Endoscopy for celiac disease and related small bowel disorders

Shirley Paski, MD FRCPC
University of Washington/VA Puget Sound

29yo F with fertility issues, multiple miscarriages

- OB/Gyn → TTG IgA >100 → referred to GI
- Hx:
  - Normal growth and development
  - Tendency to constipation, occasional polyethylene glycol
  - Occasional apthous stomatitis
  - No known family history of celiac disease
- Px: healthy, well developed, unremarkable
- Labs: CBC, CMP, vit D, folate, vit B_{12} normal, ferritin 20

Celiac disease presentation

- Classic:
  - chronic diarrhea, weight loss, bloating
- Common:
  - iron deficiency +/- anemia, recurrent abdominal pain, constipation, lactose intolerance, aphthous stomatitis, dental enamel defects, short stature, elevated transaminases, chronic fatigue, arthralgias, reduced bone mineral density, nutrient deficiencies, dermatitis herpetiformis, infertility
- Uncommon:
  - gluten ataxia, celiac crisis, enteropathy associated T-cell lymphoma

Serologic tests for celiac disease

- Highly sensitive and specific serologic tests:
  - Tissue transglutaminase IgA (TTG IgA)
  - Deaminated gliadin peptide IgG (DGP IgG)
  - Endomysial IgA (EMA)
- Screening:
  - TTG IgA + total IgA level or
  - TTG IgA + DGP IgG

Differential of elevated TTG

- Crohns disease
- Diabetes
- Inflammatory arthritis
- Connective tissue disease
- Liver disease (cirrhosis)
- Heart failure
- Down syndrome

Higher TTG, EMA → ↑ mucosal damage

Vecchi et al Scand J Gastroenterol 2003.
Leon et al Scand J Gastroenterol 2001; 36:849-53.
Clemente et al Pediatr Gastroenterol Nutr 2002.
Peracchi et al Am J Gastroenterol 2002.
Spadaro et al Reumatismo 2002; 54:344-50.
Feighery et al Br J Biomed Sci 2003.
Koninckx et al. J Pediatr Gastroenterol Nutr 1984.
Lepore et al Acta Paediatr 1993. Uibo et al Dig Dis Sci 1993

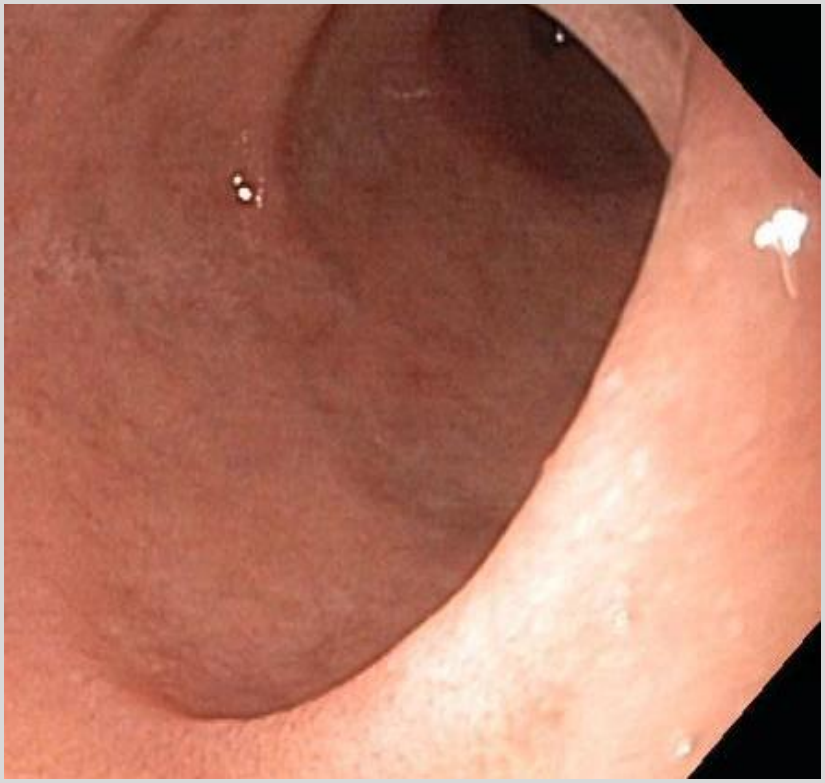
EGD with duodenal biopsy

- ESPGHAN guidelines:
  - Children with classic diarrheal symptoms, HLA DQ2/DQ8 genotype, TTG >10x upper limit of normal, positive EMA can receive secure diagnosis without intestinal biopsy
- Adults:
  - EGD with duodenal biopsy recommended to secure diagnosis in all adults
  - Non-classic presentation more common

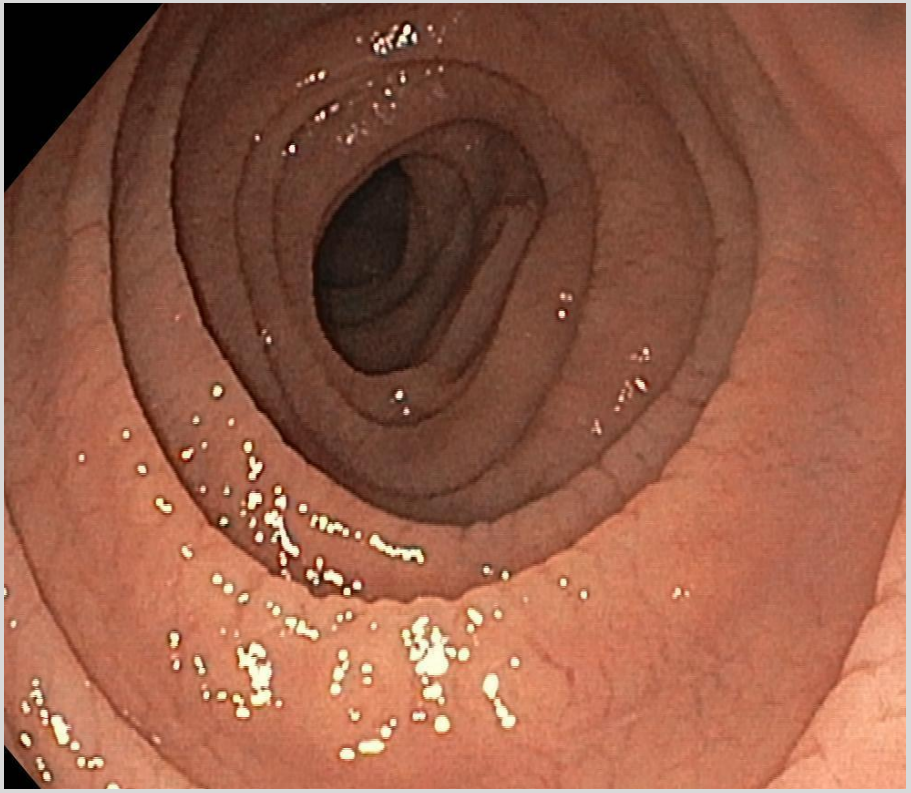
J Pediatr Gastroenterol Nutr 2012;54:136-60
Am J Gastroenterol 2013;108:656-76.

Endoscopic features of celiac disease

Reduced, atrophic folds



Scalloped folds



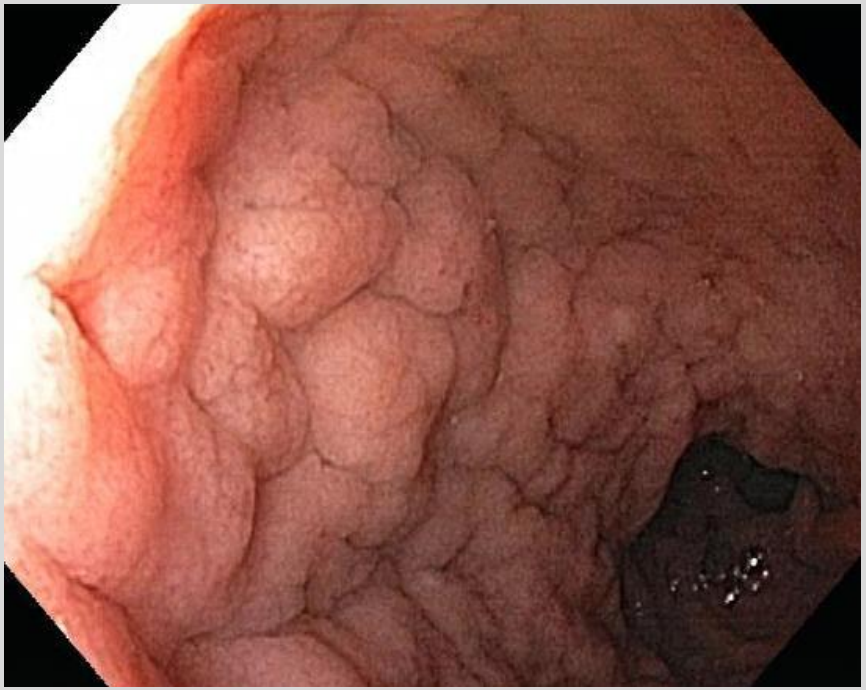
Endoscopic features of celiac disease

Mosaic pattern

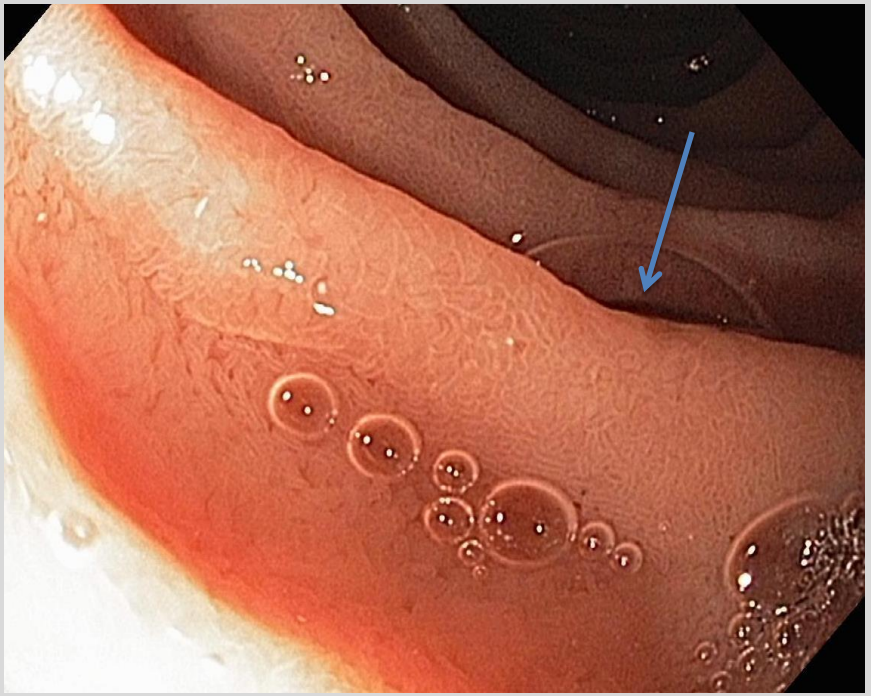
Mosaic pattern

Endoscopic features of celiac disease

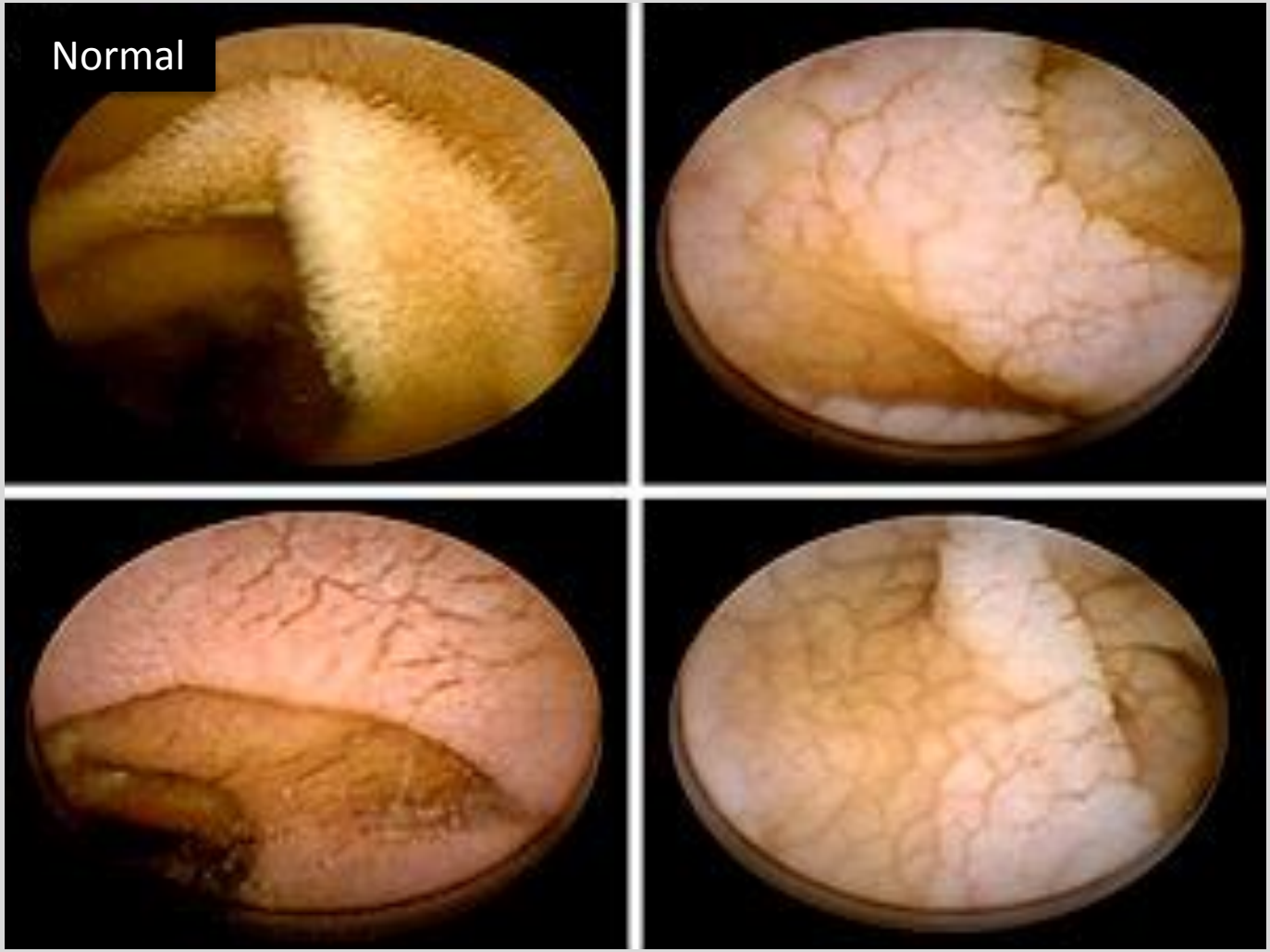
Micronodularity



Patchy loss of villi



Features of villous atrophy on capsule



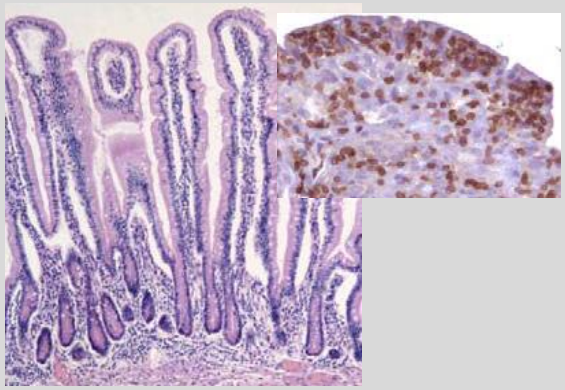
Capsule endoscopy in celiac disease

- Diagnosis:
  - Generally not used for initial diagnosis
    - Sensitivity 89%, specificity 95%
  - Supports diagnosis in patient with positive celiac serology who refuses EGD with biopsy
- Evaluation of celiac disease complications:
  - Extent of mucosal damage
  - Stenosis, erosions, ulcers
  - Suspected lymphoma, adenocarcinoma, ulcerative jejunitis

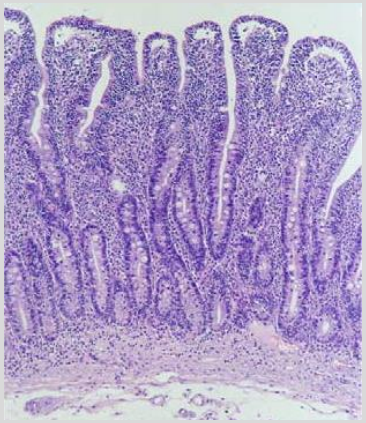
Duodenal biopsies

Marsh 0 Normal

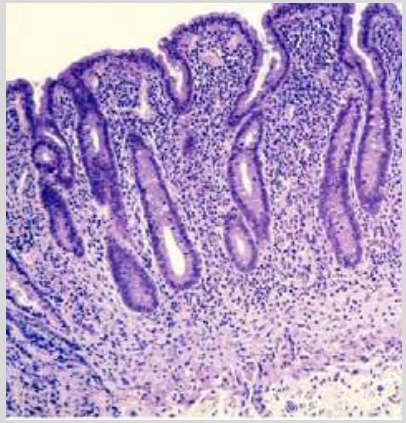
Marsh 1 ↑ IEL



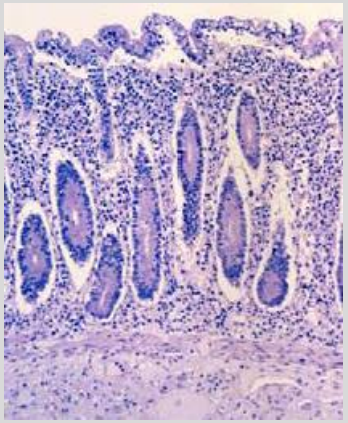
Marsh 2 ↑ IEL,
crypt hyperplasia



Marsh 3a ↑ IEL,
crypt hyperplasia,
partial villous atrophy



Marsh 3b ↑ IEL,
crypt hyperplasia,
subtotal villous atrophy



Marsh 3c ↑ IEL,
crypt hyperplasia,
total villous atrophy

Take minimum of 4 biopsies from D2/D3

Difference in histologic grades within patients with celiac disease

Difference in grade	# patients (n=102)
No difference	77
1 grade difference	16
2 grade difference	6
3 grade difference	3
4 grade difference	0
5 grade difference	0

Frequency of distribution of highest histologic grade

Highest grade lesion	# patients (n=102)
Grade 0	0
Grade 1	8
Grade 2	1
Grade 3a	19
Grade 3b	47
Grade 3c	27

- 2 bx secured celiac diagnosis in 90%
- 4 bx secured celiac diagnosis in 100%

GIE 2008;67:1082-7.
Am J Gastroenterol 2013;108:656-76.

Villous atrophy (VA) may only be in bulb

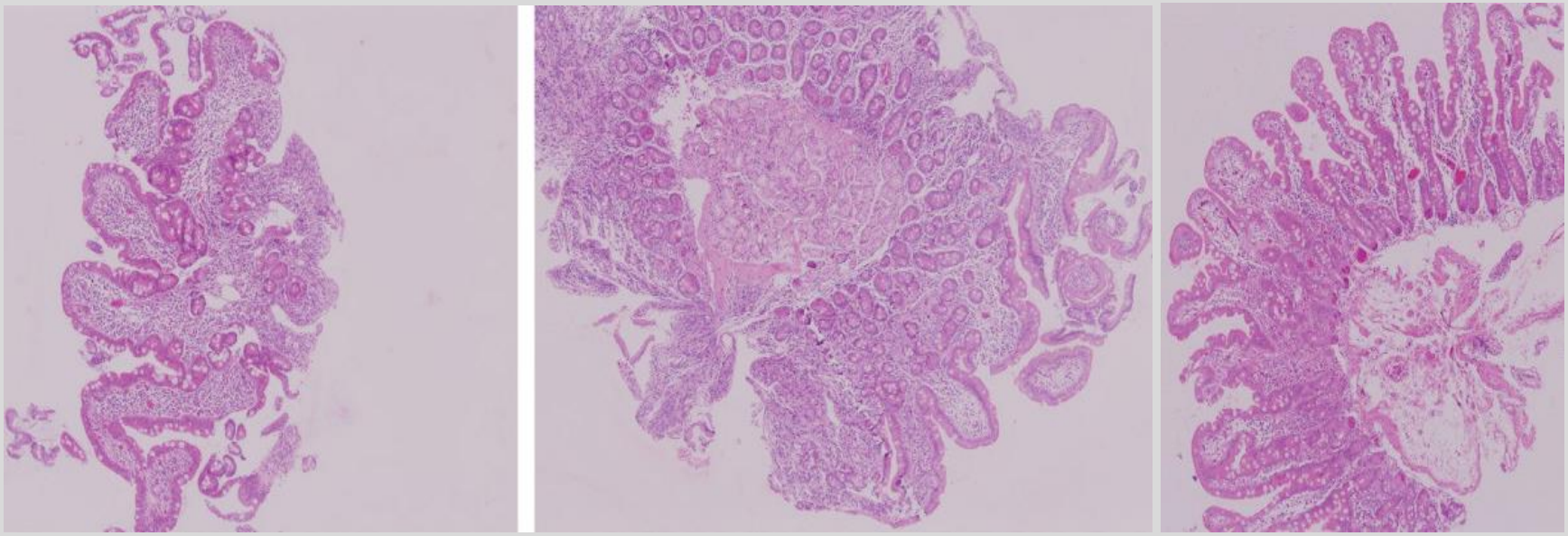
	n	VA in D1	VA in D2	VA in D1 only	VA in D2 only	Variable VA D1 vs D2	Non-uniformity D1 vs D2
New dx	126 (27%)	115 (91%)	108 (86%)	11 (9%)	4 (3%)	6 (5%)	21 (17%)
Established	85 (18%)	33 (39%)	24 (28%)	12 (14%)	2 (2%)	14 (16%)	31 (36%)

- Bulb biopsy increases detection of VA in adult celiac
  - 9% in new diagnosis, 14% in established celiac
- Include biopsy from the duodenal bulb when evaluating for celiac disease

Am J Gastroenterol 2011;106:1837-742.
Am J Gastroenterol 2013;108:656-76.

Histology varies with biopsy orientation

Poor Moderate Good



- Reporting can be variable among pathologists

Celiac disease endoscopy & biopsy guidelines

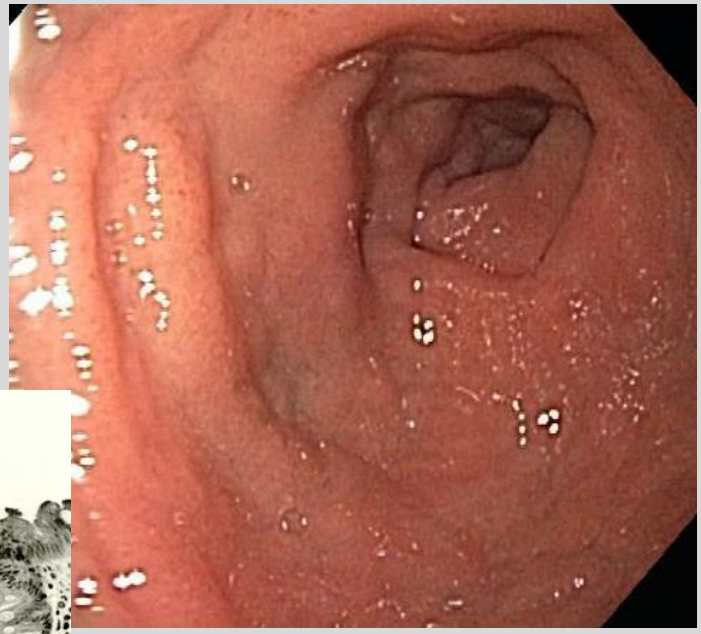
- ACG Guidelines 2013
  - EGD with biopsy is a critical component of diagnostic evaluation and recommended to confirm diagnosis
  - Multiple biopsies (1-2 bulb and ≥4 distal duodenum) recommended
- NASPGHAN 2005
  - Currently recommend small bowel biopsy to confirm diagnosis when TTG is elevated
  - Small bowel biopsy also recommended when clinical suspicion high even with negative serology (esp age <2)

Celiac disease diagnosis

- No single criteria secures diagnosis
  - History – physical exam
  - Serology – endoscopy/histology – HLA genotyping
  - Improvement on a gluten free diet
- Villous atrophy not required
  - Marsh 1/2 with strongly positive TTG/positive EMA ***and*** improvement documented with gluten free diet
  - HLA genotyping helpful here

22yo M with chronic diarrhea and frequent sinusitis & pneumonia

- TTG IgA and DGP IgG negative
- HLA DQ2 positive



Am J Surg Path 2996;20:1240

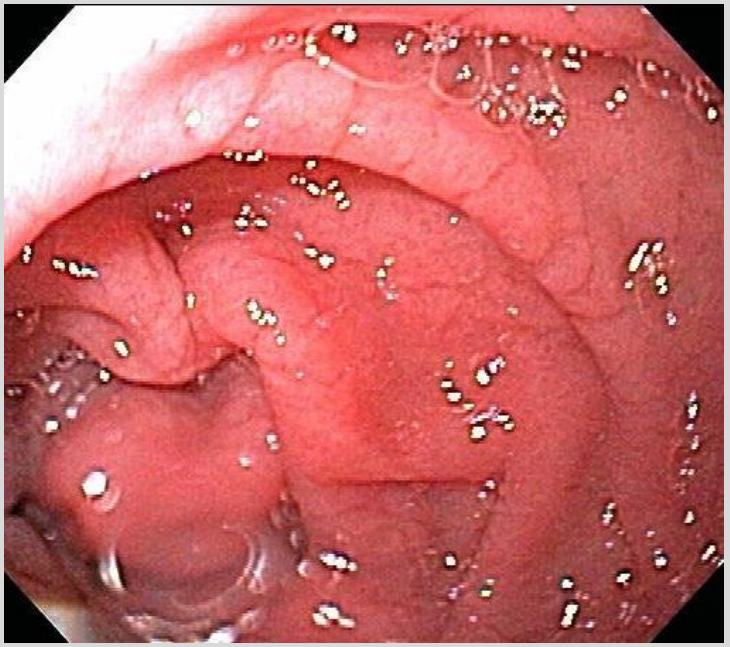
Dx: common variable immunodeficiency

Not all that scallops is celiac

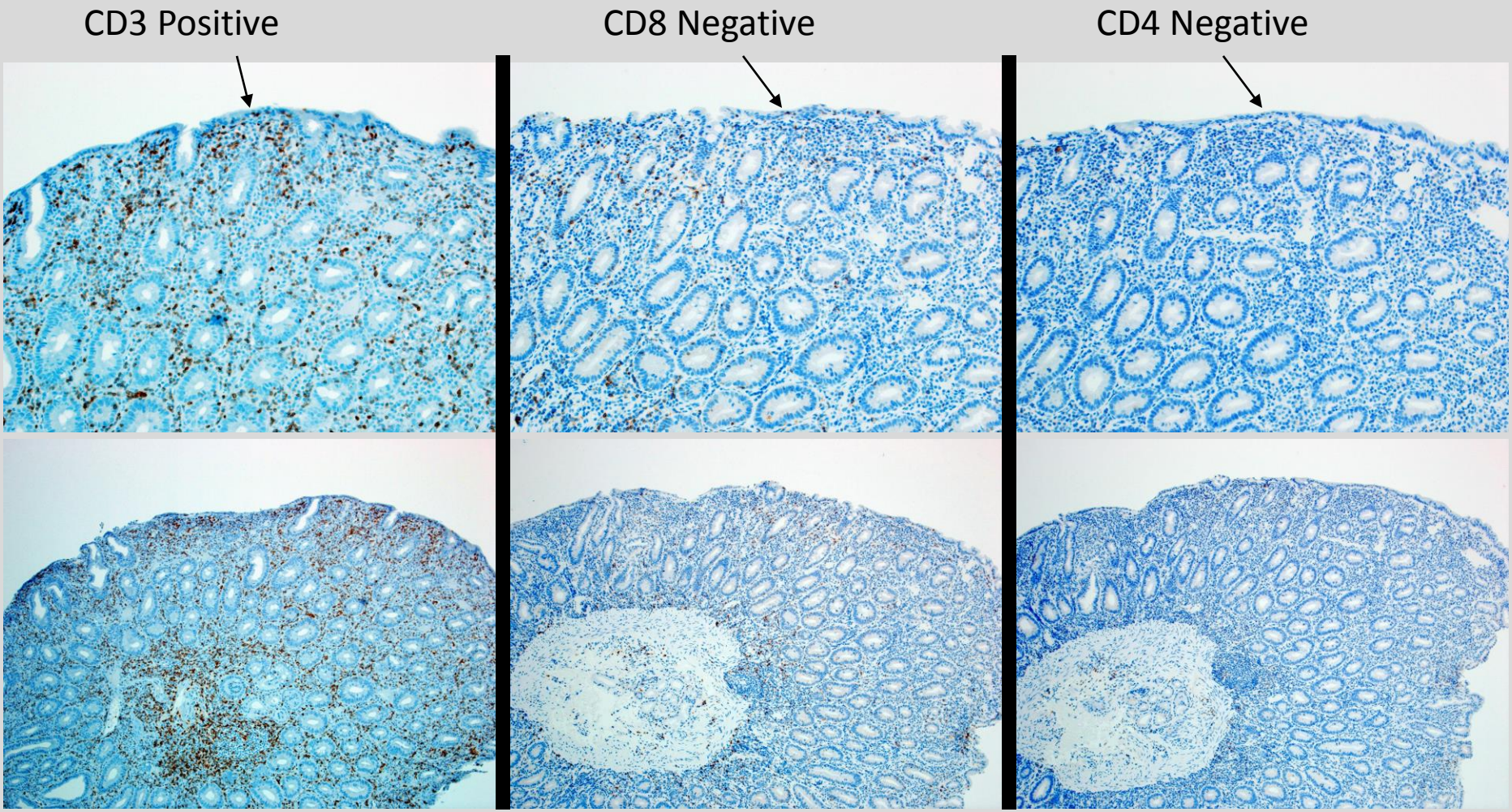
- Drug-associated enteropathy (eg NSAID, olmesartan)
- Autoimmune enteropathy
- Post-viral enteritis
- H. pylori infection
- Eosinophilic gastroenteritis
- Small bowel bacterial overgrowth
- Tropical sprue
- Food allergy
- Intestinal lymphoma
- GVHD
- HIV enteropathy
- Common variable immunodeficiency

73yo M with longstanding celiac disease

- History:
  - Variable adherence to gluten free diet
  - Persistently elevated TTG, DGP
  - Increasing diarrhea, weight loss, fatigue
  - No symptom relief in spite of strict gluten free diet
- Physical exam:
  - Malnourished with muscle wasting, mild edema
- Labs:
  - WBC 3.2, Hgb 8.1, Plt 154
  - Albumin 2.5, Na 134, K 3.4, Mg 1.5, Phos 2.6
  - Multiple micronutrient deficiencies
  - TTG IgA 5, DGP IgG 3



RCD type II

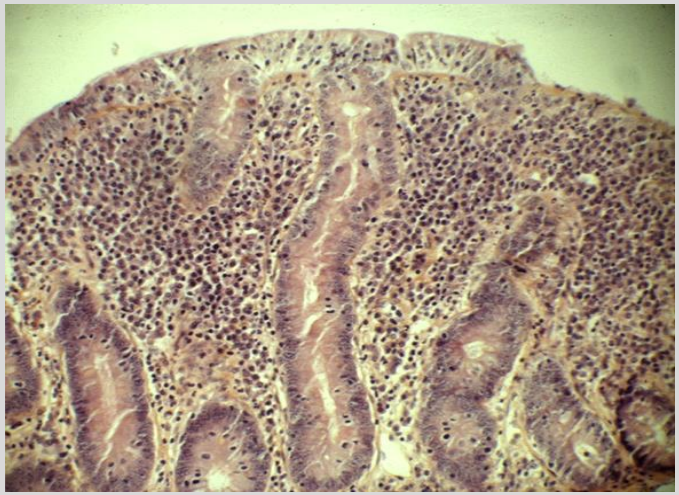


Immunohistochemistry

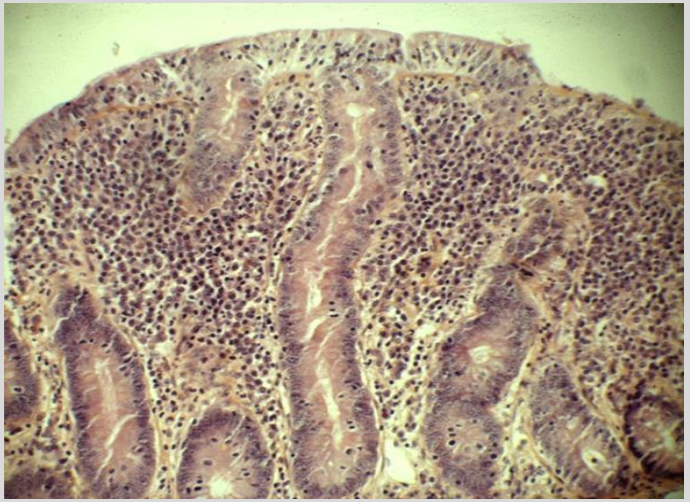
Slide courtesy C Semrad

Refractory celiac disease

- Clinical Definition:
  - Persistent symptoms and inflammation despite a strict gluten-free diet for 1 year
  - Deterioration despite a strict gluten-free diet



Strict
GF diet

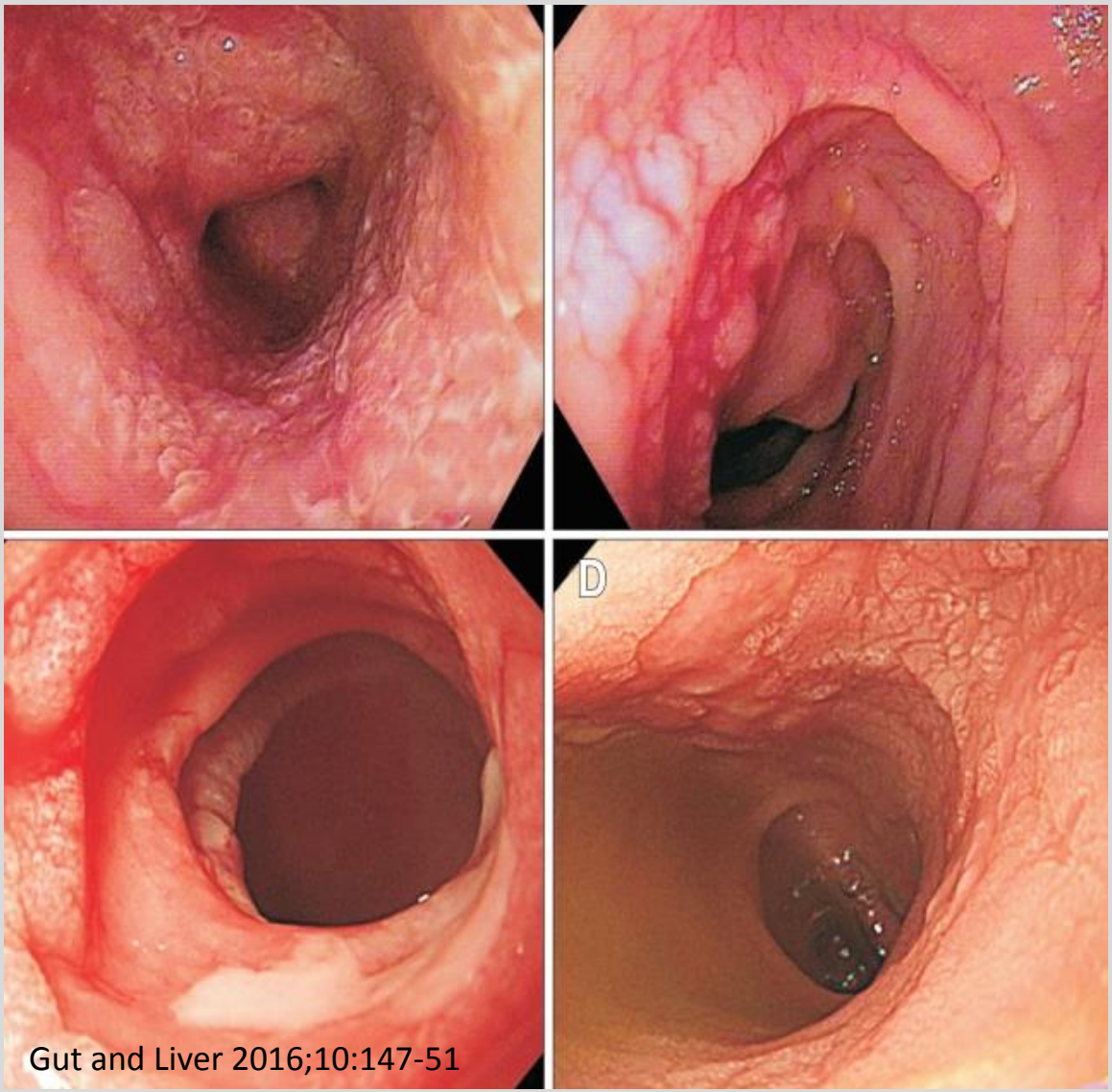


RCD immunologic classification

- **Type I**
  - polyclonal population of IELs
  - most CD3+, CD7+, CD8+, CD103, TCRb
- **Type II**
  - aberrant IELs (most CD3-, CD8-, CD4-)
  - monoclonal population TCRg gene rearrangements
  - ?Early Enteropathy-Associated T-Cell Lymphoma
- Overlap reported in both groups

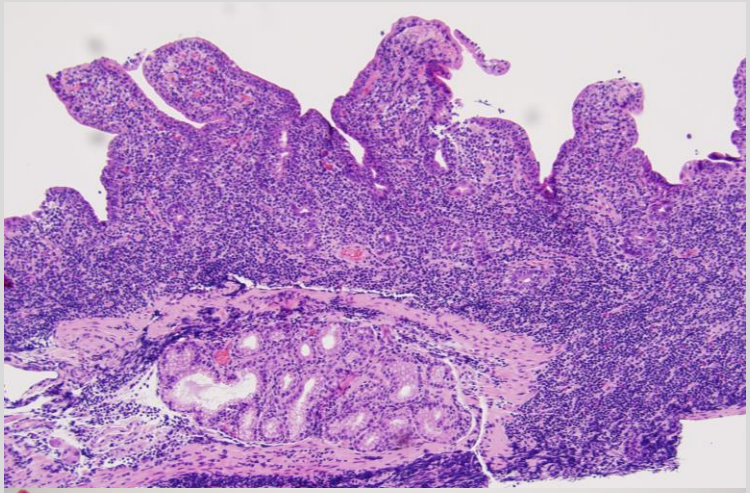
Cellier et al. Lancet 2000;356:203
Goerres et al. Aliment Pharmacol Ther 2003;18:487
Olaussen et al. Clin Gastroenterol Hepatol 2005;3:875

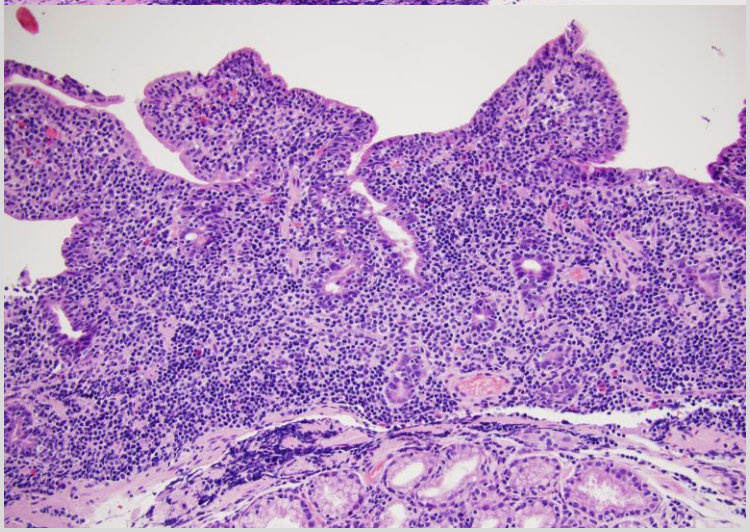
Enteropathy-associated T-cell lymphoma (EATL)

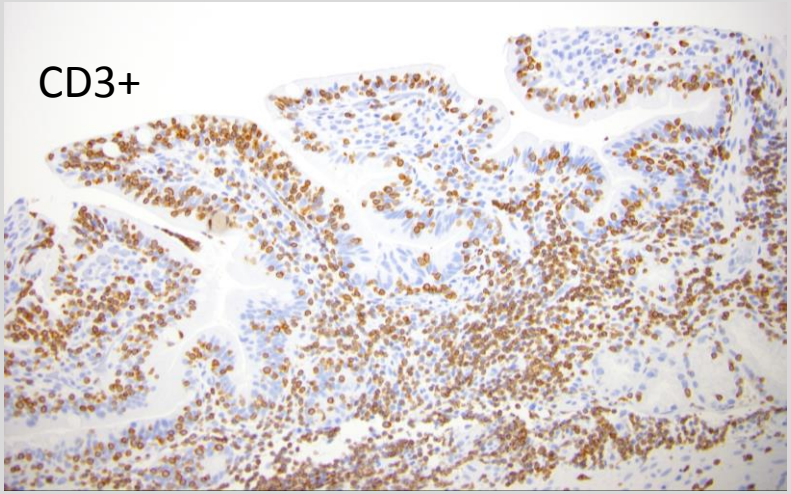


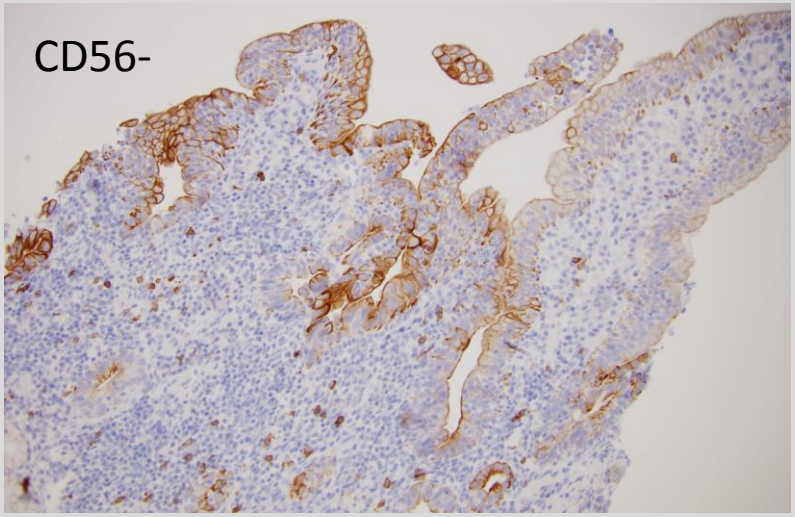
Gut and Liver 2016;10:147-51

Enteropathy-associated T-cell lymphoma (EATL)









Suspected RCD evaluation

- Assess gluten free status: serology, dietitian
- Confirm diagnosis of celiac disease: HLA, serology/biopsy at time of diagnosis
- EGD with biopsies:
  - Histology
    - If no villous atrophy, eval for other causes of nonresponsive celiac like microscopic colitis, SIBO. If villous atrophy, exclude other causes of VA
  - Refractory celiac disease confirmed
    - Flow cytometry (3-4 biopsies, fresh processing), immunohistochemistry, TCR gene rearrangement studies
- Capsule endoscopy & MR/CT enterography
- Deep enteroscopy if needed
- If RCD II, PET-CT to evaluate for EATL

Nat Rev Gastroenterol Hepatol 2015;12:572-79.

Take home points

- Celiac disease has a wide variety of presentations
- Examine the small bowel carefully & obtain adequate biopsies
- Differential dx exists for elevated TTG, villous atrophy- particularly in non-response to a gluten free diet
- Refractory celiac disease and EATL are rare, require additional testing