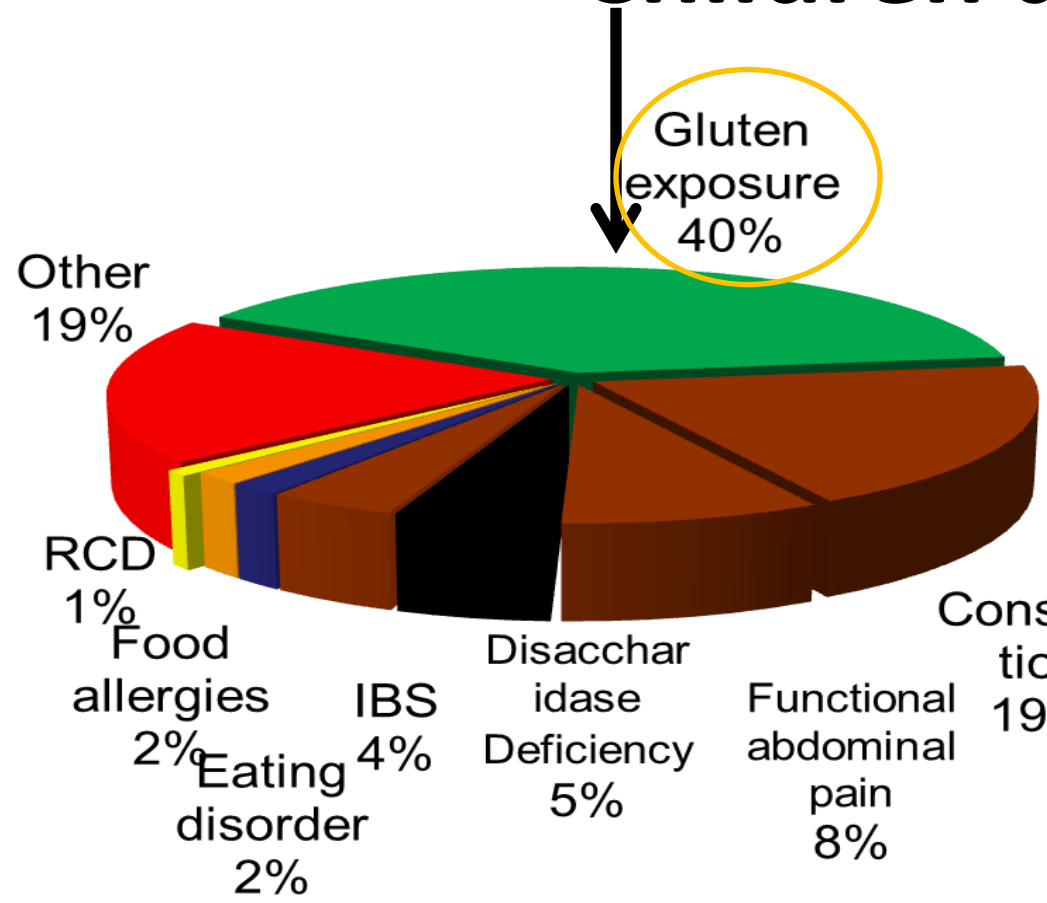
Hopper, AD, et al, Endoscopy 39:219, 2007
Bonamico, M et all, JGN, 47, 618, 2008
Weir, DC, et al Am J Gastroenterol 2009
Lebwohl, B., et al, GI Endoscopy, 74:103, 2011

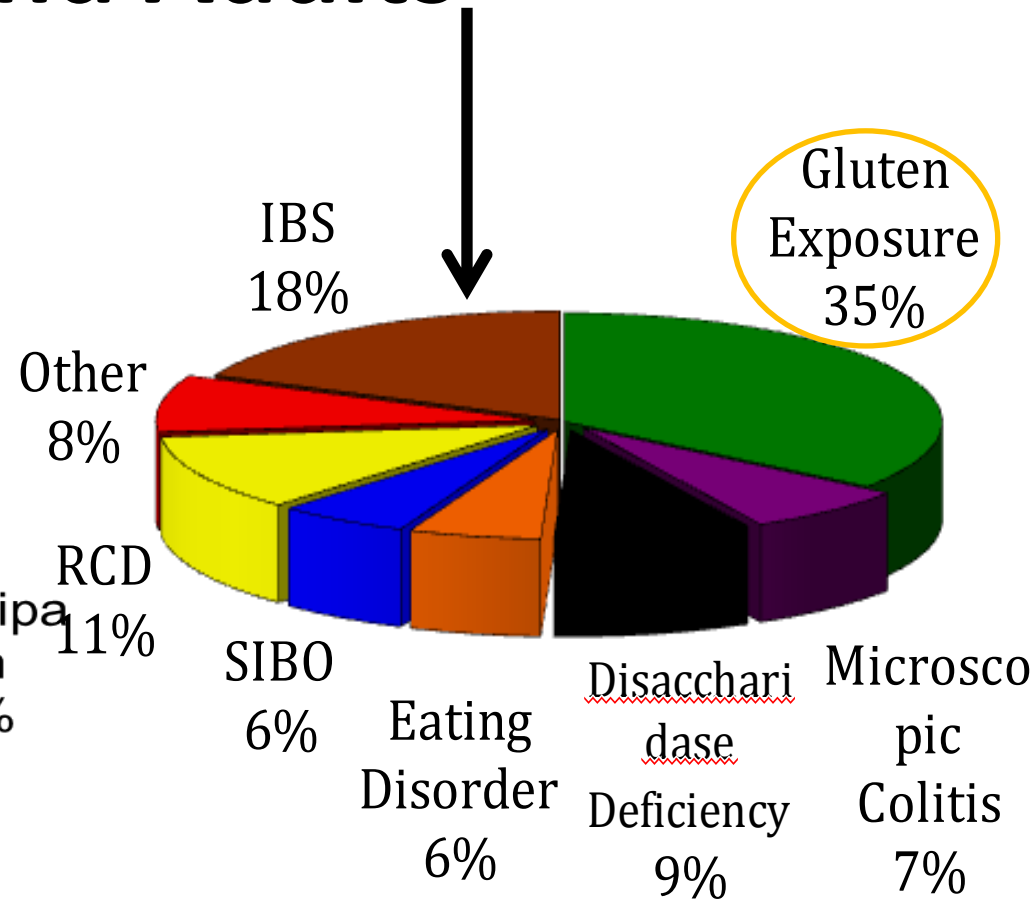
Non-Responsive Celiac Disease (NRCD)

- Usually due to ongoing or recurrent gluten exposure
- Coincident disorders
  - Lactose intolerance
  - Pancreatic insufficiency
  - Small intestinal bacterial overgrowth
  - Microscopic colitis
  - **IBS (post-inflammatory or overlap of two common diseases)**
- Unrelated to celiac disease – incorrect or additional diagnoses
- Over or erroneous interpretation of the pathology
- Complications of celiac disease
  - Refractory celiac disease
  - Malignancy

Krauss, GI Endosc Clin NA, 16: 317, 2006
Leffler, DA, et al. Clin Gastro & Hepatol, 5:445, 2007

Spectrum of NRCD in Children and Adults





Leffler et al, CGH 2007;
Veeraraghavan DDW 2016

Nonresponsive Celiac Disease in Children - Boston, MA

- **23% of children with celiac disease**
  - **Persistent symptoms**
  - **Persistently elevated celiac disease serologies**

- **Abdominal pain**
- **Constipation**
- **Gluten exposure common (40%)**

Veeraraghavan, et al. DDW 2016. Sp999

What to Do When the GFD Fails? – Case 1

- 49 year old male veterinarian with longstanding bloating, abdominal discomfort, altered bowel habits
- Duodenal biopsies show celiac disease, tTG IgA normal
- Exam reveals slim male with normal exam, abdomen unremarkable
- Labs show normal CBC and other labs
- Gluten free diet did not help him, referring GI doctor started him on prednisone for “refractory celiac disease” but patient worsens

What is the cause for his apparent failure to respond to dietary treatment? What to do next for his evaluation?

Case 1 of NRCD: Evaluation and Management

- A thorough review of his diet and medications reveals no source of gluten
- Review of duodenal biopsies by GI pathologist shows peptic duodenitis
- After discontinuing prednisone and the gluten free diet (GFD) and treating with proton pump inhibitor the patient's worsened symptoms of dyspepsia improve and the longstanding symptoms due to functional GI disorder remain
- He was relieved not to have celiac disease

Refractory Celiac Disease (RCD)

Villous atrophy associated with persistent or recurrent malabsorptive symptoms despite strict adherence to a GFD for at least 6-12 months in the absence of other causes of nonresponsive CD or overt malignancy

- Rare, prevalence is low even in major referral centers
- Primary form – no initial response to GFD
- Secondary form (more common) - after an initial period of response no longer responds to GFD
- tTG IgA often normal in RCD if patient is GF

Rubio-Tapia & Murray, Gut, 59: 547; 2010

Refractory Celiac Disease

- Variants - collagenous, ulcerative, stricturing
- Risks for RCD:
  - Older age, two DQ2 alleles
- Two main forms based on T cell receptor (TCR):
  - RCD type I – phenotypically normal IEL
  - RCD type II – associated with clonal expansion of IEL bearing CD3ε but lacking expression of CD4, CD8 and the β-chain of TCR

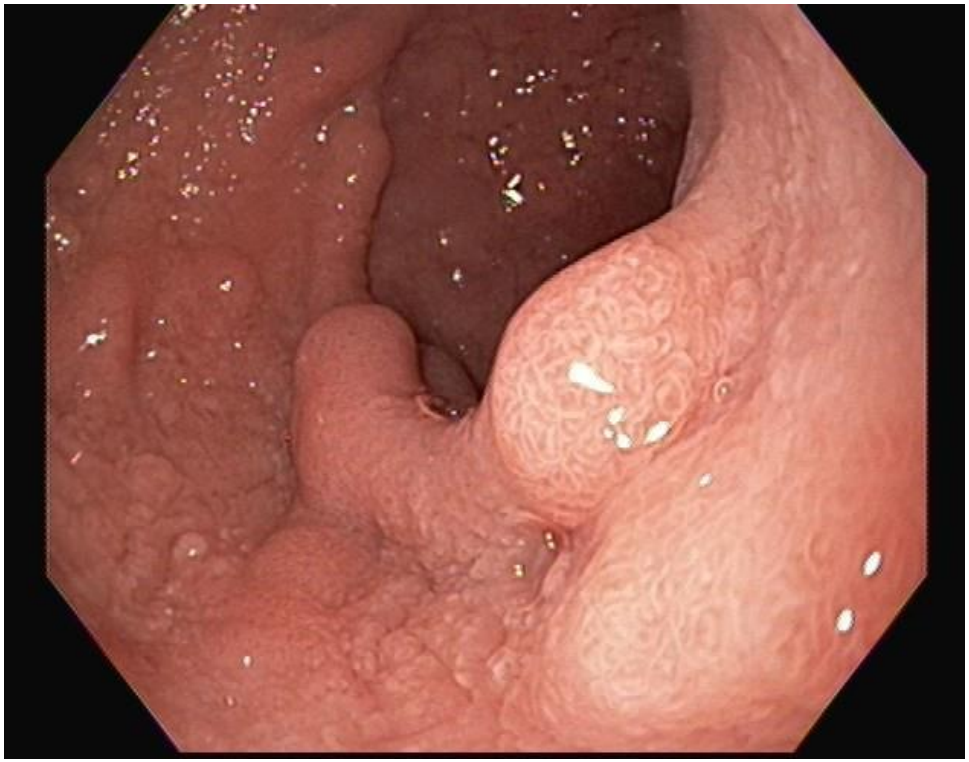
Rubio-Tapia & Murray, Gut, 59: 547; 2010

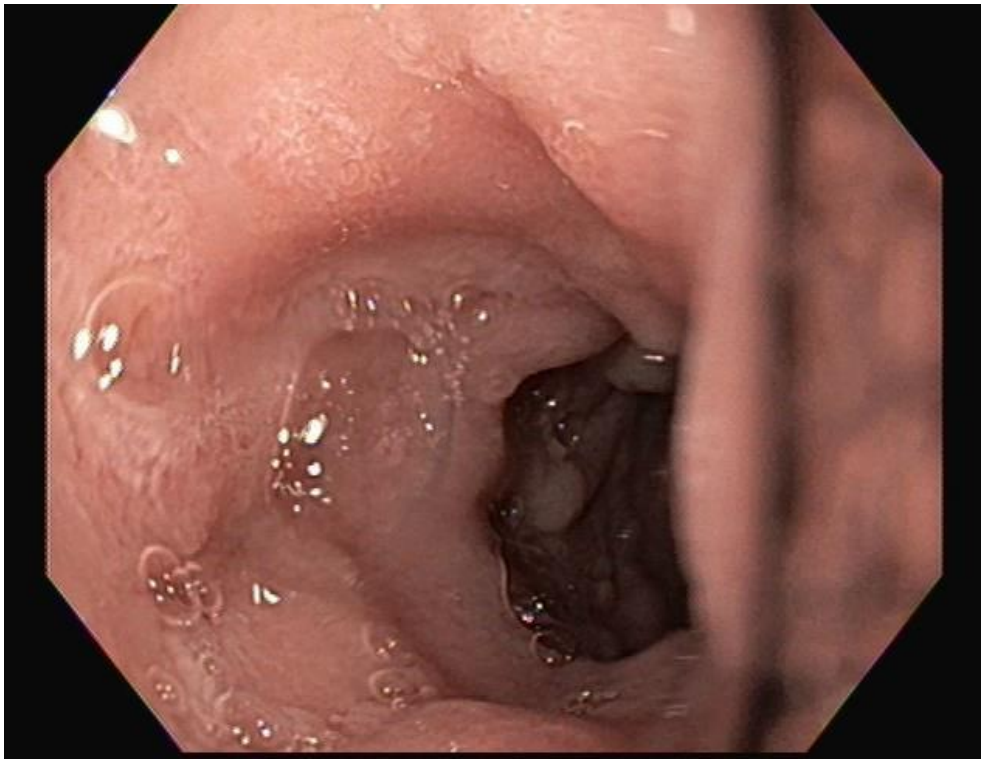
When the GFD Fails – Case 2

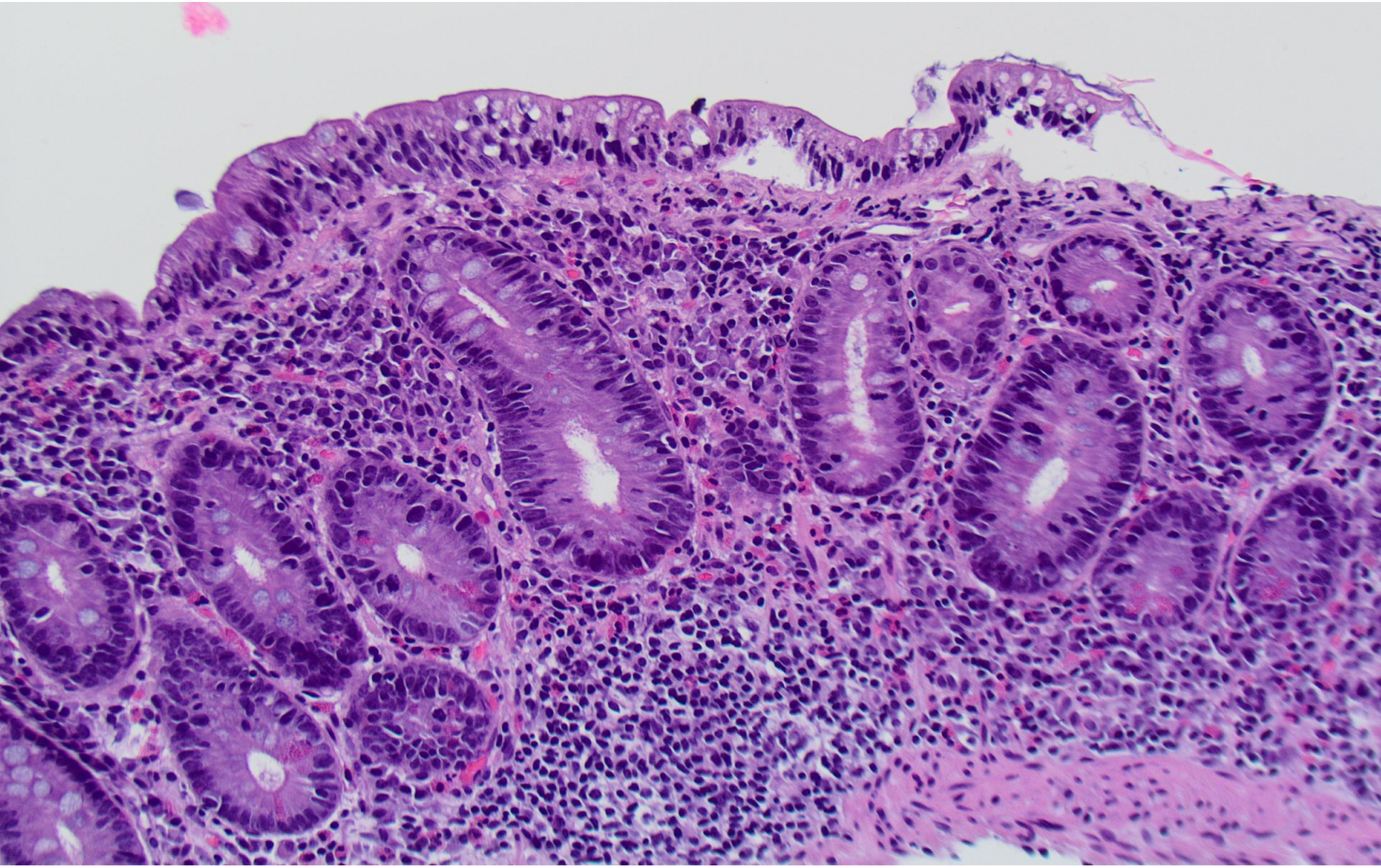
- Case 2. Mr. PG
- 82 yr old man referred to me for unresponsive celiac disease with continued diarrhea, ongoing weight loss and anemia in spite of a GFD.
- Exam reveals thin male with pallor, abdomen soft, slightly distended, no organomegaly or masses, no enlarged LNs, normal thyroid
- Initial labs showed Hgb 11.1 with MCV 90, total IgA of 61, tTG IgA in normal range, vitamin D low, vitamin B12 164

What is the cause for his apparent failure to respond to diet Rx?

Endoscopic Images of Case 2

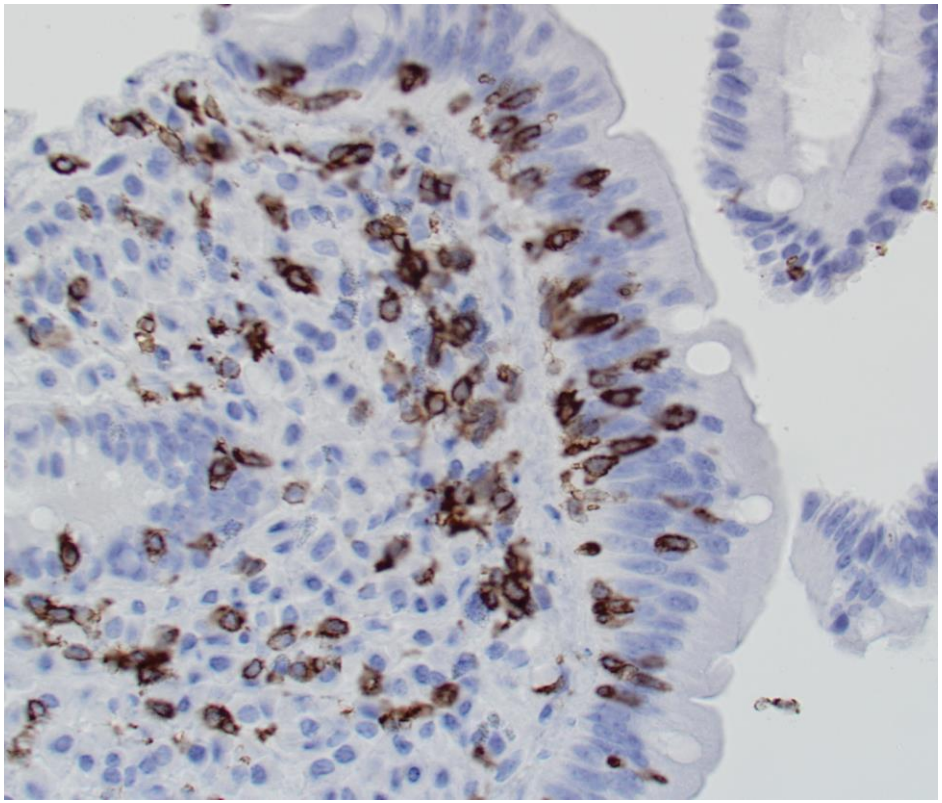




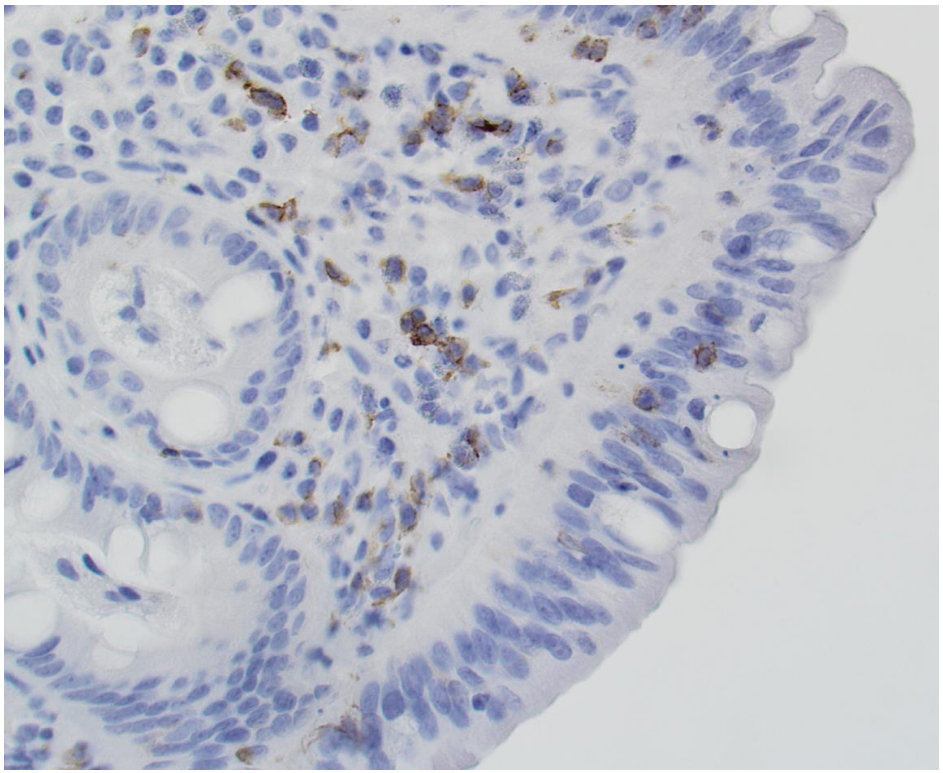


Immunohistochemistry

CD3 staining



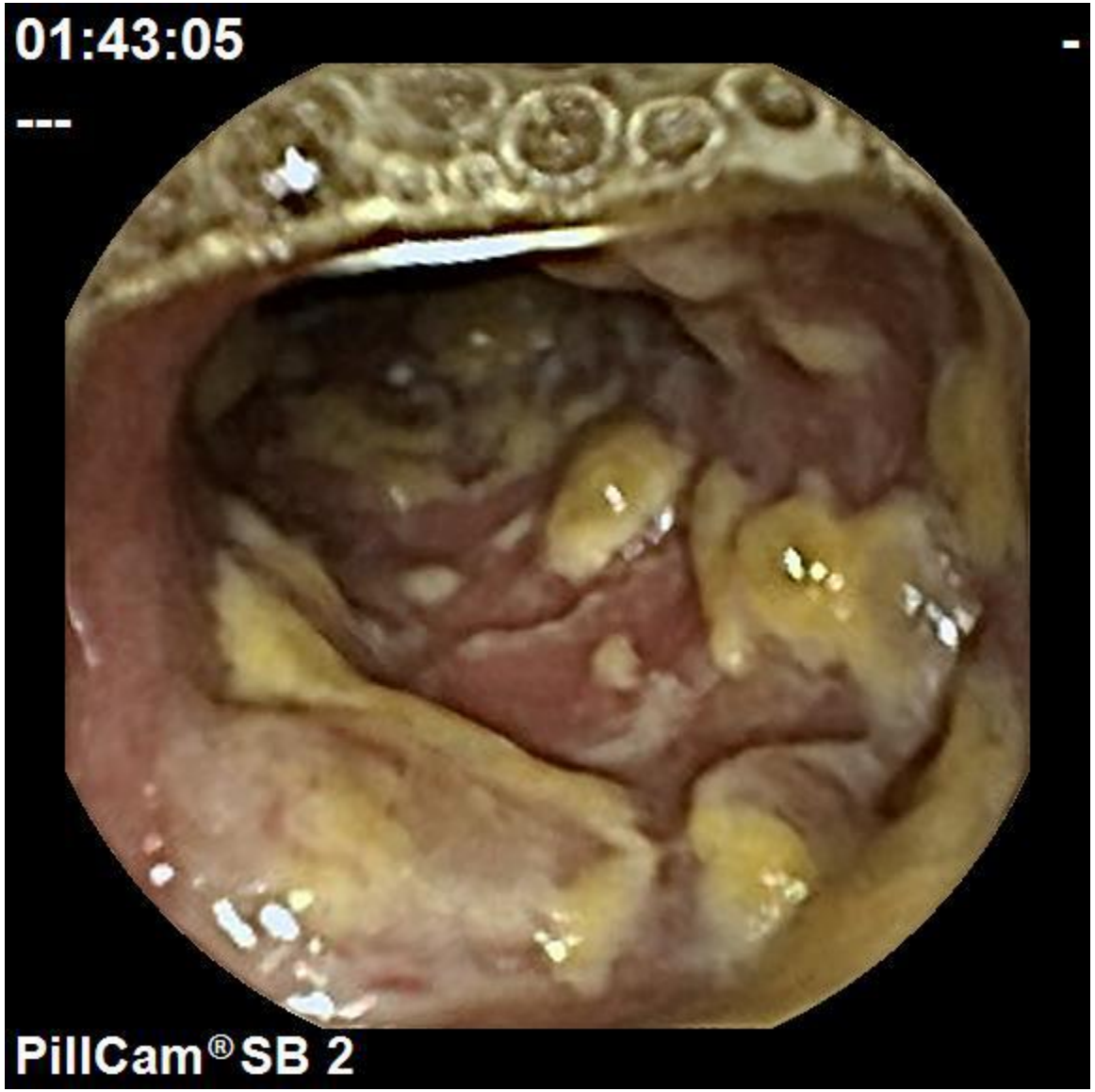
CD8 staining



Severe RCD Type II

- Case 3. Mrs. MP
- 35 yr old woman referred to me for unresponsive celiac disease with persistent diarrhea, weight loss, MRSA sepsis, DVT, GI bleeding transferred to UCI. VCE showed severe ulcerative jejunitis. Referred to UCSD for further opinion.
- Thin female with pallor; abdomen soft, slightly distended, no organomegaly or masses; no enlarged LNs; normal thyroid . Initial labs showed mild increase of TTG IgG not TTG IgA but DGP IgA/G both elevated

Is this actually celiac disease or something else?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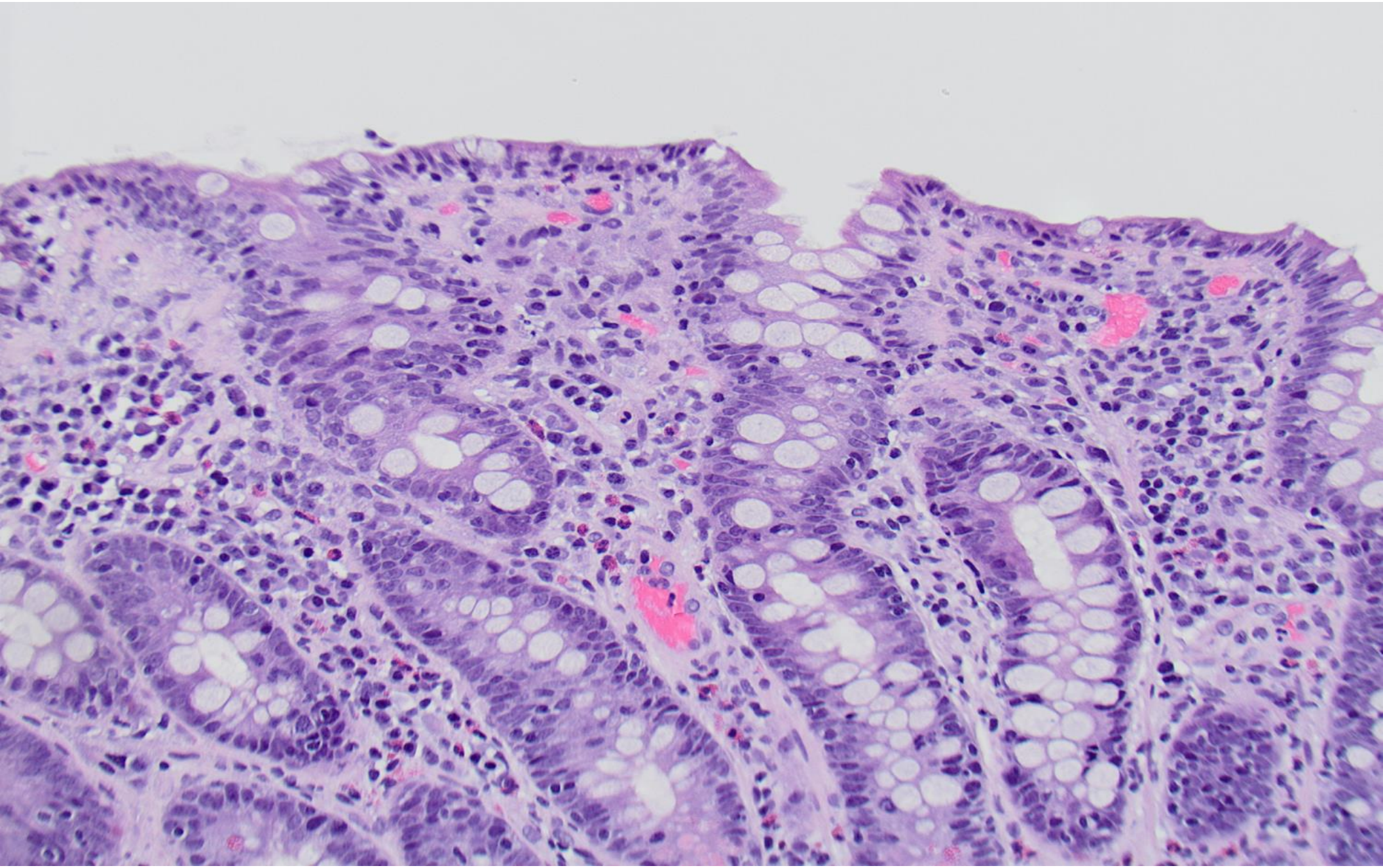
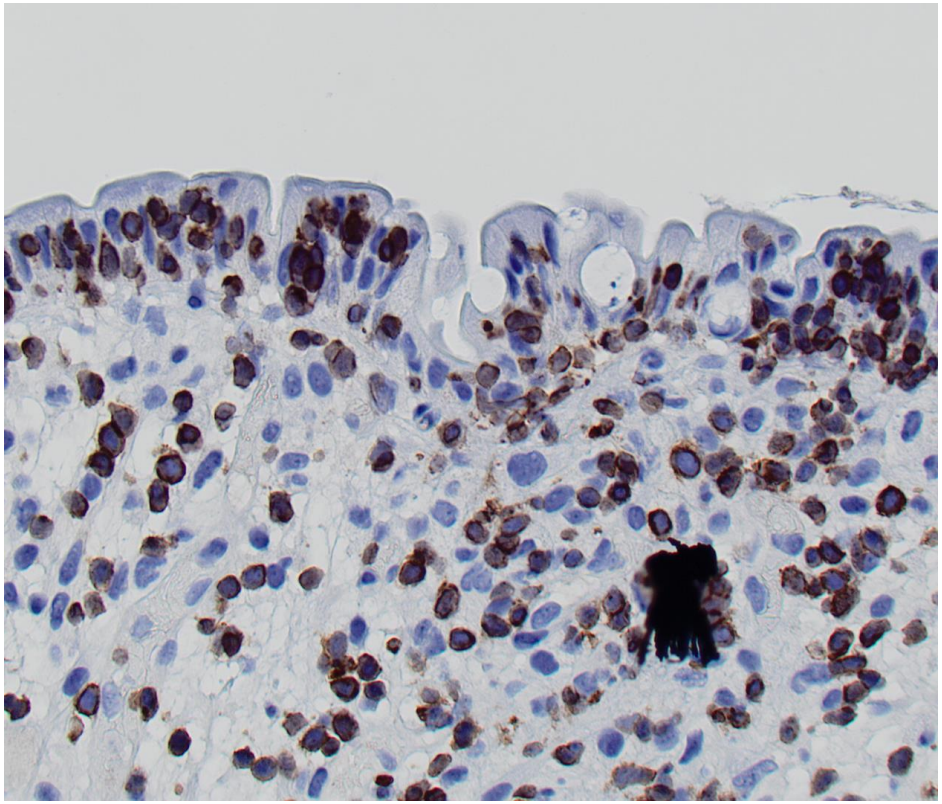
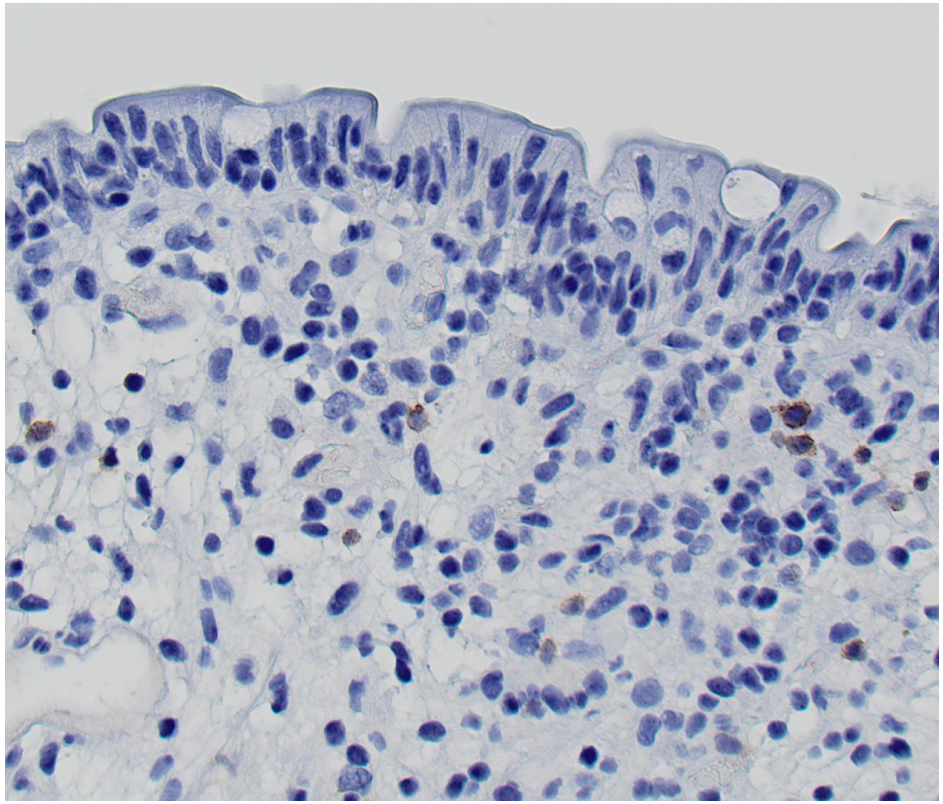


Immunohistochemistry – Case 3

CD3 staining



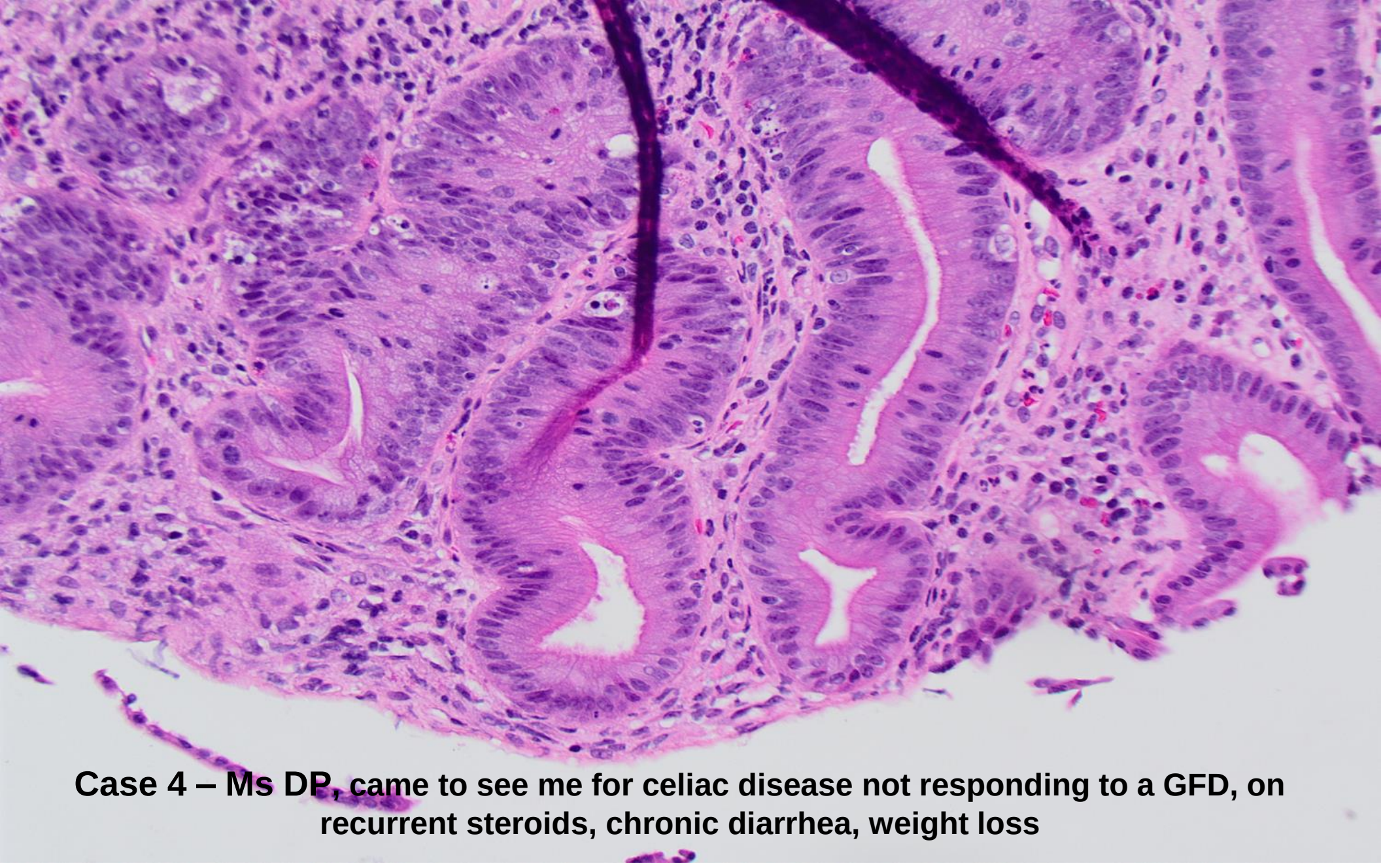
CD8 staining



Differential Diagnosis of RCD

- Adult-onset autoimmune enteropathy
  - Anti-epithelial antibodies (enterocyte, goblet cell)
- Common Variable Immunodeficiency (CVID)
  - Absent plasma cells on biopsy, reduced serum Ig levels
- Medication-associated enteropathy
- Tropical sprue
- Collagenous sprue (a form of RCD)
- Eosinophilic gastroenteritis
- Crohn disease

Rubio-Tapa & Murray, Gut, 59: 547, 2010
Malamut, Am J Gastroenterol, 2010



Case 4 – Ms DP, came to see me for celiac disease not responding to a GFD, on recurrent steroids, chronic diarrhea, weight loss

Autoimmune Enteropathy (AIE)

- Adult-onset autoimmune enteropathy
  - Rare condition, series of 15 at MCR, median age 55 yrs
  - Anti-epithelial antibodies (enterocyte, goblet cell)
    - 14 tested, 93% for anti-enterocyte and/or anti-goblet cell Abs
  - Subtotal villous atrophy, lymphoplasmacytic infiltration in the lamina propria, relatively few IELs
  - Absence of goblet cells, apoptotic epithelial cells
    - Apoptotic ECs are only found in AIE and GVHD
  - Immunosuppressive therapy needed in 93% of cases

Alkram, et al Clin Gastroenterol Hepatol, 5:1282;2007

Autoimmune Enteropathy Syndromes

- IPEX syndrome – Immune dysregulation, Polyendocrinopathy, Enteropathy, and X-linked syndrome
  - Deficiency of FoxP-3 expressing T reg cells
  - AIE-related 75 kDa (AIE-75) and antibody to villin are markers of IPEX syndrome
- APECED – Autoimmune Polyendocrinopathy, Candidasis, Ectodermal Dystrophy
  - Classic triad of candidiasis, Addisons, hypoparathyroidism
  - Up to 25% have GI symptoms
  - Anti-tryptophan hydrolase-1 (TPH-1) Ab – central tolerance defect

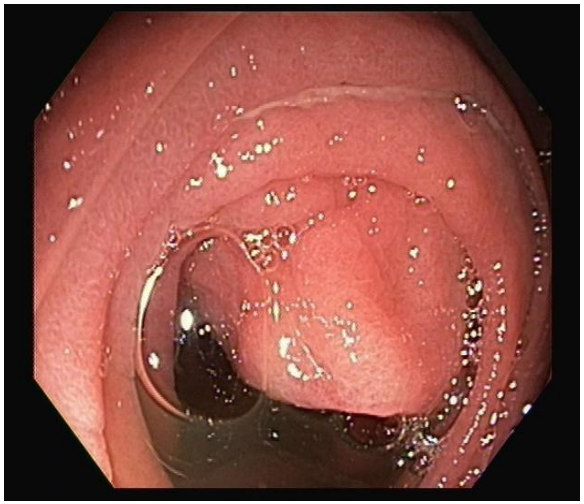
Chida, N, et al,Clin Imuunol, 156: 36, 2015

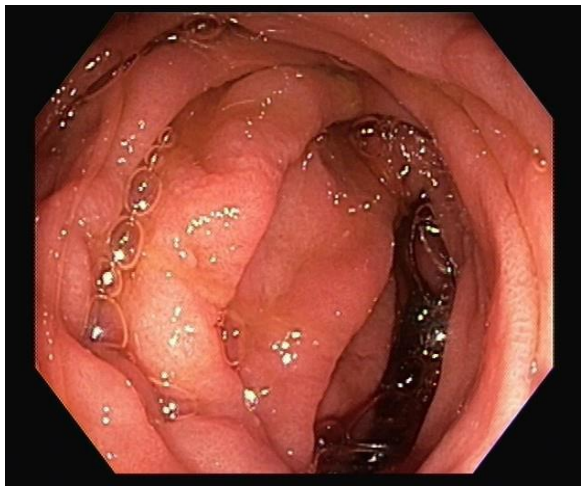
Common Variable Immunodeficiency Disorder (CVID)

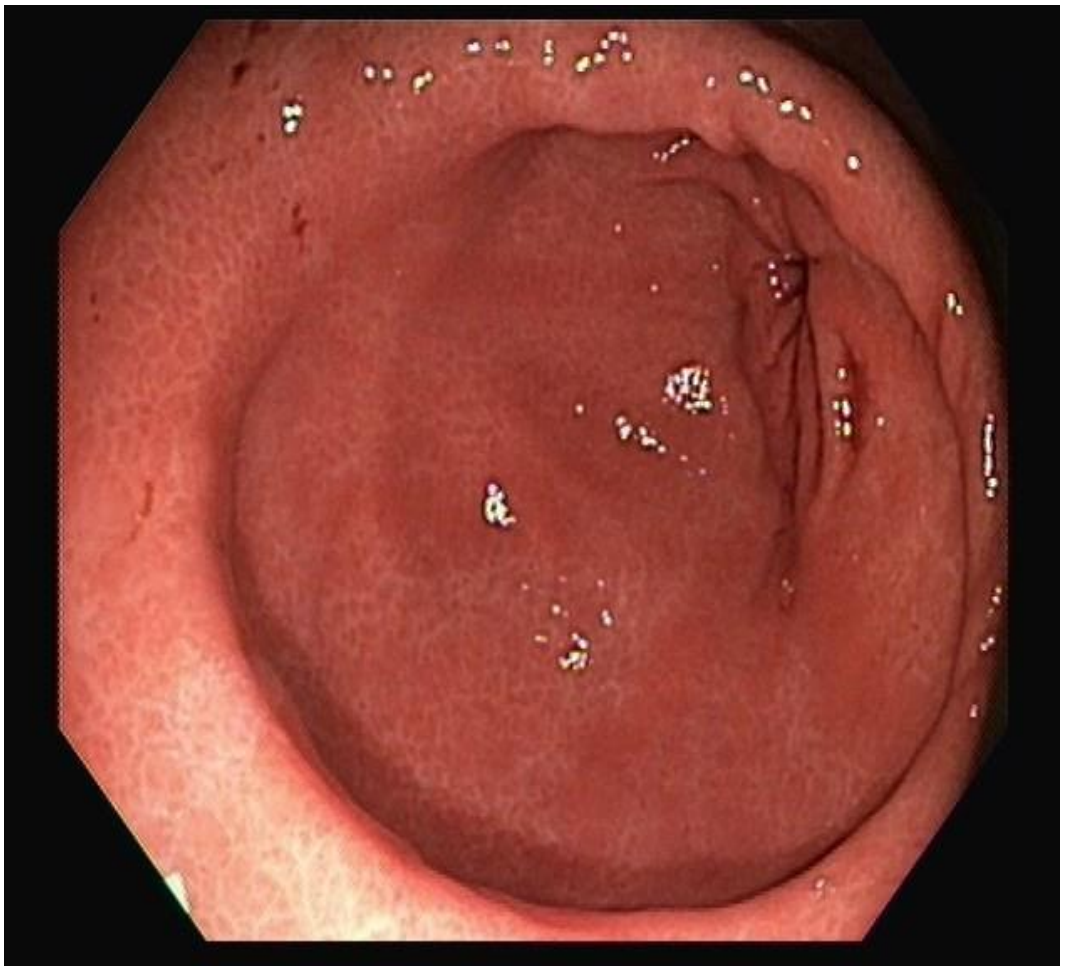
- CVID pathology
  - Absent plasma cells on biopsy
  - Follicular lymphoid hyperplasia
  - Villous atrophy, moderate increase IELS
- Clinical manifestations
  - Chronic diarrhea, malabsorption
  - Reduced serum Ig levels (at least of two isotypes)
- Associated with microscopic colitis, chronic gastritis
- Rare, 1 per 50,000 to 100,000
- GFD or IV Ig is of no significant benefit for GI symptoms
- Corticosteroids improve GI symptoms, immunosuppressives and biologics are used but limited experience

Malamut et al, Am J Gastroenterol, 105: 2262;2010

Case 5 - CVID Enteropathy





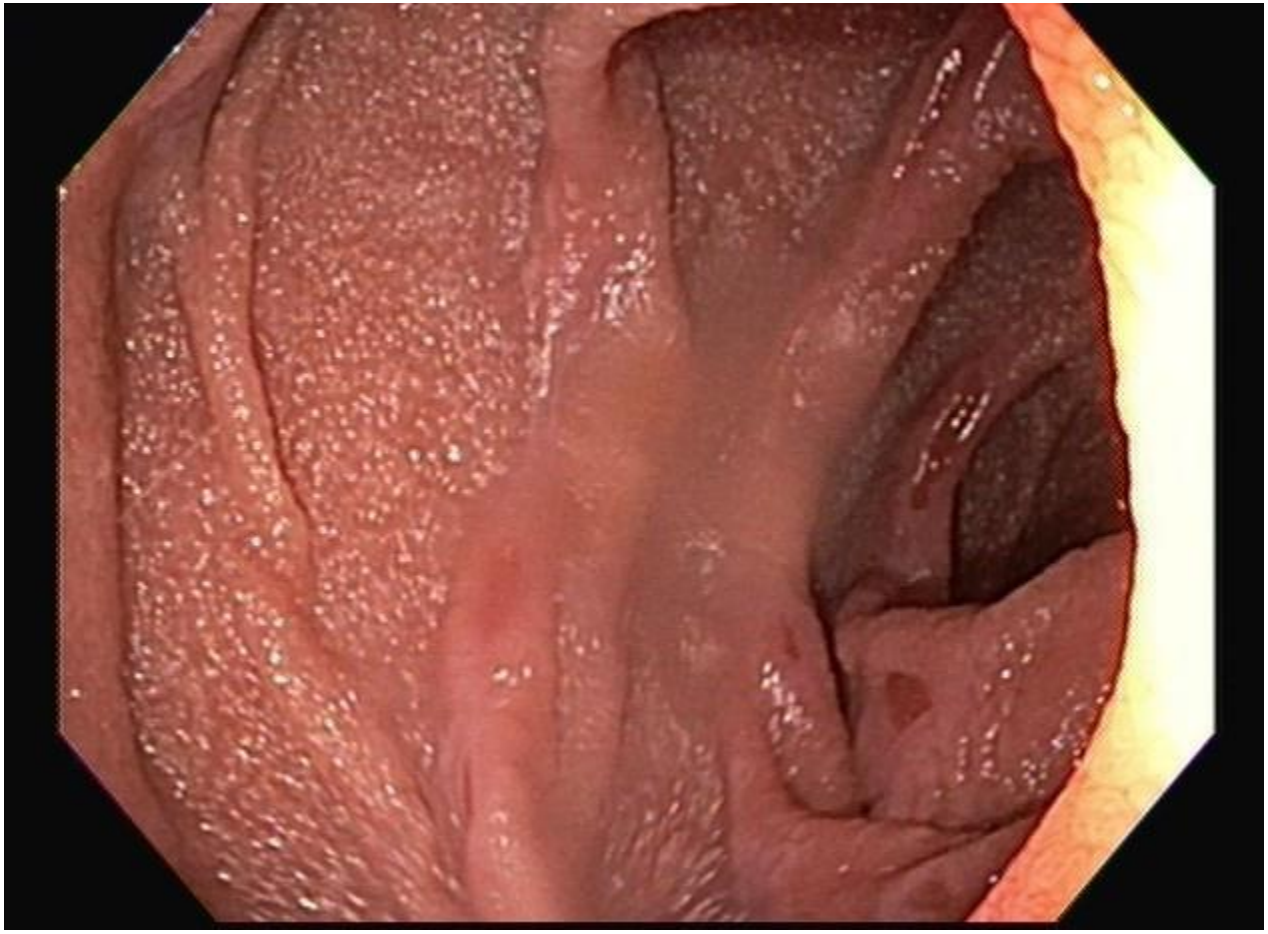


Case 6 - What Was Causing Her Illness?

- Case 4. Mrs. RP - 49 yr old woman comes to me for a second opinion for possible celiac disease or other enteropathy
- 2010 - positive thyroid autoantibodies
- 2012 - developed lower extremity edema, anemia, but improved with furosemide.
- April 2014 - developed recurrent edema, low albumin and iron deficiency anemia.
- Started taking Aleve (ibuprofen) for menstrual periods from age 18yr and for sinus and ear problems in 2011, and then for swelling of her legs in 2012

Case 6 - What Was Causing Her Illness?

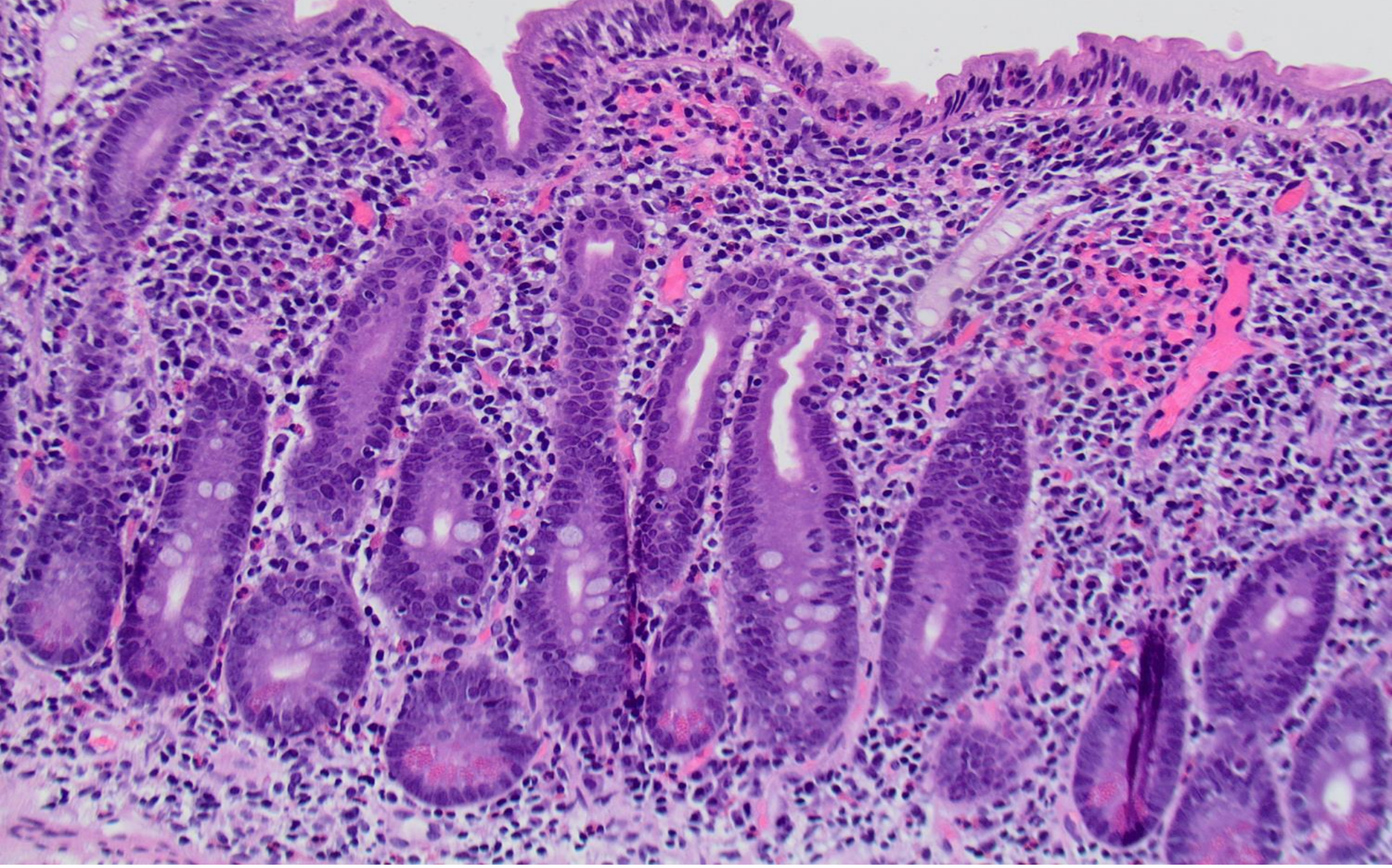
- 2015- saw a GI doctor
- Had video capsule, SBFT xray suggesting NSAID, Crohn disease- Steroids were suggested, patient declined
- Dx of Protein Losing Enteropathy, anemia
- Advised stop NSAIDs, start regular PPI, ferrous sulfate
- Sent to me for a second opinion
- Previous biopsies reviewed increased eosinophils, villous blunting
- Enteroscopy showed normal stomach and duodenum but patchy areas without villi and erythematous – pathology as per prior biopsies



Case 7 - What Was Causing Her Illness?

- Case 5. Mrs. SA (initial visit in late 2012)
- 65 yr old woman comes to me for poorly responsive celiac disease with sudden onset of severe diarrhea after Abx for dental work, liters of diarrhea, ongoing weight loss in spite of a GFD and many other interventions.
- Extensive testing at Scripps and EGD/EUS at UCSD with duodenal biopsies at Scripps and UCSD in fall 2011, both read as celiac disease
- By my visit she had pudding-like stools, some weight gain
- Seronegative but later found to be HLA DQ2.5 bearing

What is the cause for her apparent failure to respond to diet Rx?



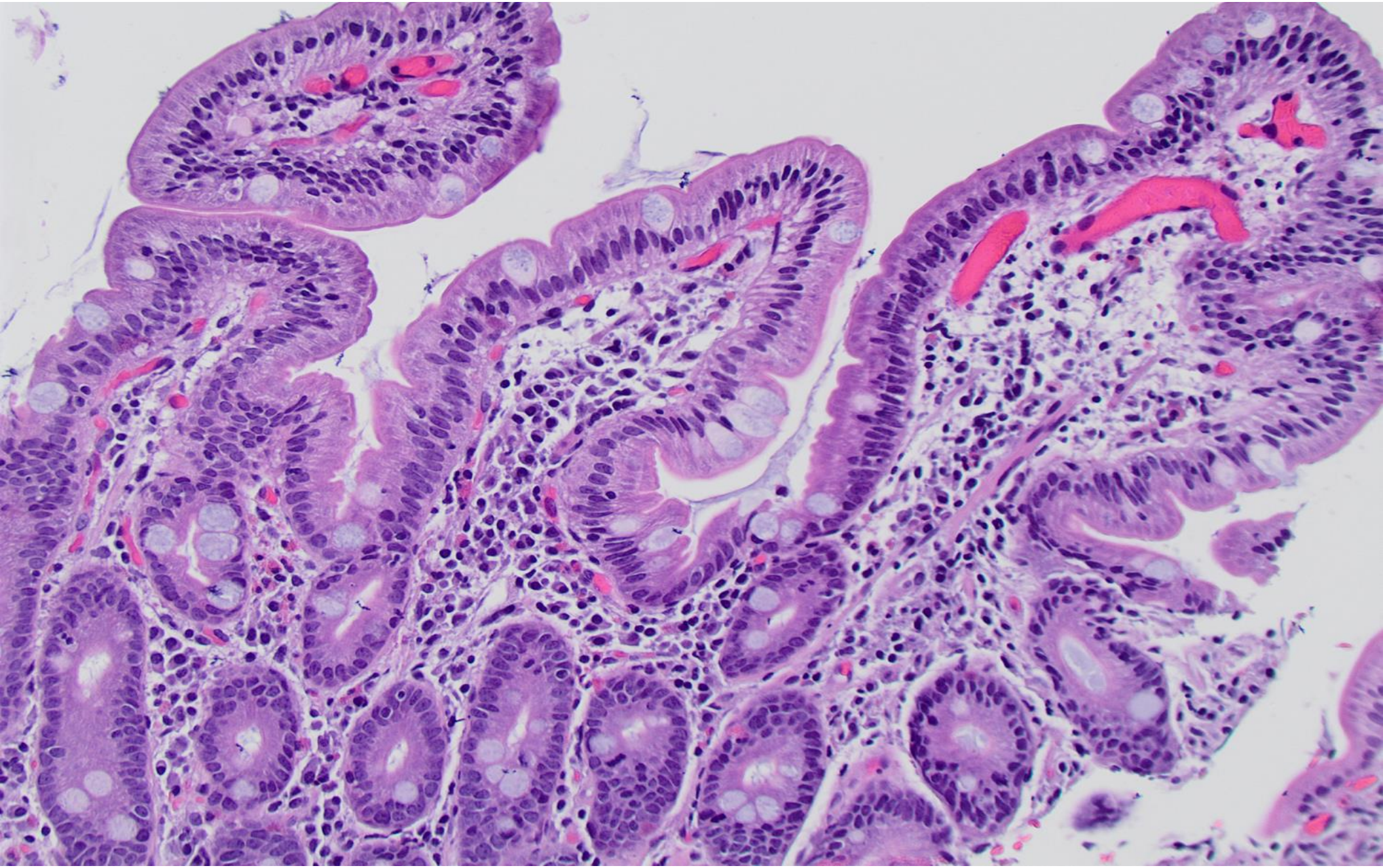
ORIGINAL ARTICLE

MAYO CLINIC

Severe Spruelike Enteropathy Associated With Olmesartan

Alberto Rubio-Tapia, MD; Margot L. Herman, MD; Jonas F. Ludvigsson, MD, PhD; Darlene G. Kelly, MD, PhD; Thomas F. Mangan, MD; Tsung-Teh Wu, MD, PhD; and Joseph A. Murray, MD

 ■ Mayo Clin Proc. 2012;87(8):732-738



Olmesartan and Other Medications

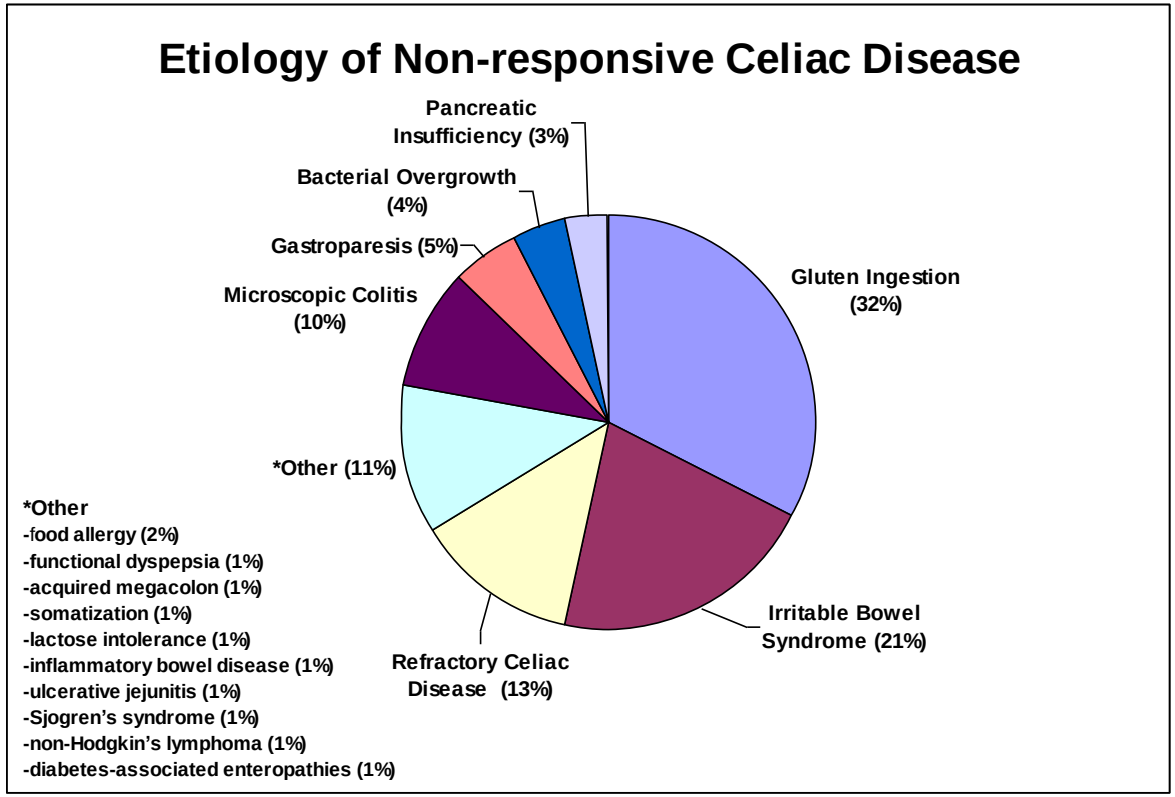
- Olmesartan - angiotensin II receptor blocker associated with a severe enteropathy
  - Appears to be drug specific, not a class effect although a few enteropathy cases reported associated with other “sartans”
  - In a large RCT trial of olmesartan vs placebo (ROADMAP study) no difference in enteropathy, malabsorption (Clin Drug Invest, 30: 473, 2010)
  - Olmesartan associated with 22% of unclassified enteropathy in Columbia University study (Am J Gastro ’13)
- Mycophenolate mofetil

UVA NRCD Study

- 32% non-compliance
- 21% IBS
- 10% microscopic colitis
- 5% gastroparesis
- 4% SIBO
- 3% pancreatic insufficiency
- 13% RCD

272 with CD (69% F, 96% white)

97 of the 272 had NRCD



Basile, JM, Hammerle, CW, Crowe, SE. et al

Experience with RCD at UVA

- 19 of 97 with NRCD had RCD (20%)
  - 3 type I
  - 14 type II (assessed by PCR)
  - 2 untyped
- All had evidence of malabsorption
- Several were exposed to olmesartan
- 17 (89%) received steroids, 14 (74%) thiopurines
- 11 received temporary enteral and/or parenteral nutrition
- 2 died of celiac disease associated process
  - EATL
  - Inflammatory neurological disorder

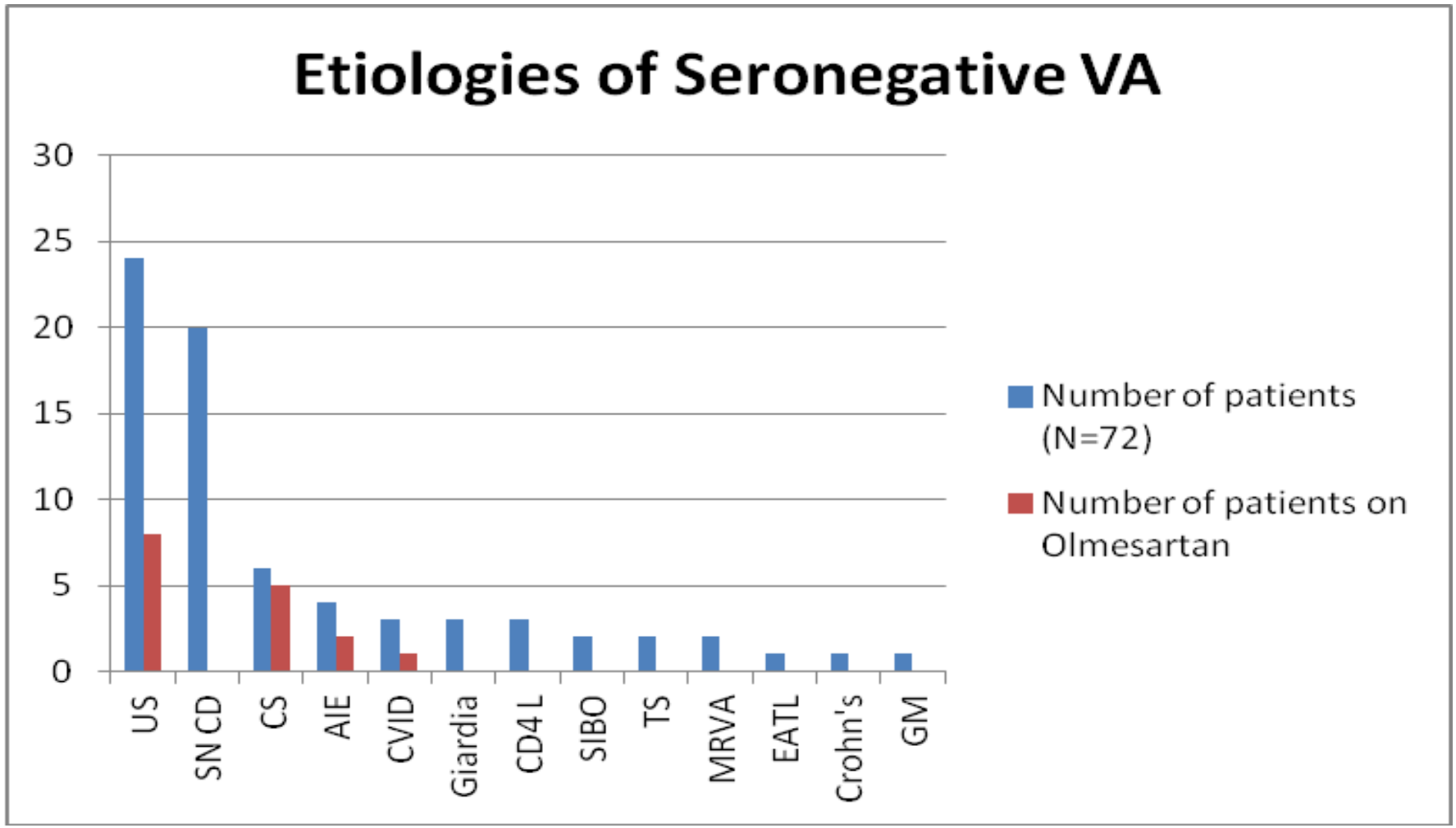
Basile, JM, Hammerle, CW, Crowe, SE. DDW 2011

Study of Non-celiac Enteropathy - Boston

- Reviewed all cases of duodenal villous atrophy
- 30 cases of non-celiac enteropathy (NCE)
  - 24 of these were HLA DQ2/DQ8 negative
  - 26 negative for TTG IgA
  - 10 had no increased IEL
- 21 misdiagnosed as CD, 1 gluten intolerance - no response to a GFD, no biopsy improvement
- Most common diagnosis was “unspecified immune enteropathy “(10)

Pallav, K. Leffler, DA, et al, APT, 35: 380, 2012

10 Year Retrospective Assessment - NYC



DeGaetani, M. et al, Am J Gastroenterol, 108: 647; 2013

Management of Non-Responsive CD

- Confirm the original diagnosis of CD - Review intestinal pathology
- Thoroughly review diet and medications for sources of gluten
- Evaluate and separately treat for lactose intolerance, pancreatic insufficiency, SIBO and microscopic colitis
- Obtain HLA DQ2/8 testing
- Assess for complicated CD (ulcerative, collagenous, strictures, malignancy)
- Determine if clonal IEL (T cells) are present by immunohistochemistry , flow cytometry and/or PCR studies of duodenal biopsies
- Further assess the small bowel with VCE and following that enteroscopy to obtain additional biopsies - study showed value in adults with AIE*

Rubio-Tapia & Murray, Gut, 59: 547; 2010
****Gram-Kampmann EM, et al, BMJ Case Rep. 2015***

ACG Guidelines for Non-Responsive or Refractory CD: Recommendations

1) Patients with NRCD should be evaluated carefully to identify and treat the specific etiology in each patient.*(Strong rec, high level of evidence*)

2) Early steps in the evaluation should include measurement of celiac serologies and a thorough review of the patient's diet by a dietitian who is experienced in CD management.(*Strong recommendation, high level of evidence*)

3) Differentiation should be made between Type I and Type II refractory CD as this is important for management and prognosis. (*Strong rec, moderate level of evidence*)

4) Treatment with medication, as an adjunct to the GFD, should be considered in refractory CD.

(*Conditional recommendation, moderate level of evidence*)

5) Patients with RCD should be monitored closely and receive aggressive nutritional support including parenteral nutrition whenever indicated.

(*Strong recommendation, high level of evidence*)

Rubio-Tapia, A et al,
Am J Gastroenterol, 108; 656; 2013

Refractory Celiac Disease Prognosis

- Poor prognosis – 50% of RCD type II die within 3 to 10 years usually due to:
  - Lymphoma, intractable diarrhea, severe infections
- 5 yr survival rates for RCD II - 40-58%
- Better prognosis for RCD I but higher mortality than uncomplicated CD
- No proven treatment for RCD

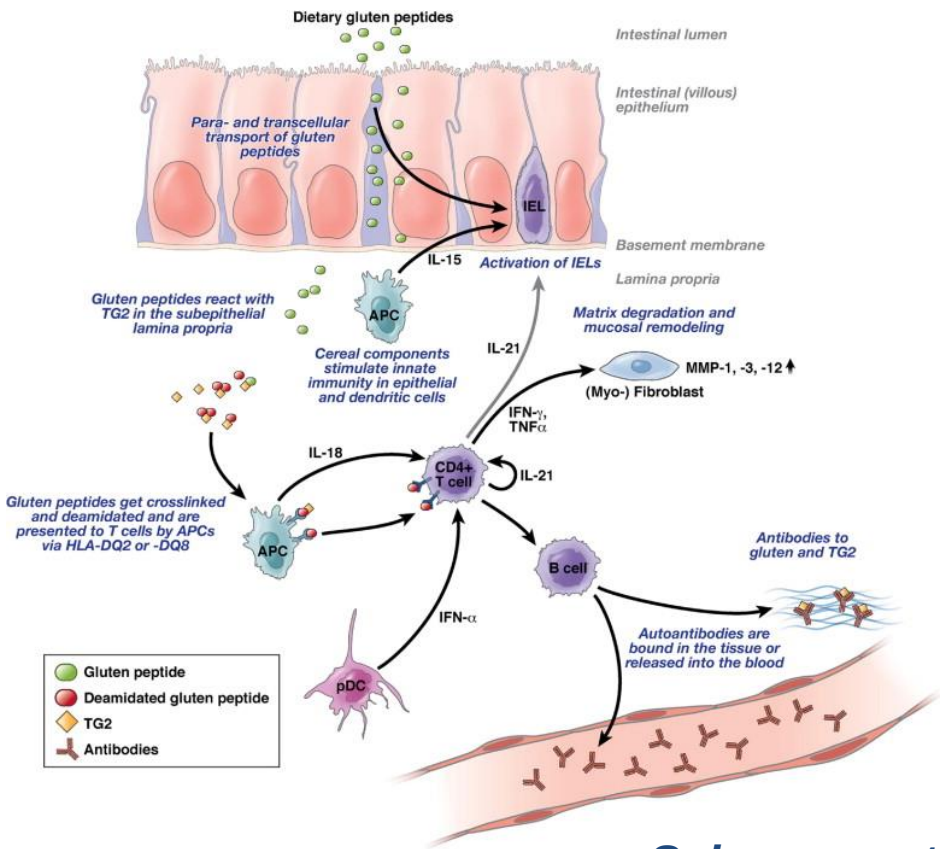
AGA Technical Review, Gastroenterology, 131:1981; 2006
Cellier, c et al Clin Gastro & Hepatol, 4: 1320; 2006

RCD Treatment Options

- Corticosteroids including budesonide
- Immunosuppressives
- Infliximab , other biologics
- Mesalamine
- Hypoallergenic-elemental enteral feeds
- Parenteral nutrition
- Cladribine, alemtuzumab
- Hematopoietic stem cell transplantation
- Anti-IL-15

Rubio-Tapa & Murray, Gut, 59: 547, 2010
Cellier, Clin Gastro & Hepatol, 4: 1320, 2006

Pathogenesis of Refractory CD and EATL



- HLA DQ2 or DQ8 bind/present gluten-derived peptides to T cells
- Increased IL-15 enhances receptor-ligand interaction between IEL and enterocytes leading to enterocyte killing
- Chronic stimulation of T cells leads to clonal expansion of IEL characterized by T cell TCR-γ gene rearrangements

Schuppan et al, Gastroenterology, 137:1912, 2009
Mulder, CJ, Scan J Gastroenterol, 232, S32, 2000
Konig, F, Gastroenterology, 129:1294, 2005

AMG 714: A first-in-class IL15-neutralizing therapeutic antibody

Human IgG1κ anti-human IL15 mAb

Prevents in vitro activities of native and recombinant human IL15

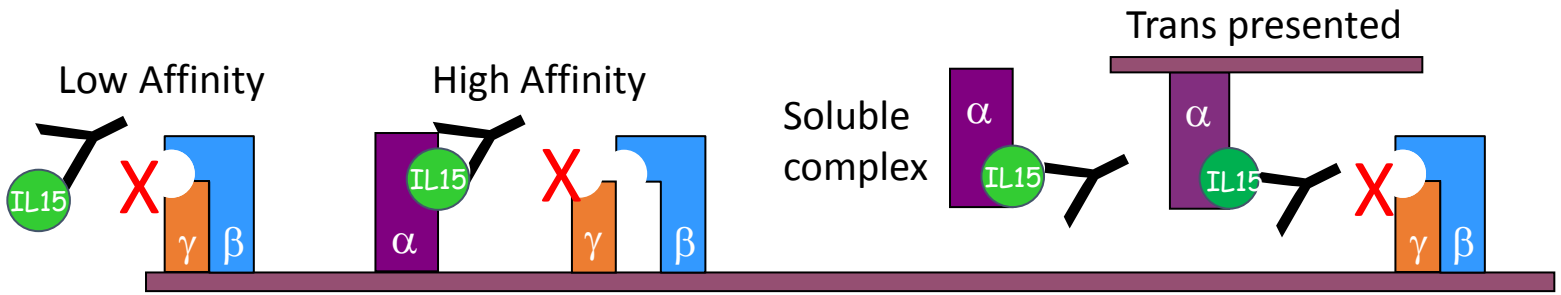
pSTAT5 induction, cytokine/chemokine production, proliferation, activation marker upregulation, etc

Villadsen et al, J. Clin. Invest. 2003 112: 1571
Lebrec et al, J Immunol 2013 191:5551

Hybridoma developed by Genmab as 146B7 and HuMax-IL15

Re-engineered by Amgen for recombinant expression

Inhibits bioactive IL15 in all its forms (cis, trans, soluble receptor-bound)



celimmune

Enteropathy Associated T Cell Lymphoma (EATL)

- Also known as EATCL, enteropathy-type intestinal T cell lymphoma (EITL/EITCL)
- Occurs in setting of enteropathy
- Characterized by IEL T cell TCR-γ gene rearrangements
- Can occur in setting of refractory sprue, ulcerative and collagenous forms

Cellier, C et al, Lancet, 356:203, 2000

Malignant Complications

- Important to note that malignancies are associated with celiac disease are rare cancers in the general population
  - NHL – 0.5-1 per 1,000,000/yr in western populations
  - SB adenoCa – 0.6-0.7 per 100,000/yr
- **The risk of getting lymphoma with celiac disease is that of a plane flying in to your house**

Blumer, I & Crowe, SE et al, Celiac Disease for Dummies, 2010

Take Home Messages

- Ingestion of gluten is the major cause of non-responsive celiac disease (NRCD)
- Also consider lactase deficiency, pancreatic insufficiency, SIBO, microscopic colitis, NSAIDs, Hp
- IBS can coexist with celiac disease
- Always confirm the original diagnosis
- A very small minority of NRCD will be refractory celiac disease (RCD) or celiac disease mimics (other immune-mediated or drug-induced enteropathies)