

# ATROFIA DEI VILLI: SEMPRE CELIACHIA?

**Gino Roberto Corazza**

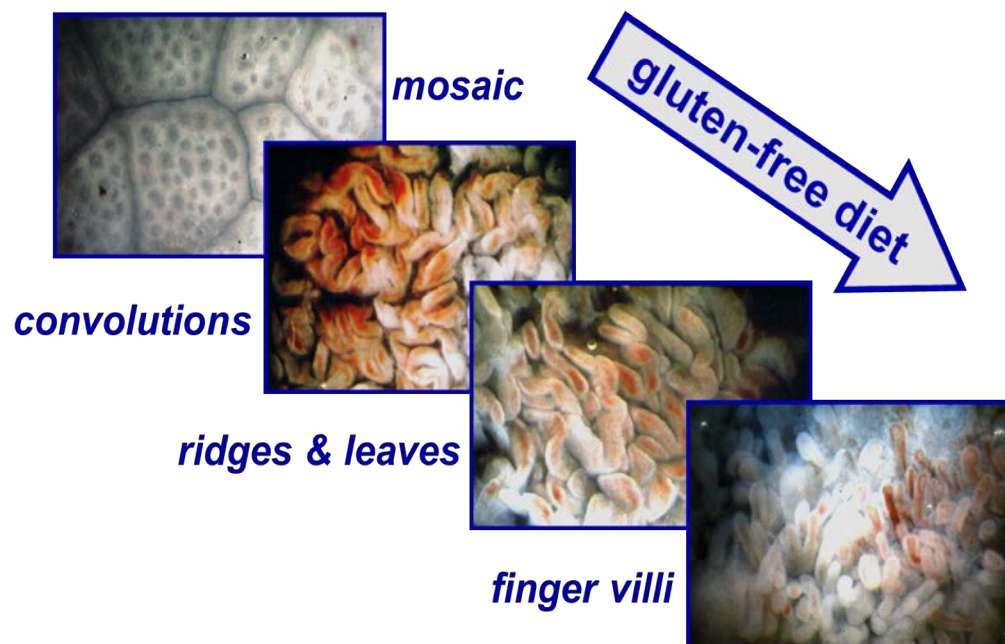
**I Clinica Medica – IRCCS Policlinico San Matteo  
Università di Pavia**



## DEFINITION OF COELIAC DISEASE (CD)

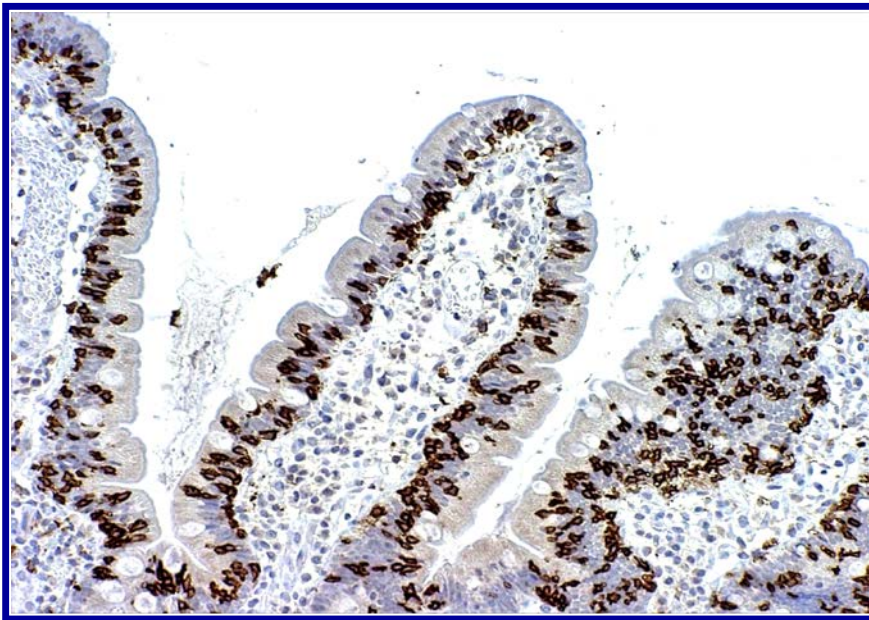
CD is a chronic inflammatory disease characterised by flattened villi on the small bowel mucosa and is induced in genetically susceptible people by the ingestion of proline-rich and glutamine-rich proteins contained in wheat, rye and barley (gluten)

*Lancet 2009*



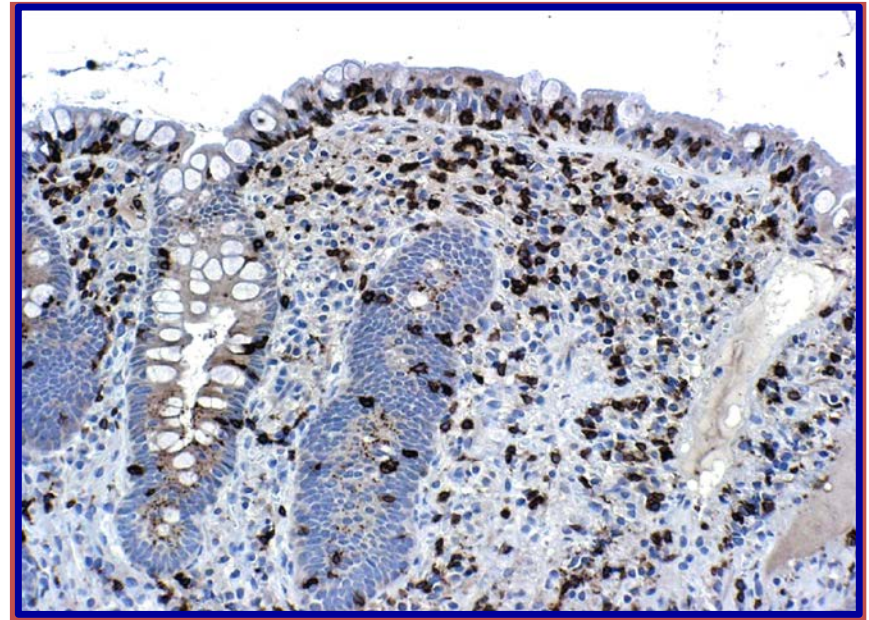
## THE PATHOLOGICAL SPECTRUM OF CD

**M-H type 1**



**C-V type A**

**M-H type 3c**



**C-V type B2**

## DUODENAL LYMPHOCYTOSIS. KEY POINTS TO CONSIDER

1. Do not suggest celiac disease if IELs are not increased. Other histologic features may vary, but increased IELs are invariable.
2. Not everything with increased IELs is celiac disease. Some clues to other conditions:
  - a. Absent or sparse plasma cells: common variable immunodeficiency (CVID)
  - b. Villous atrophy without increased IELs: drug injury, autoimmune enteropathy
  - c. Too many neutrophils: drug injury, autoimmune enteropathy, tropical sprue
  - d. Too many eosinophils: eosinophilic gastroenteritis, drug injury
  - e. Increased subepithelial collagen: collagenous sprue, drug injury
  - f. Absence of Paneth cells and/or goblet cells: autoimmune enteropathy
  - g. Increased apoptosis: autoimmune enteropathy, drug injury, CVID
  - h. Granulomas: CVID, infection, Crohn disease
  - i. Atypical or monotonously regular cells in lamina propria: T-cell lymphoma, systemic mastocytosis

*Smyrk, Surg Pathol 2017*

- other possible causes
  - autoimmune conditions
  - viral enteritis & bacterial overgrowth
  - Hp infection
  - GVHD
  - giardiasis
  - food hypersensitivity
- a common response to a number of noxious and inflammatory signals

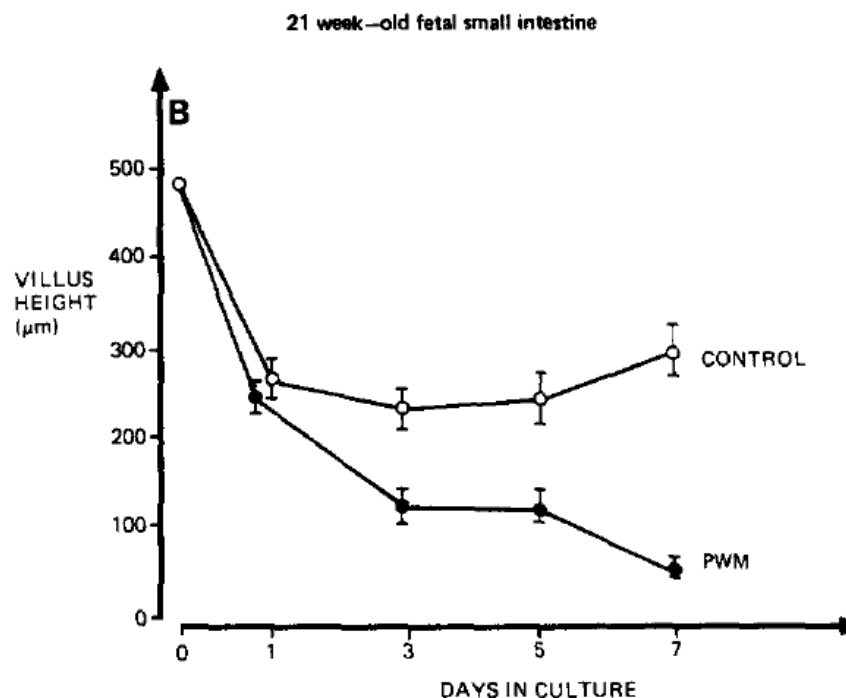
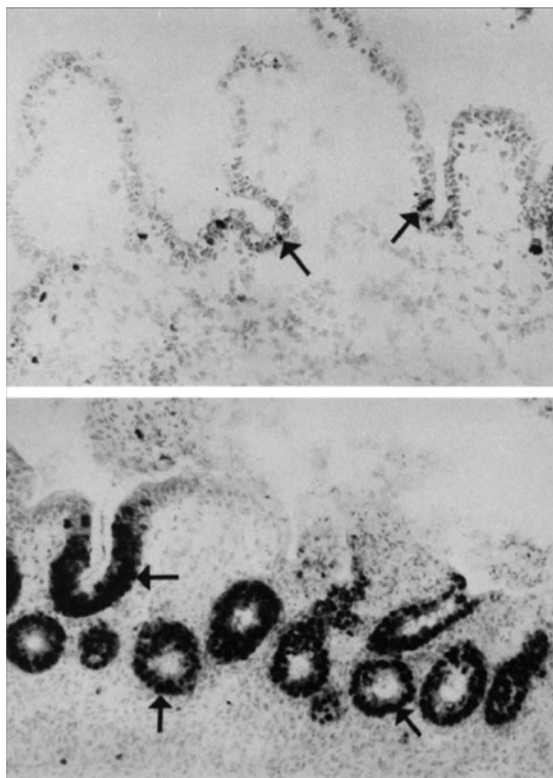
## CAUSES OF FLAT MUCOSA OTHER THAN COELIAC DISEASE

- Autoimmune enteropathy
- Primary immunodeficiency
- Collagenous sprue
- Tropical sprue
- Giardiasis
- Whipple's disease
- HIV enteropathy
- Crohn's disease

- Bacterial overgrowth
- Eosinophilic gastroenteritis
- Cow's milk enteropathy
- Soy protein enteropathy
- Graft-versus-host disease
- Chemotherapy
- Radiation damage
- Protein energy malnutrition

*Lancet 2009*

## PWM-INDUCED MUCOSAL T-CELL ACTIVATION AS A CAUSE OF VILLOUS ATROPHY IN FETAL HUMAN SMALL INTESTINE



MacDonald & Spencer, *J Exp Med* 1988

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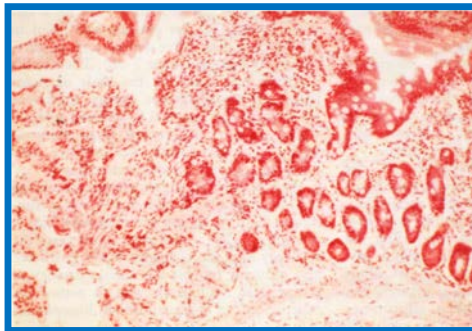
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*Lancet 2009*

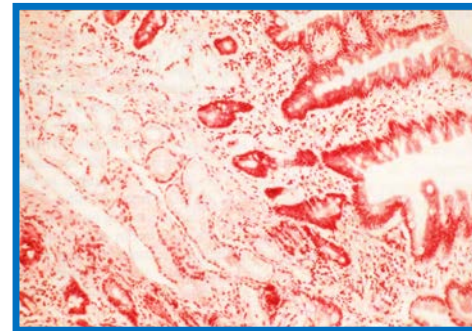
## PITFALLS IN DIAGNOSING RCD

Six patients referred with a diagnosis of refractory CD

**Tangential artifact**



**Proper orientation**



**Subtotal villous atrophy**

**Normal mucosa**

**Failure to respond to a GFD should always  
raise doubt regarding the initial diagnosis**

Shidrawi et al, *J Clin Pathol* 1994

## "FALSE" REFRACTORY CD

- concurrent conditions
  - IBS
  - Microscopic Colitis
  - Bacterial Overgrowth
  - Lactase Deficiency
  - Pancreatic Insufficiency
- dietary non-compliance or inadvertent gluten intake
- slow histological recovery after diet
- misinterpretation of the original biopsy
  - *poor sample quality*
  - *non-coeliac flat mucosa*

## UNCLASSIFIED SPRUE PATIENTS

|                                   | Patient 1              | Patient 2              |
|-----------------------------------|------------------------|------------------------|
| Gender                            | Male                   | Female                 |
| Age, yrs                          | 43                     | 39                     |
| Symptoms                          | Diarrhoea, weight loss | Diarrhoea, weight loss |
| HLA-DQ2/DQ8                       | Negative               | Negative               |
| EMA IgA                           | Negative               | Negative               |
| TTA IgA (U/ml)                    | 1.2                    | 0.8                    |
| Total IgA (mg/dl)                 | 134                    | 156                    |
| Duodenal histology                | Villous atrophy (B2)   | Villous atrophy (B2)   |
| Aberrant IELs                     | Absent                 | Absent                 |
| Lamina propria B cells            | Rare                   | Very rare              |
| TCR-γ gene rearrangement          | Polyclonal             | Polyclonal             |
| Hb (g/dl)                         | 14.6                   | 10.8                   |
| Faecal calprotectin (mg/kg)       | 47                     | 34                     |
| Family history of coeliac disease | None                   | None                   |
| Treatment                         | Azathioprine           | Budesonide             |

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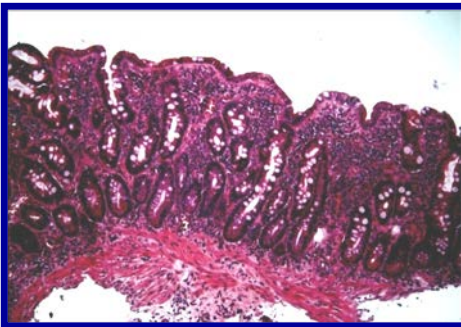
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- Protein energy malnutrition

*Lancet 2009*

## A 56 yr-old PHISYCIAN WITH BLOOD HYPERTENSION & TYPE 2 DIABETES

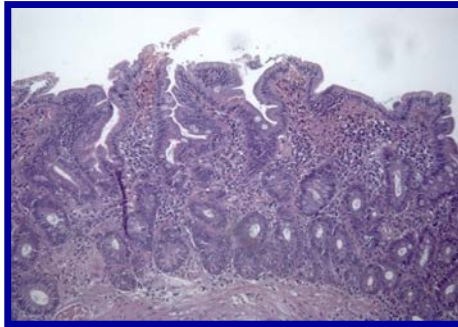
### 2011

- diarrhoea (10mov/d)
- weight loss (10kg/3mo)
- ve<sup>+</sup> coeliac ABs
- BX complete villous atrophy



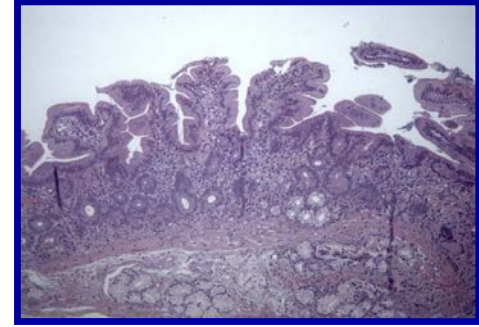
### 2012

- RCD I diagnosis
- steroids added to GFD
- only mild clinical improvement
- BX partial villous atrophy



### 2013

- olmesartan withdrawal
- BX villous regrowth
- symptom resolution
- marked weight gain



## HISTOLOGIC FINDINGS IN 22 PTS WITH SPRUE-LIKE ENTEROPATHY ASSOCIATED WITH OLMESARTAN

**AUGUST 2012**

**Severe Spruelike Enteropathy Associated With Olmesartan**

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

**Abstract**

**Objective:** To report the response to discontinuation of olmesartan, an angiotensin II receptor antagonist commonly associated with enteropathy, in patients with suspected severe spruelike enteropathy.

**Patients and Methods:** All 22 patients included in this report were seen at Mayo Clinic in Rochester, Minnesota, between August 1, 2008, and August 1, 2011, for evaluation of unexplained chronic diarrhea and enteropathy while taking olmesartan. Colonic disease was ruled out in all cases. To be included in the study, the patients also had to have clinical improvement after suspension of olmesartan.

**Results:** The 22 patients (13 women) had a median age of 69.5 years (range, 45-81 years). Most patients were taking 40 mg/d of olmesartan (range, 10-40 mg/d). The clinical presentation was of chronic diarrhea and weight loss (median, 11 kg; range, 2.5-57 kg), which required hospitalization in 14 patients (64%). Intestinal biopsies showed both villous atrophy and variable degrees of mucosal inflammation in 19 patients, and marked subepithelial collagen deposition (collagenous spruel) in 7. Tissue transglutaminase antibodies were not detected. A gluten-free diet was not helpful. Collagenous or lymphocytic gastritis was documented in 7 patients, and microscopic colitis was documented in 5 patients. Clinical response, with a mean weight gain of 12.2 kg, was documented in all cases. Histologic recovery or improvement of the histologic short discontinuation of olmesartan was confirmed in all 18 patients who underwent follow-up biopsies.

**Conclusions:** Olmesartan may be associated with a severe form of spruelike enteropathy. Clinical response and histologic recovery are expected after suspension of the drug.

© 2012 Mayo Foundation for Medical Education and Research • Mayo Clin Proc. 87(8):950-958

| Patient No. | Villous atrophy | IELs (/100 epithelial cells) <sup>b</sup> | Baseline duodenal biopsy results |                         |                                   | Outcome follow-up duodenal biopsy results  | Time d <sup>d</sup> | Other GI findings <sup>e</sup>                                              |                             |
|-------------|-----------------|-------------------------------------------|----------------------------------|-------------------------|-----------------------------------|--------------------------------------------|---------------------|-----------------------------------------------------------------------------|-----------------------------|
|             |                 |                                           | Acute/active inflammation        | Thickened collagen band | Aberrant cells/clone <sup>c</sup> |                                            |                     | Gastric                                                                     | Colorectal                  |
| 1           | Total           | Normal                                    | Yes                              | No                      | No/No                             | Normal                                     | 404                 | Lymphocytic gastritis (I-HP negative, immunostain)                          | Collagenous colitis         |
| 2           | Total           | 80-100                                    | Yes                              | Yes                     | No/NA                             | Improvement, focal partial villous atrophy | 54                  | Chronic gastritis (I-HP negative, immunostain)                              | Normal                      |
|             | Total           | Normal                                    | Yes                              | No                      | No/No                             | Normal                                     | 231                 | NA                                                                          | Collagenous colitis         |
|             | Total           | 40                                        | Yes                              | Yes                     | No/No                             | Normal                                     | 263                 | Collagenous gastritis                                                       | NA                          |
|             | Total           | >100                                      | Yes                              | No                      | NA/NA                             | Normal                                     | 54                  | NA                                                                          | Normal                      |
|             | Partial         | 60                                        | Yes                              | No                      | NA/NA                             | NA                                         | NA                  | NA                                                                          | NA                          |
|             | Partial         | >100                                      | No                               | No                      | No/No                             | Normal                                     | 159                 | NA                                                                          | Normal                      |
|             | Total           | 40-60                                     | Yes                              | No                      | NA/NA                             | Normal                                     | 143                 | Lymphocytic gastritis (I-HP negative, immunostain)                          | Normal                      |
|             | Total           | 60-80                                     | Yes                              | No                      | No/No                             | Normal                                     | 188                 | NA                                                                          | NA                          |
|             | Partial         | Normal                                    | No                               | No                      | No/No                             | Normal                                     | 404                 | NA                                                                          | NA                          |
|             | Partial         | 50                                        | Yes                              | No                      | No/No                             | NA                                         | NA                  | Mild lymphocytic gastritis (I-HP negative, immunostain)                     | NA                          |
|             | Partial         | Normal                                    | Yes                              | No                      | No/No                             | Normal, focal active duodenitis            | 116                 | Mild active chronic gastritis (I-HP negative, immunostain)                  | Mild active chronic colitis |
|             | Total           | 40                                        | Yes                              | Yes                     | NA/NA                             | Normal                                     | 171                 | Active chronic gastritis (I-HP negative, immunostain)                       | NA                          |
|             | Partial         | 60-80                                     | No                               | No                      | NA/NA                             | Normal                                     | 240                 | Mild active chronic gastritis (I-HP negative, immunostain)                  | NA                          |
|             | Total           | Normal                                    | No                               | Yes                     | NA/NA                             | Normal                                     | 181                 | Mild chronic gastritis (I-HP negative, no immunostain)                      | Normal                      |
|             | Total           | Normal                                    | No                               | Yes                     | No/No                             | Normal                                     | 607                 | Collagenous gastritis                                                       | Collagenous colitis         |
|             | Total           | 40-60                                     | Yes                              | Yes                     | No/No                             | NA                                         | NA                  | Mild chronic gastritis (I-HP negative, no immunostain)                      | Focal acute colitis         |
| 18          | Partial         | Normal                                    | No (marked eosinophilia)         | No                      | NA/NA                             | NA                                         | NA                  | NA                                                                          | NA                          |
| 19          | Total           | 30                                        | Yes                              | No                      | NA/NA                             | Normal                                     | 76                  | Severe active chronic gastritis and ulceration (I-HP negative, immunostain) | NA                          |
| 20          | Total           | Normal                                    | No                               | Yes                     | No/No                             | Normal                                     | 707                 | Lymphocytic gastritis (I-HP positive)                                       | Lymphocytic colitis         |
| 21          | Total           | 80-100                                    | Yes                              | No                      | NA/NA                             | Normal                                     | 179                 | NA                                                                          | Lymphocytic colitis         |
| 22          | Total           | 80                                        | Yes                              | No                      | NA/NA                             | Normal                                     | 184                 | Lymphocytic gastritis (I-HP negative, immunostain)                          | Normal                      |

<sup>a</sup>I-HP = *Helicobacter pylori*; IELs = intraepithelial lymphocytes; NA = not available.

<sup>b</sup>Normal, <25/100 epithelial cells.

<sup>c</sup>Aberrant cells defined by >50% CD3<sup>+</sup>/CD8<sup>+</sup> IELs on immunostaining; clone defined by T-cell receptor gene clonal rearrangement by polymerase chain reaction.

<sup>d</sup>Time from suspension of olmesartan to follow-up biopsy.

<sup>e</sup>Any time before suspension of olmesartan.

## OLMESARTAN SPRUE-LIKE ENTEROPATHY. PATHOLOGIC & CLINICAL SPECTRUM

| Entity                 | Histopathologic features                                                                                                          | Distinguishing features of ARB-enteropathy                                                                      |
|------------------------|-----------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Celiac disease         | Intraepithelial lymphocytosis<br>Crypt hyperplasia<br>Villous atrophy                                                             | IEL sometimes within, or close to, normal limits<br>Collagen deposition frequent                                |
| Tropical sprue         | Intraepithelial lymphocytosis, often worse in terminal ileum than duodenum<br>Often preserved architecture                        | Villi often flat<br>IEL sometimes within, or close to, normal limits<br>Collagen deposition frequent            |
| Autoimmune enteropathy | Variable features—villous atrophy, possible intraepithelial lymphocytosis, loss of goblet cells, loss of Paneth cells             | No known histopathologic distinguishing features                                                                |
| Crohn disease          | Patchy active inflammation<br>Intraepithelial lymphocytosis<br>Granulomas<br>Variable architectural distortion                    | Granulomas not characteristic<br>Diffuse involvement<br>Collagen deposition frequent                            |
| Mycophenolate toxicity | Typically shows only increased crypt apoptosis; however, some cases may show intraepithelial lymphocytosis and/or villous atrophy | More diffuse and severe villous atrophy<br>More chronic and active inflammation<br>Collagen deposition frequent |

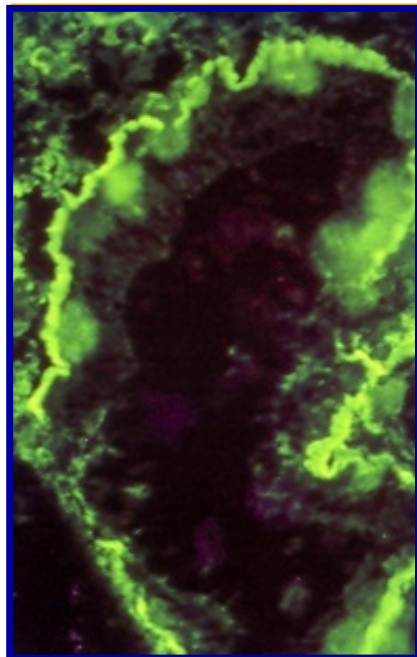
Burbure et al, *Human Pathol* 2016

- in a nationwide cohort study, olmesartan exposure is associated with an increased risk of hospitalisation for intestinal malabsorption and CD
- relative risk increases with treatment duration
- no such risk exists for other ARBs (??)

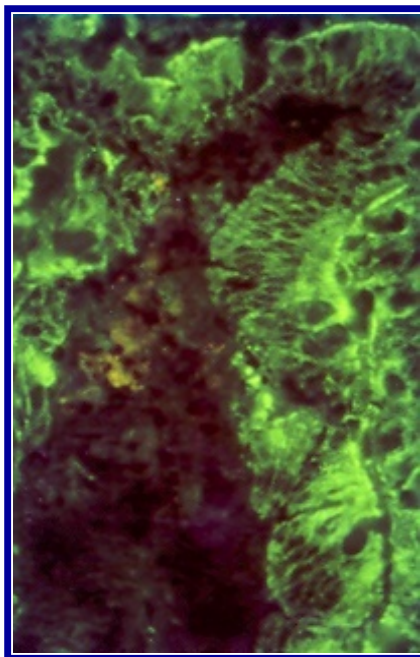
Basson et al, *Gut* 2015

## AUTOIMMUNE ENTEROPATHY IN ADULTS

**Case 1**



**Case 2**



*Lancet 1997*

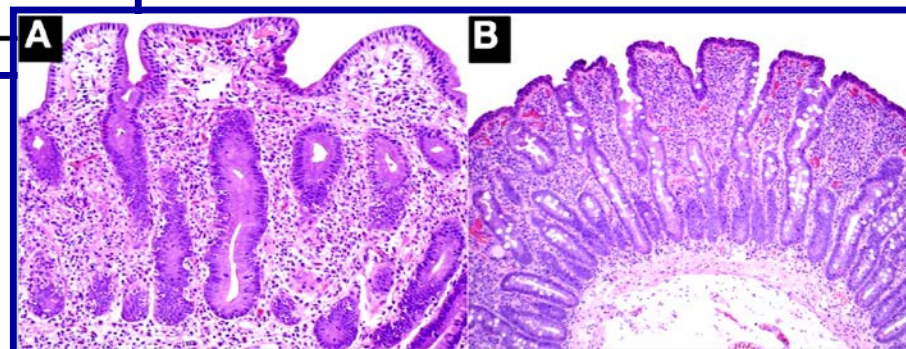
**Mayo Clinic Series**

- May 2001- June 2006
- 15 pts (47% Fe, age 55 yr)
- 15/15 severe malabsorbers
- 13/14 E/GoAb<sup>+</sup>
- 80% associated AI
- 60% clinical improvement after immunosuppressants

*Clin Gastroenterol Hepatol 2007*

## HISTOLOGIC FEATURES OF ADULT AUTOIMMUNE ENTEROPATHY COMPARED WITH RCD

|                                                                  | AIE<br>(n = 30) | RCD type I<br>(n = 42) | P<br>value |
|------------------------------------------------------------------|-----------------|------------------------|------------|
| Villous atrophy, n (%)                                           |                 |                        | .388       |
| Complete                                                         | 13 (43)         | 14 (33)                |            |
| Partial                                                          | 17 (57)         | 28 (67)                |            |
| Intraepithelial lymphocytes<br>(>40/100 epithelial cells), n (%) | 15 (50)         | 38 (91)                | <.001      |
| Colon involvement, <sup>a</sup> n (%)                            | 11/20 (55)      | 5/23 (22)              | .014       |



Sharma et al, *Clin Gastroenterol Hepatol* 2018

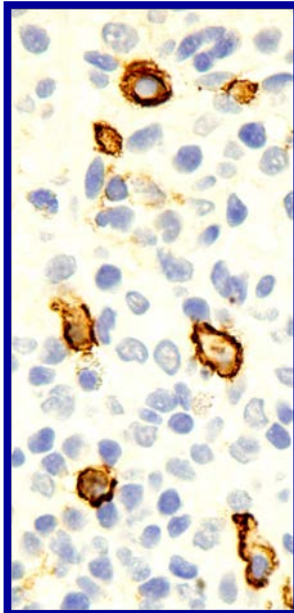
## FLAT DUODENAL MUCOSA IN PATIENTS WITH CVID

| <i>Pts.</i> | <i>Sex</i> | <i>Age (yrs)</i> | <i>Histological<br/>response to a GFD</i> | <i>Positive coeliac<br/>antibodies</i> | <i>HLA</i>         |
|-------------|------------|------------------|-------------------------------------------|----------------------------------------|--------------------|
| 1           | M          | 47               | Yes                                       | EMA IgG                                | DQ2 <sup>+</sup>   |
| 2           | F          | 27               | Yes                                       | EMA IgA-IgG                            | DQ2 <sup>+</sup>   |
| 3           | M          | 42               | Yes                                       | EMA IgG                                | DQ8 <sup>+</sup>   |
| 4           | M          | 28               | No                                        | EMA IgG                                | DQ2/8 <sup>-</sup> |
| 5           | M          | 46               | No                                        | None                                   | DQ2/8 <sup>-</sup> |
| 6           | M          | 35               | No                                        | None                                   | DQ2/8 <sup>-</sup> |
| 7           | M          | 53               | No                                        | None                                   | DQ2 <sup>+</sup>   |
| 8           | M          | 46 <sup>+</sup>  | No                                        | EMA IgG                                | DQ2 <sup>+</sup>   |
| 9           | M          | 44               | No                                        | EMA IgG                                | DQ2 <sup>+</sup>   |
| 10          | F          | 59               | No                                        | None                                   | DQ8 <sup>+</sup>   |
| 11          | F          | 52               | No                                        | None                                   | DQ2 <sup>+</sup>   |

*Am J Clin Pathol 2012*

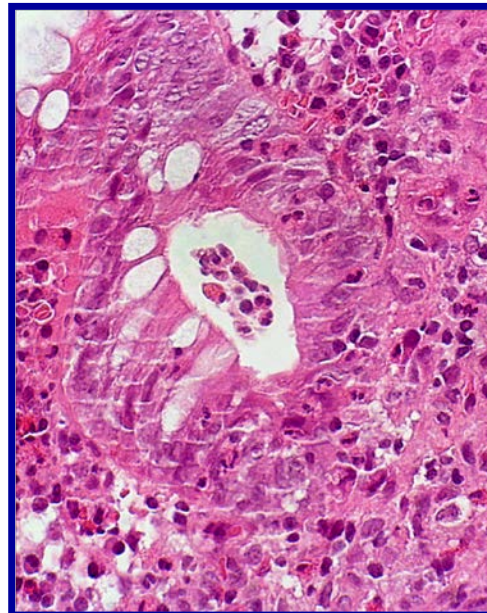
## DUODENAL MUCOSA IN PATIENTS WITH CVID

**PC DEPLETION**



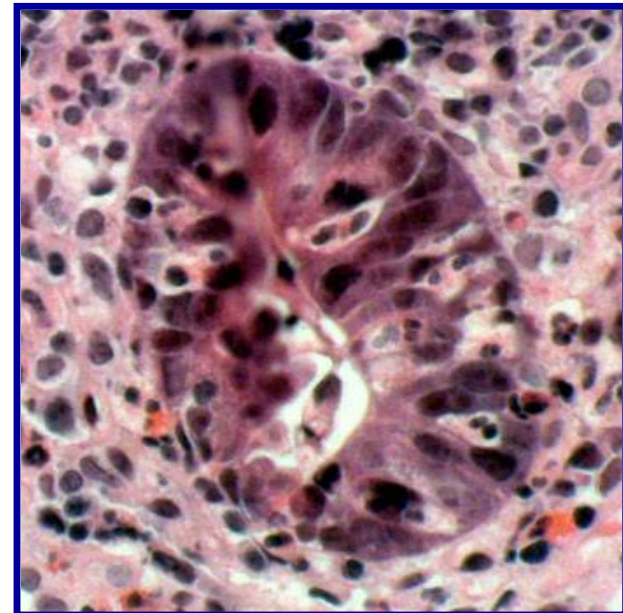
10/11

**PMN INFILTRATE**



5/10

**GVHD-like LESIONS**

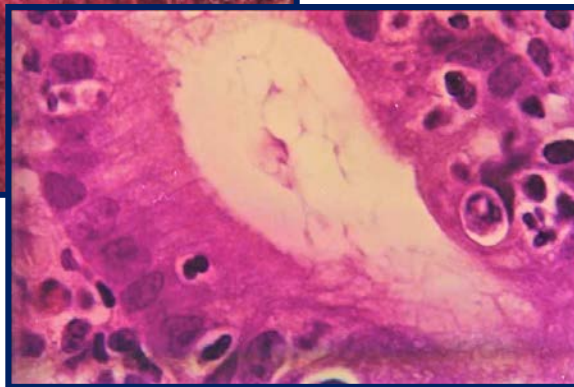
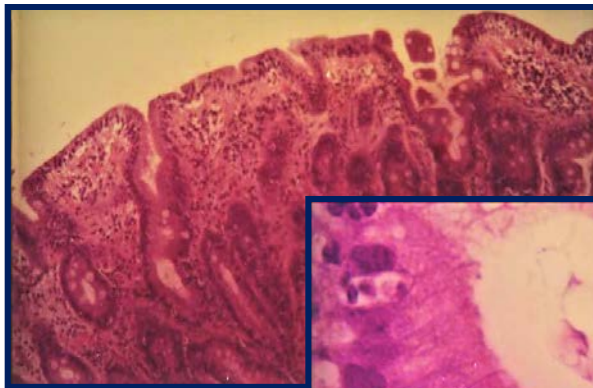


3/5

only in pts in whom CD not confirmed (#4-11)

*Am J Clin Pathol 2012*

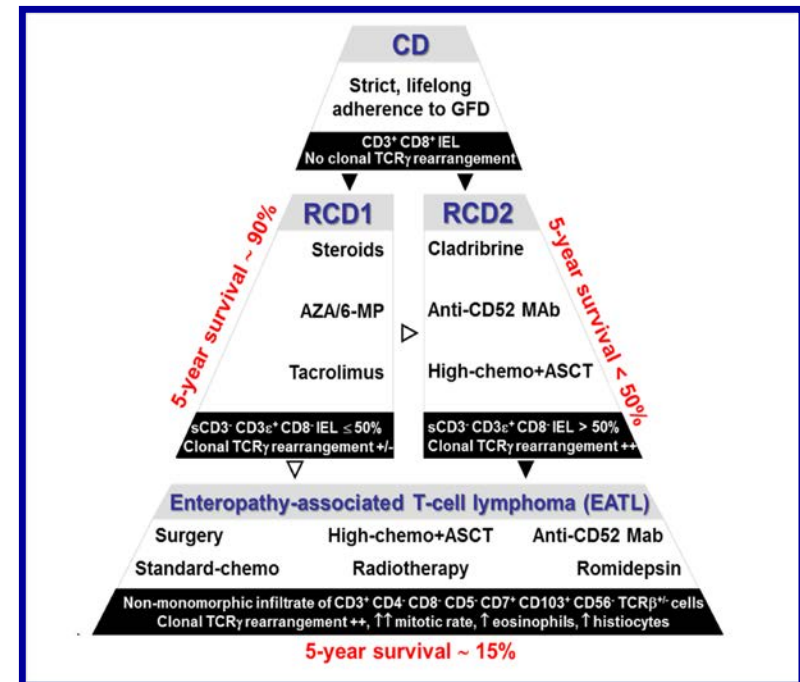
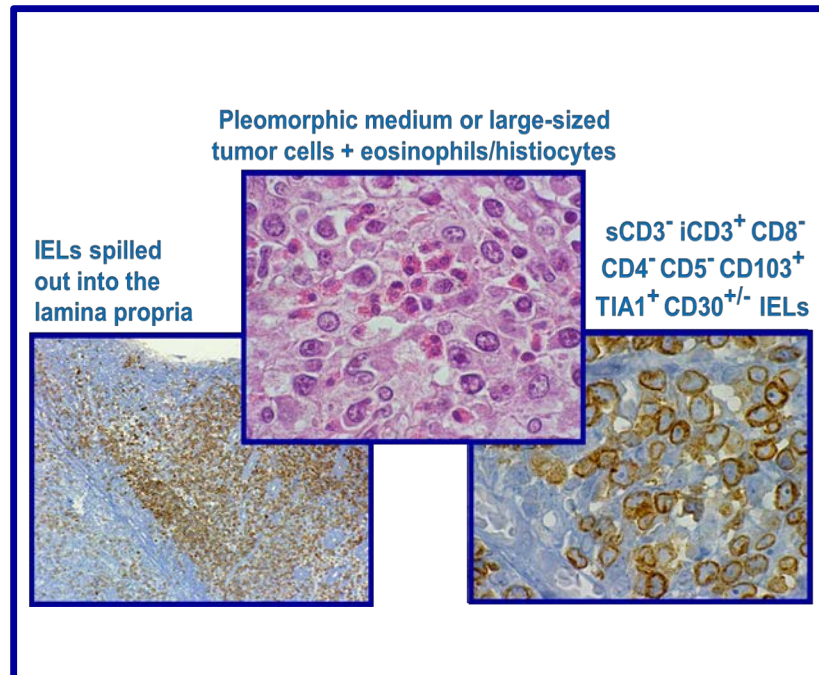
## A 31-YR OLD MAN WITH NEGATIVE SEROLOGY & MALABSORPTION SYMPTOMS: THE SPRUE-LIKE VARIANT OF GIARDIASIS



Metronidazole  
treatment



## ENTEROPATHY ASSOCIATED T-CELL LYMPHOMA (EATL)

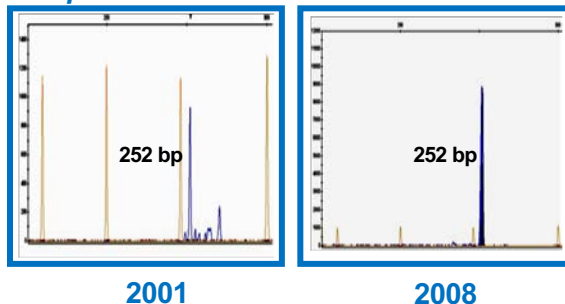


*Blood 2012*

## EATL IN ADULT AUTOIMMUNE ENTEROPATHY

- 53-yr old woman with a 30-yr history of refractory villous atrophy
- coeliac ABs-, anti-enterocyte ABs+
- initial response to steroids/thiopurines
- perforated jejunal lymphoma
- death from cerebral metastasis

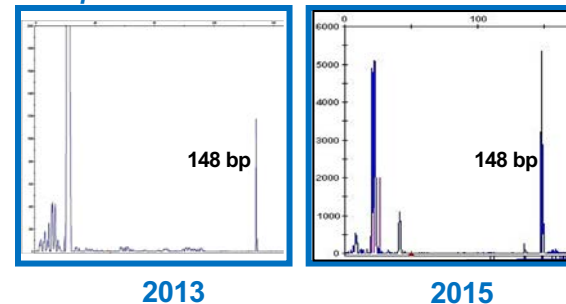
*TCR $\beta$  PCR*



Malamut et al, *Gastroenterology* 2012

- 53-yr old woman with a 15-yr history of refractory villous atrophy
- coeliac ABs-, anti-enterocyte ABs+
- prolonged response to steroids
- obstructing jejunal lymphoma
- death from cerebellar metastasis

*TCR $\gamma$  PCR*



*Hematol Oncol* 2018

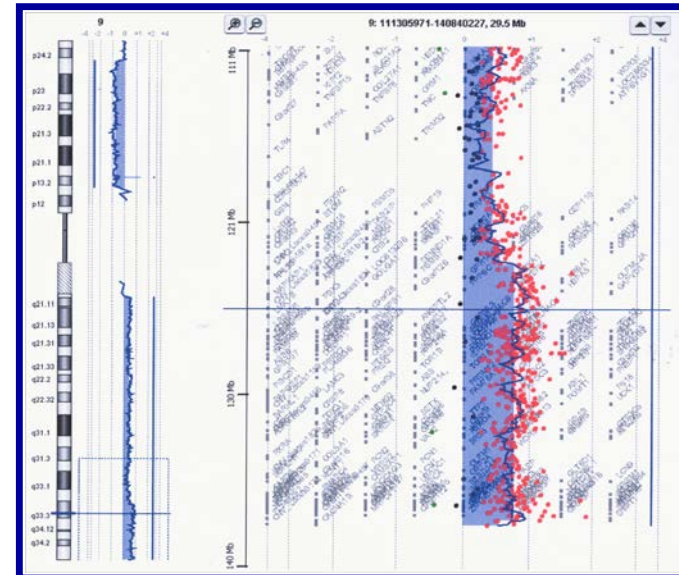
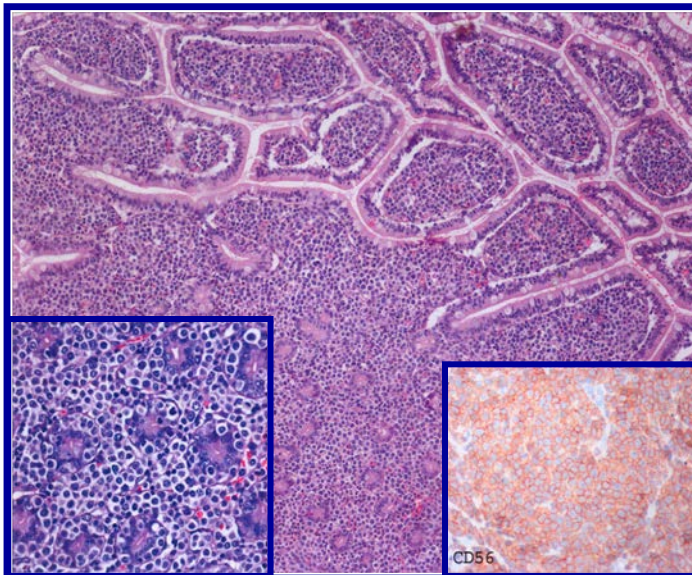
## A 57 YEAR-OLD MAN DEAD FOR TYPE 2 EATL (MEITL) ASSOCIATED WITH CD

Monomorphic medium-sized T-cells with irregular nuclei & scant CTP

Invasion of LP crypt epithelium, no inflammatory background

CD3+, CD4-, CD8+, CD30-, CD56+, MATK+

Array CGH profile of chromosome 9 showing deletion 9p13.1 - 9p24.1 & gain 9q33 - q34



*Submitted*



## THE "BIASABLE" SEROLOGY IN CD

- most of the studies performed in centres with a specific interest in CD
- most of the results obtained from stored serum samples
- comparisons between new and old ABs untenable
- lack of real prospective studies (even in risk groups [expected prevalence ~ 5-10%] → 500/1000 new upper GI endoscopies needed to collect 50 new true positives !)

in the real world the screening power of coeliac ABs is at best questionable!

## IS ADULT CD STILL WORTH A BIOPSY ?

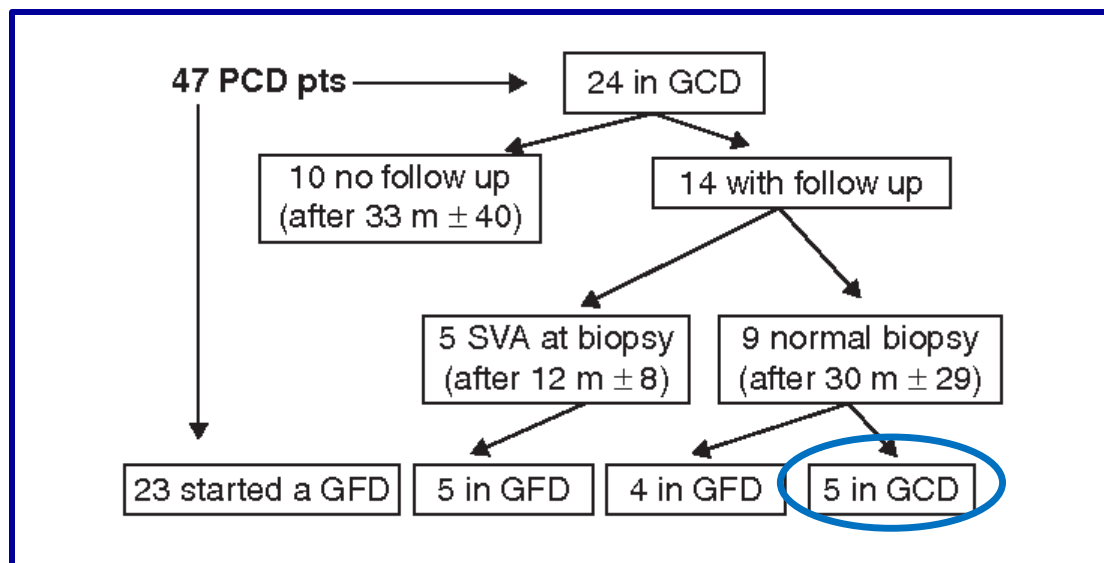
- duodenal biopsy if properly collected, processed, and evaluated does not represent a further source of misdiagnosis
  - CD may be associated with other upper GI conditions
  - individuals with unsuspected CD have been diagnosed in the course of endoscopic examination
  - commercially available TTA-ELISA kits may entail a very variable performance
  - patients not diagnosed on histological grounds, may be less compliant to GFD
  - without a comparison of different specimens, taken at different times, diagnosis of refractory CD could be jeopardised or delayed
  - positive serology alone would miss potential CD, the treatment and follow-up of which may differ
- ➡ novel multicentre, prospective, controlled studies are needed, involving also individuals assessed in primary and secondary care

## SERONEGATIVE (IgA & IgG) COELIAC DISEASE

- diagnosis relies on the histological response to a GFD after other forms of villous atrophy have been excluded
- family history and DQ2/DQ8 positivity are supportive criteria
- possible causes include concomitant immunodeficiency, GFD prior to testing, immunosuppressants, > mucosal avidity due to complications
- uncommon condition (2% of CD population, ~30% of seronegative villous atrophy)
- poor prognosis

*Eur J Gastroenterol Hepatol 2017*  
*Curr Opin Gastroenterol 2018*

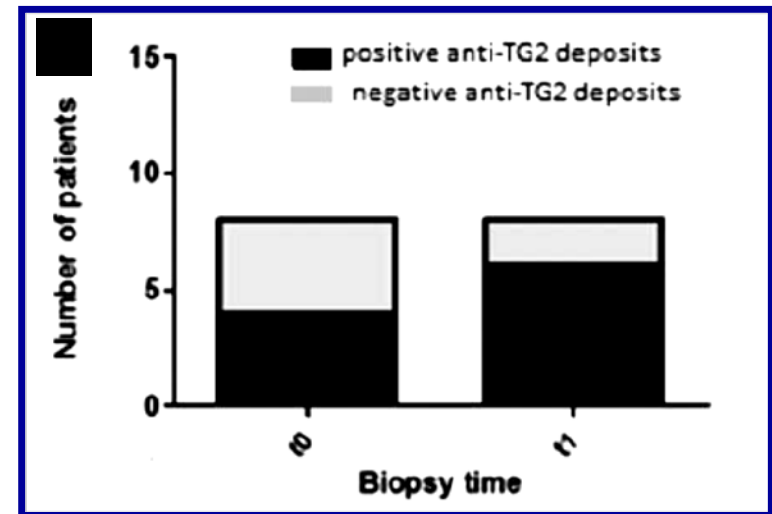
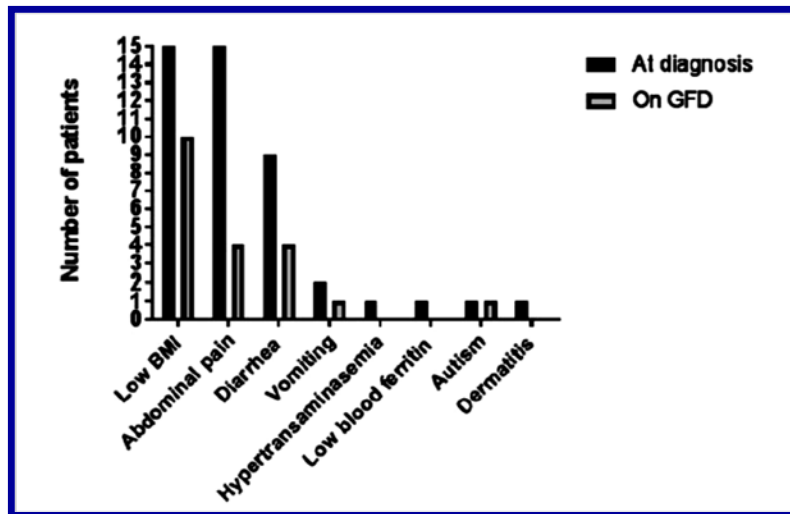
## NATURAL HISTORY OF POTENTIAL COELIAC DISEASE IN ADULTS



*Scand J Gastroenterol 2013*

- some pts maintained a normal mucosa and symptoms improved after many years of GCD
- potential CD is not a prodrome of CD, but a separate entity that can subsequently evolve

## EFFECT OF GFD (34 mo) ON SYMPTOMS & LESIONS IN PTS WITH POTENTIAL CD

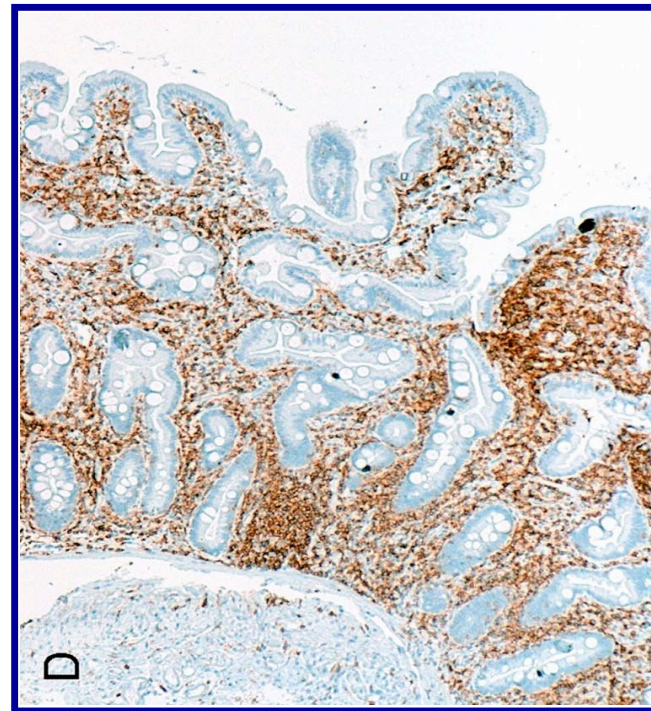


Mandile et al, *JPGN* 2018

caution is necessary in potential CD before attributing all the abnormalities to gluten

## INDOLENT SMALL INTESTINAL CD4<sup>+</sup> T-CELL LYMPHOMA IS A DISTINCT ENTITY

- 3 pts misdiagnosed for CD
- CD8<sup>-</sup>, CD103<sup>-</sup>, CD4<sup>+</sup> T-cells
- clonal TCR- $\nu\beta$  chain
- indolent course



Margolskee et al, *PlosOne* 2013