



ULB

# Coeliac disease

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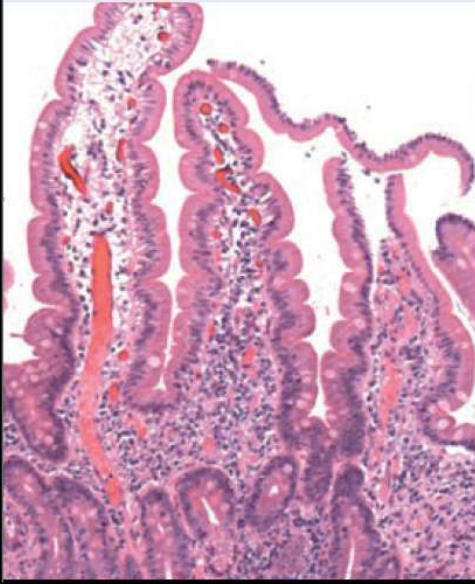
*SRBGE, 30 avril 2011*

# Coeliac disease (CD)

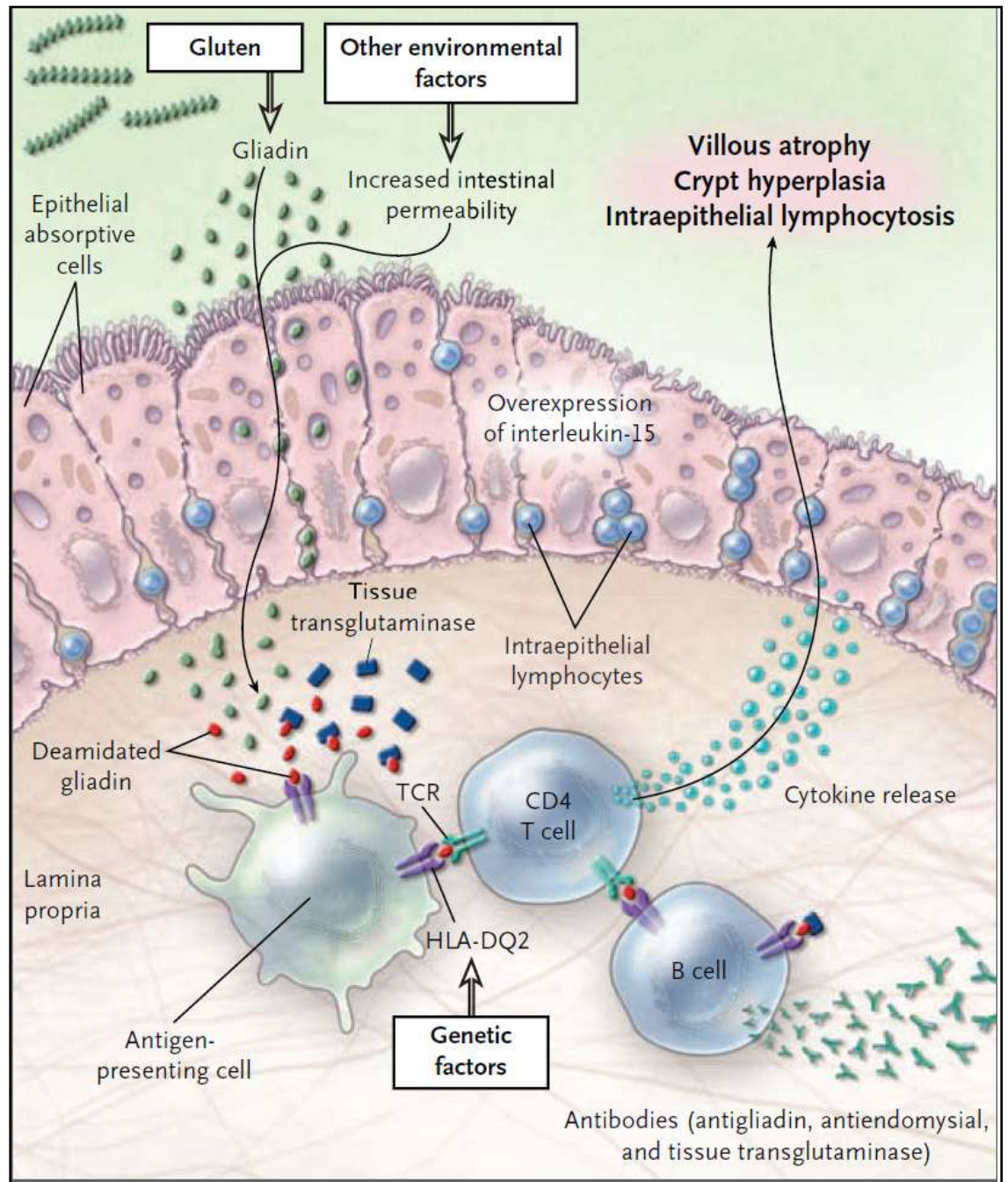
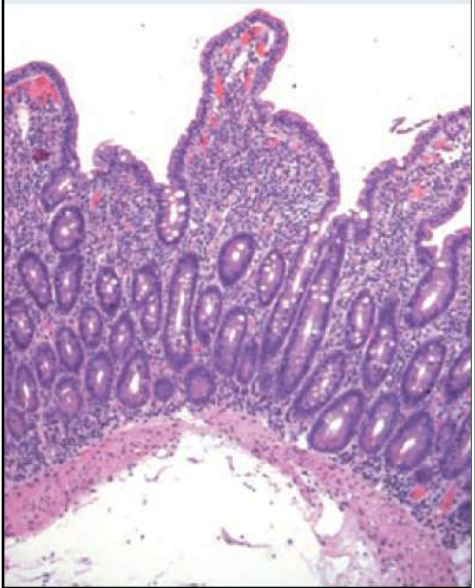
## Natural history

- **Mechanism of gluten intolerance**
- **Prevalence**
- **Coeliac disease as a risk factor**
- **Forms of CD**
- **Therapy**

Normal duodenal mucosa

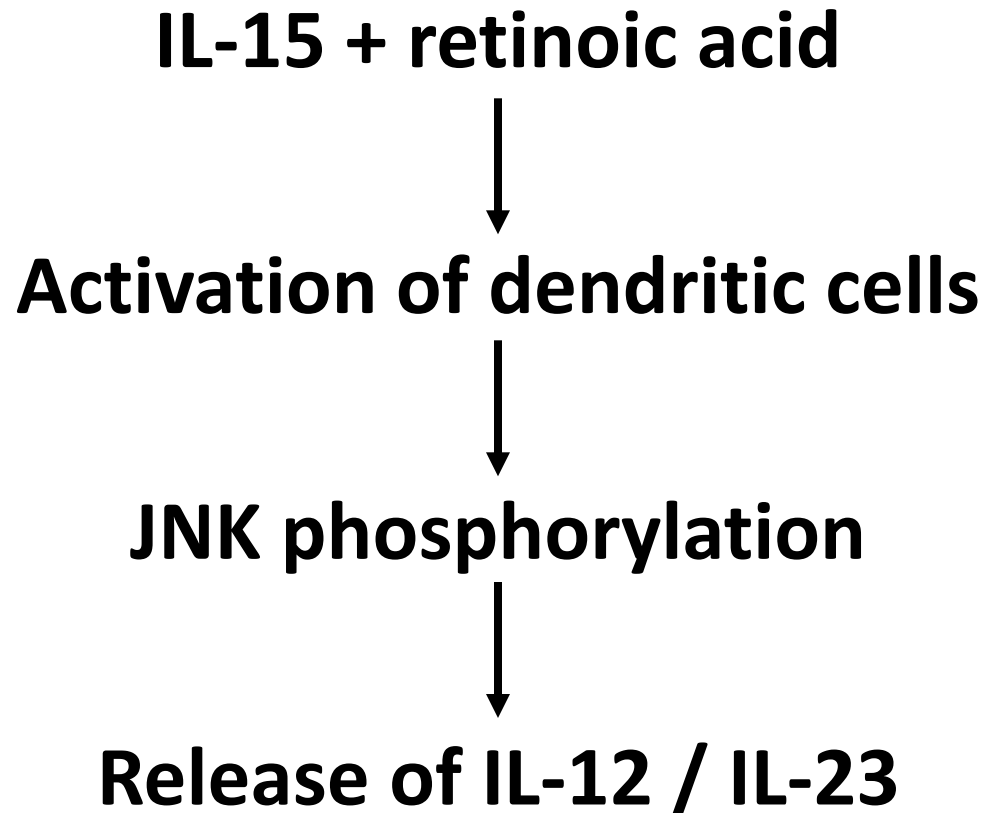


Duodenal mucosa in celiac disease



# Mécanismes de la perte de tolérance vis-à-vis d'antigène alimentaire

## Mice:



# The Prevent CD study

**Hypothesis**: is that possible to induce tolerance to gluten by introducing small quantities of gluten to infants\* (preferably while they are still being breast-fed)

**\* from families with high risk of CD**

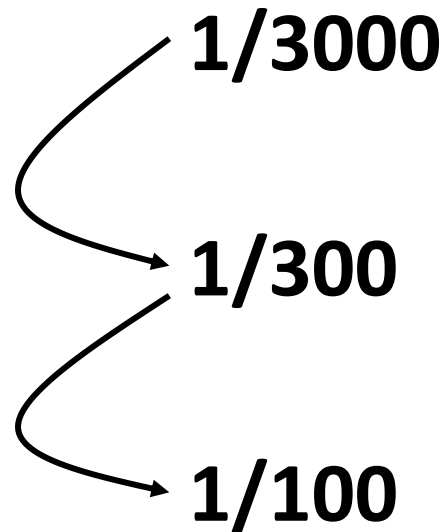
# Coeliac disease (CD)

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# Coeliac disease

## Prevalence



# Screening for celiac disease in a North American population

- **US: prevalence of CD < 1/2000**
- **Serum tissue transglutaminase antibodies in 3850 healthy volunteers (< 18 y)**
- **31 (0.8%) with positive celiac serology**
  - ↳ **17/18 with biopsy: at least partial atrophy**

# Prevalence of coeliac disease

## Children vs adults

- **n = 4230 subjects**
- **n = 21 had coeliac diseases (male:female: 1:2,5)**
- **Prevalence:**
  - **total population 1:204**
  - **children 1:71**
  - **adults 1:351**
- **Explanation: environmental factors influencing infancy or latency of CD in adulthood**

# Additional autoimmune disease at Type 1 diabetes diagnosis

n = 491 children with type I

122

Thyroid peroxidase  
antibodies



15

Autoimmune thyroid  
disease

57

Tissue transglutaminase  
antibodies



14

Coeliac  
disease

# Refractory coeliac disease (RCD)

- **Prevalence of RCD: unknown but rare (< 1% of CD)**
- **3 females / 1 male**
- **Most of the cases > 50 y**

# Incidence and clinical spectrum of refractory celiac disease in North-America

844 patients with CD



34 RCD (refractory)



3 RCD type II

weight loss	76% vs 16%
diarrhea	79% vs 40%

2 died of enteropathy-associated lymphoma  
within 24 months

# Coeliac disease (CD)

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# Small intestinal histopathology and mortality risk in coeliac disease

		HR
Marsh 3 (villous atrophy)	n = 29,096	1.39 (1.33-1.45)
Marsh 1-2 (inflammation)	n = 13,306	1.72 (1.64-1.79)
Marsh 0 (latent)	n = 3,712	1.35 (1.14-1.58)

# Increased suicide risk in celiac disease (Sweden)

		HR
Marsh 3 (villous atrophy)	n = 29,083	1.55 (1.15-2.10)
Marsh 1-2 (inflammation but no atrophy)	n = 12,263	1.96 (1.39-2.77)
Marsh 0 (normal mucosa but positive coeliac serology)	n = 3,719	1.06 (0.37-3.02)

# Risk of lymphoproliferative malignancy

		Absolute risk
Coeliac atrophy (Marsh 3)	n = 28,989	70/100,000* persons/year
Inflammation (Marsh 1 + 2)	n = 13,140	83/100,000 persons/year
Latent (serology + mucosa normal)	n = 3,711	28.0/100,000 persons/year

\*Hodgkin; both T-cell and B-cell non-Hodgkin lymphomas

# Gluten-sensitive hypertransaminasemia in coeliac disease

## Cross-sectionnal study

	Elevated AST
Patients: 331 untreated	11%
339 treated	8%
237 non-coeliac	9%

## Prospective study:

serum AST decreased although in the normal range

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# Coeliac disease

Coeliac disease



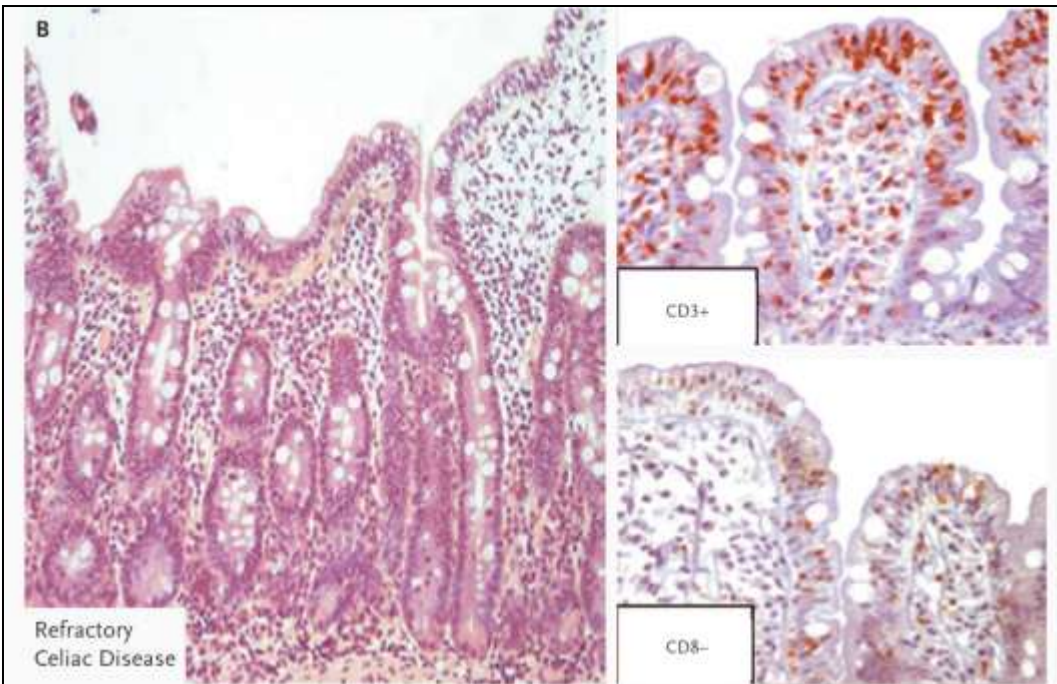
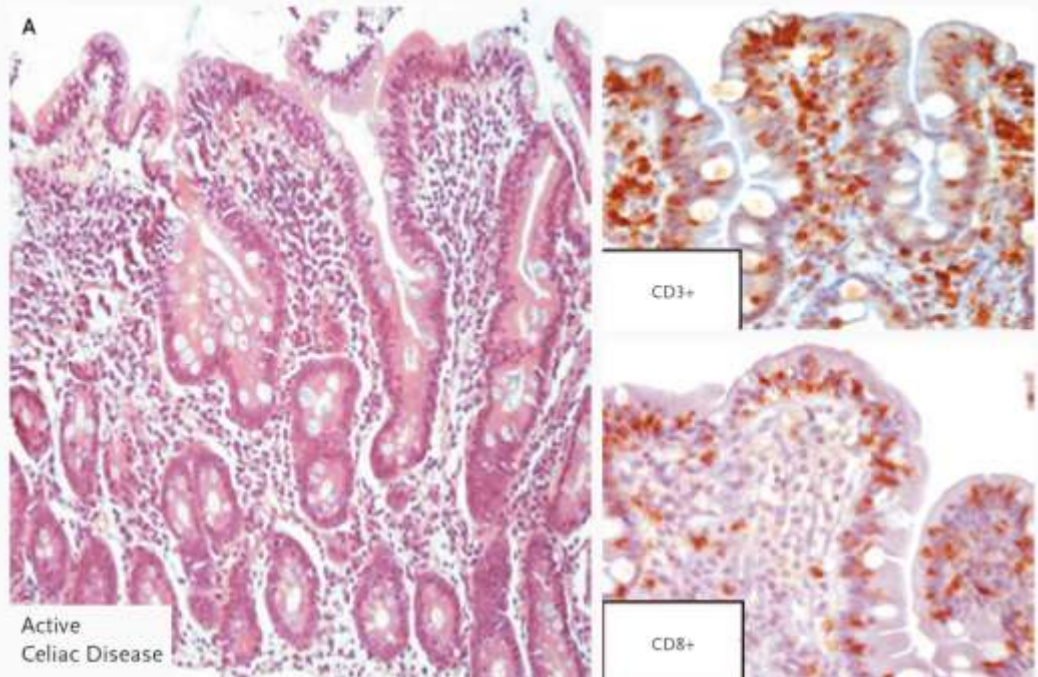
Refractory coeliac disease



**Cryptic enteropathy-associated T-cell lymphoma**  
(aberrant IE lymphoid population CD3+ CD8-)



**T-cell lymphoma**



*Green, Cellier, NEJM 2007*

# **Cryptic genetic gluten intolerance revealed by intestinal antitransglutaminase antibodies**

- **Antitransglutaminase (anti-TG2) antibodies are synthesized in the intestine**
- **Is the presence of mucosal antibodies an early stage of gluten intolerance? (with normal mucosa and normal serum anti-TG2 antibodies)**

# **Cryptic genetic gluten intolerance revealed by intestinal antitransglutaminase antibodies**

## **Methods**

- **22 relatives of patients with CD genetically predisposed to gluten intolerance**
- **No mucosal damage**
- **No serum anti-TG2 antibodies**
- **15 symptomatic and 7 asymptomatic**
- **12 months gluten-free**

# Cryptic genetic gluten intolerance revealed by intestinal antitransglutaminase antibodies

## Results

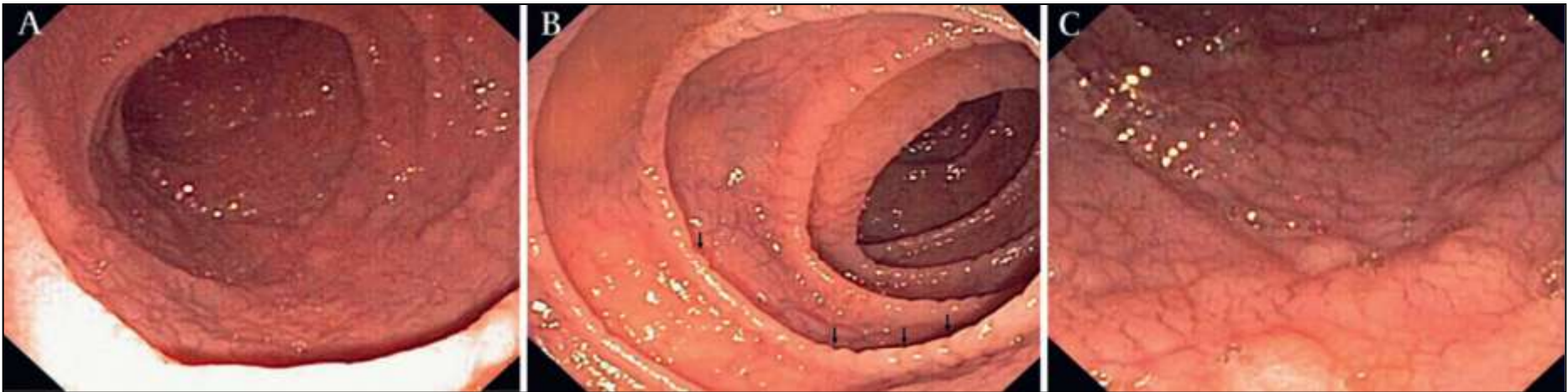
- Intestinal mucosa normal: 18/22
- Slight increase in IE lymphocytes: 4/22
- Mucosal anti-TG2 antibodies: 15/22 (68%)
- Correlation between mucosal anti-TG2-antibodies and I-FABP (marker of early intestinal mucosal damage)
- After gluten-free diet – anti-TG2 antibodies disappeared in 12/15
- Extra- and –intestinal symptoms disappeared

# Does gluten cause GI symptoms in subjects without coeliac disease?

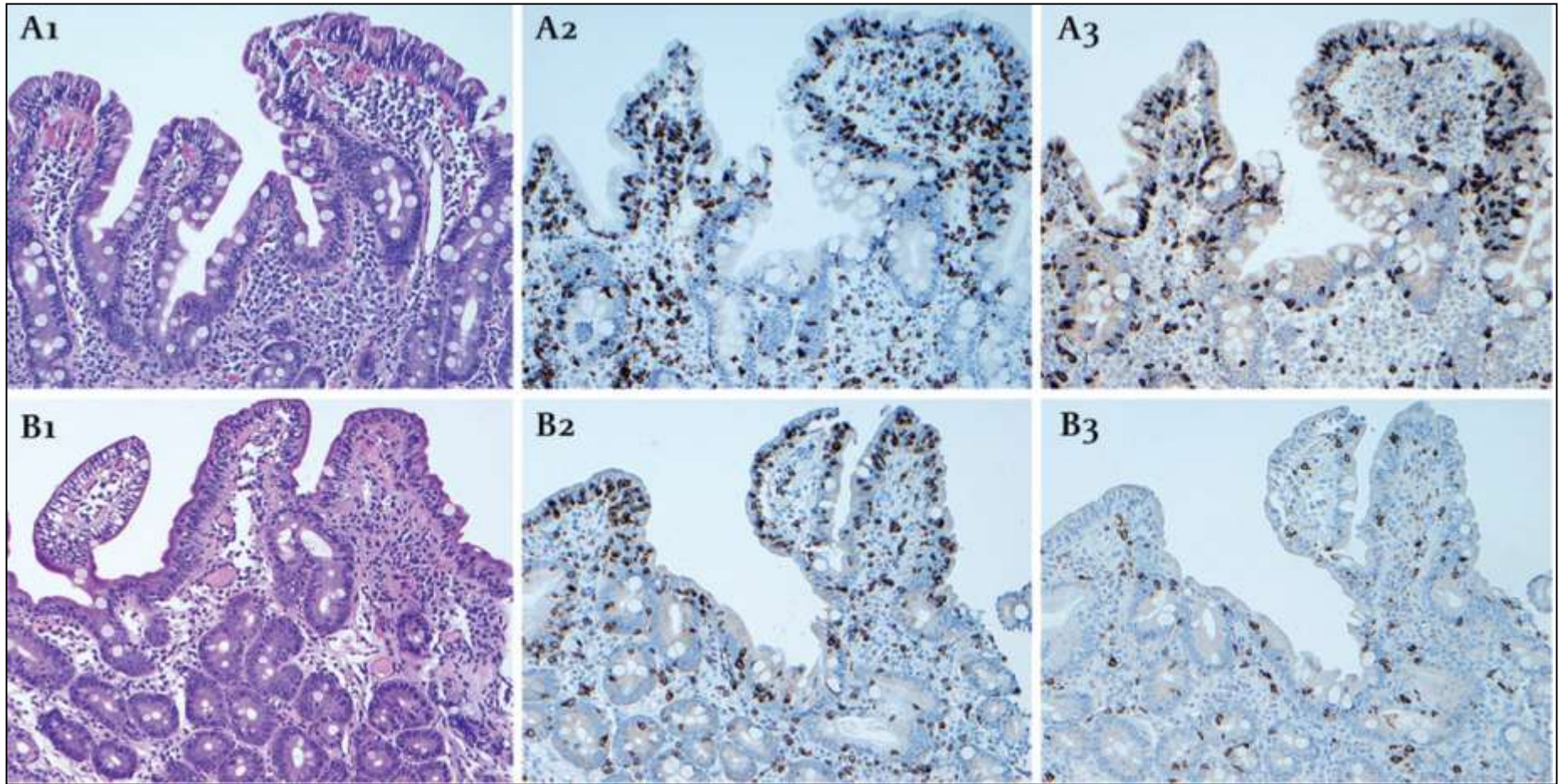
- **Patients with symptoms but normal biopsy and serology**
- **Symptoms previously improved on gluten free diet**
- **n = 19 gluten**
- **n = 15 placebo**
- **Change in symptoms (0.047)**
- **Non-coeliac gluten intolerance exists**

# Refractory coeliac disease

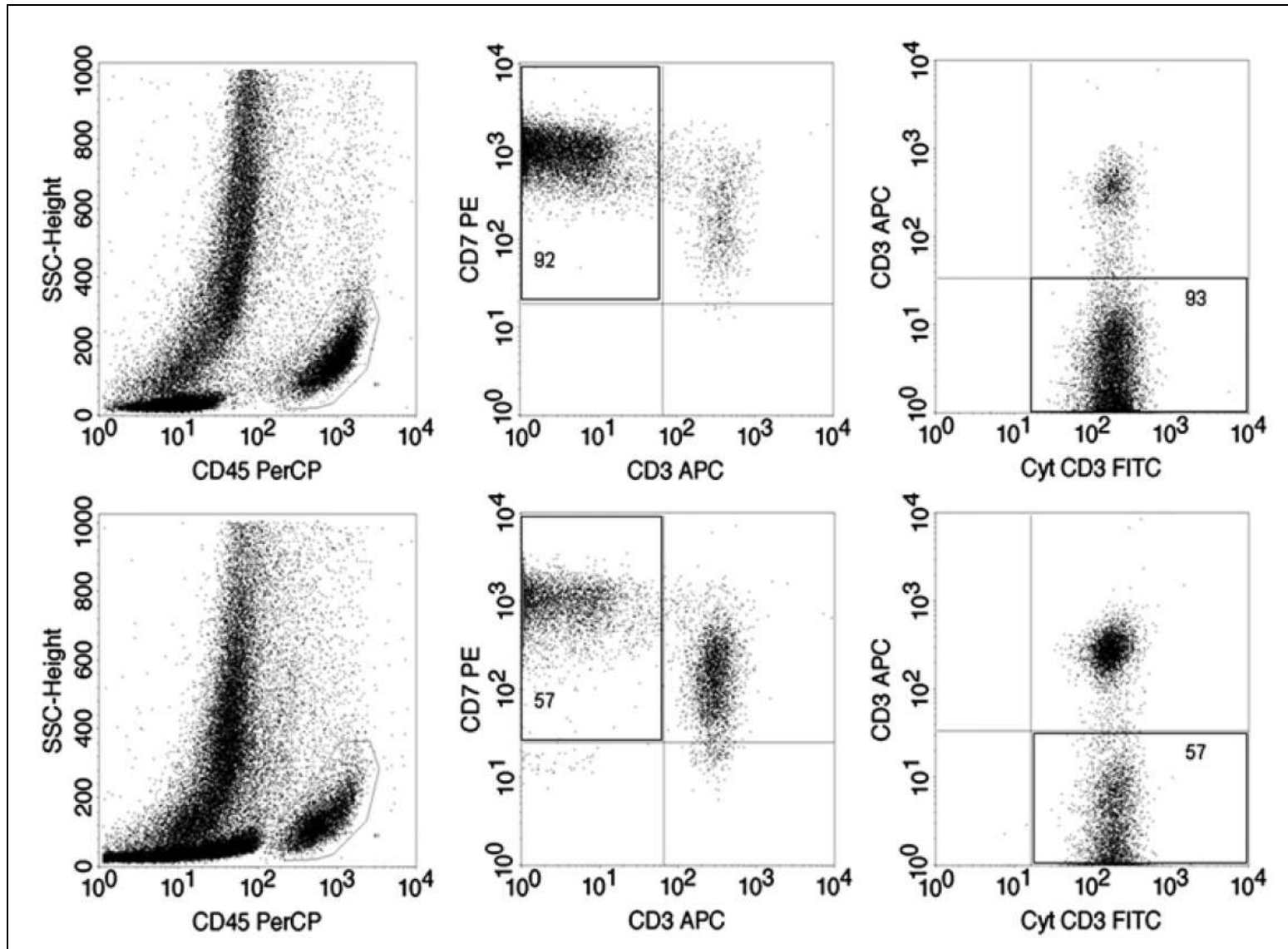
- **Persistent or recurrent malabsorptive symptoms and villous atrophy despite strict adherence to a GFD for at least 6-12 months in the absence of other causes of non-responsive treated coeliac disease and overt malignancy**



# Immunophenotype of IE lymphocytes in RCD (CD3 / CD8)



# Flow cytometry of intestinal lymphocytes



# MR enteroclysis in refractory CD

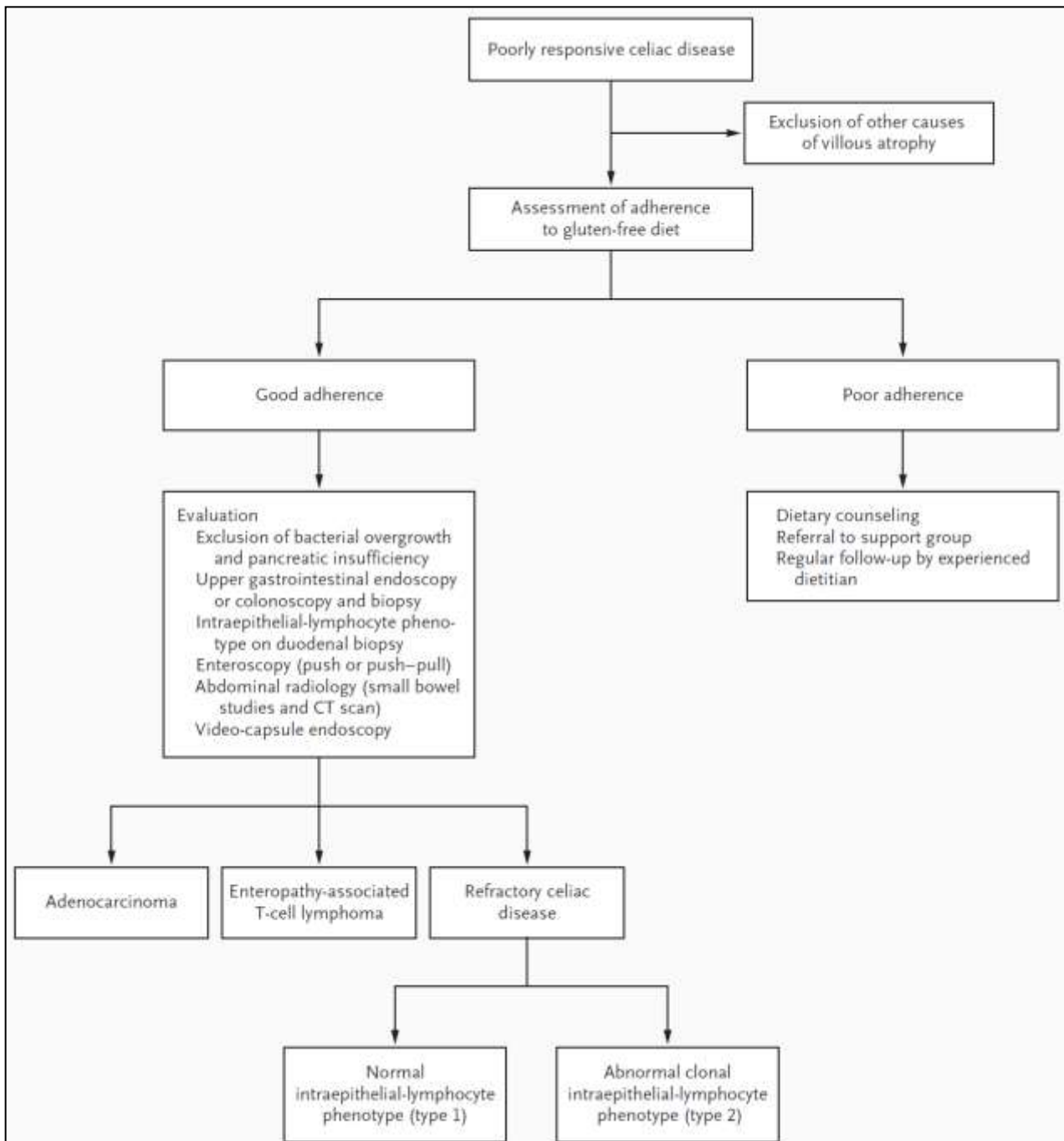
## A severity score

- **No difference between uncomplicated CD and refractory I**
- **Refractory II:**
  - less than 10 folds/5 cm jejunum
  - mesenteric fat infiltration
  - bowel wall thickening
- **Validation score: 15 patients with RCD II and 25 CD**  
→ **sensitivity: 0.87**
- **5 year survival:**
  - negative MR score: 95%
  - positive MR score: 56%

# Coeliac disease (CD)

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# Coeliac disease

- **Responder to GFD:**
  - clinical/serological responses: a few weeks or months
  - histological recovery: a few years
- **Non-responder to GFD → see causes**
- **“Latent” refractory: persistent inflammation and atrophy without symptoms**
- **Refractory CD**

# **Non-responsive coeliac disease**

## **Causes**

- **Overt or inadvertent gluten contamination**
- **Microscopic colitis**
- **Small bowel overgrowth**
- **Lactose intolerance**
- **Functional bowel disorders**

**Table 2** Aetiologies of non-responsive coeliac disease

Aetiology	Representative case series			Diagnostic approach
	Abdulkarim <sup>10</sup> (n = 49)	Leffler <sup>11</sup> (n = 99*)	Fine <sup>45</sup> (n = 11 †)	
Gluten contamination	25	36	1	Dietary review, coeliac serology
Microscopic colitis	9	6	3	Colonic biopsies
Bacterial overgrowth	7	6	0	Breath tests, culture of small bowel aspirate, antibiotics trial
Pancreatic insufficiency	6	0	2	Pancreatic testing, enzymes trial
Fructose/lactose intolerance	1	7	2	Breath tests, exclusion trial
Irritable bowel syndrome	4	22	2	Clinical criteria
Refractory coeliac disease	4	10	0	Discussed in this review
Other	4	12	1	Miscellaneous tests
Total	60 ‡	99	11	

\*99 of 113 with confirmed aetiologies.

†11 of 13 with persistent diarrhea after a gluten-free diet (GFD).

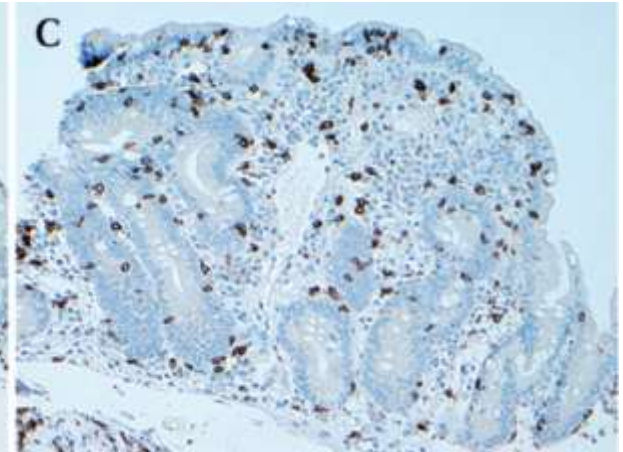
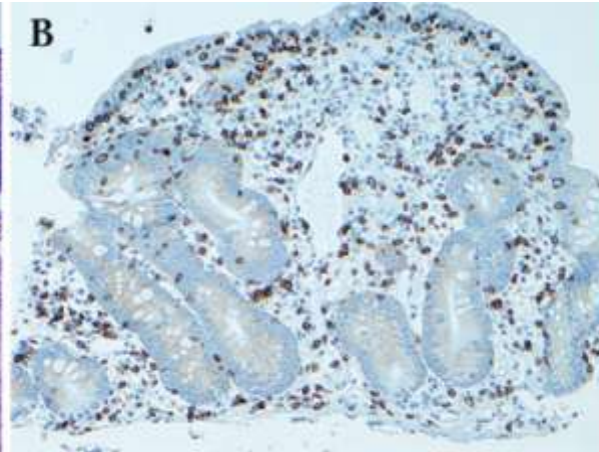
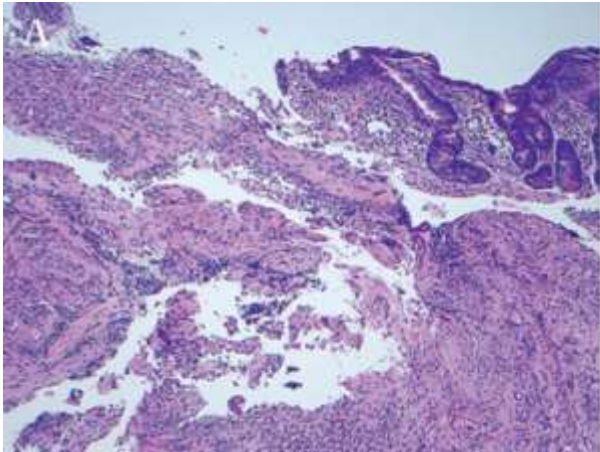
‡Some patients had more than one condition likely associated with persistent symptoms.

# Refractory celiac disease

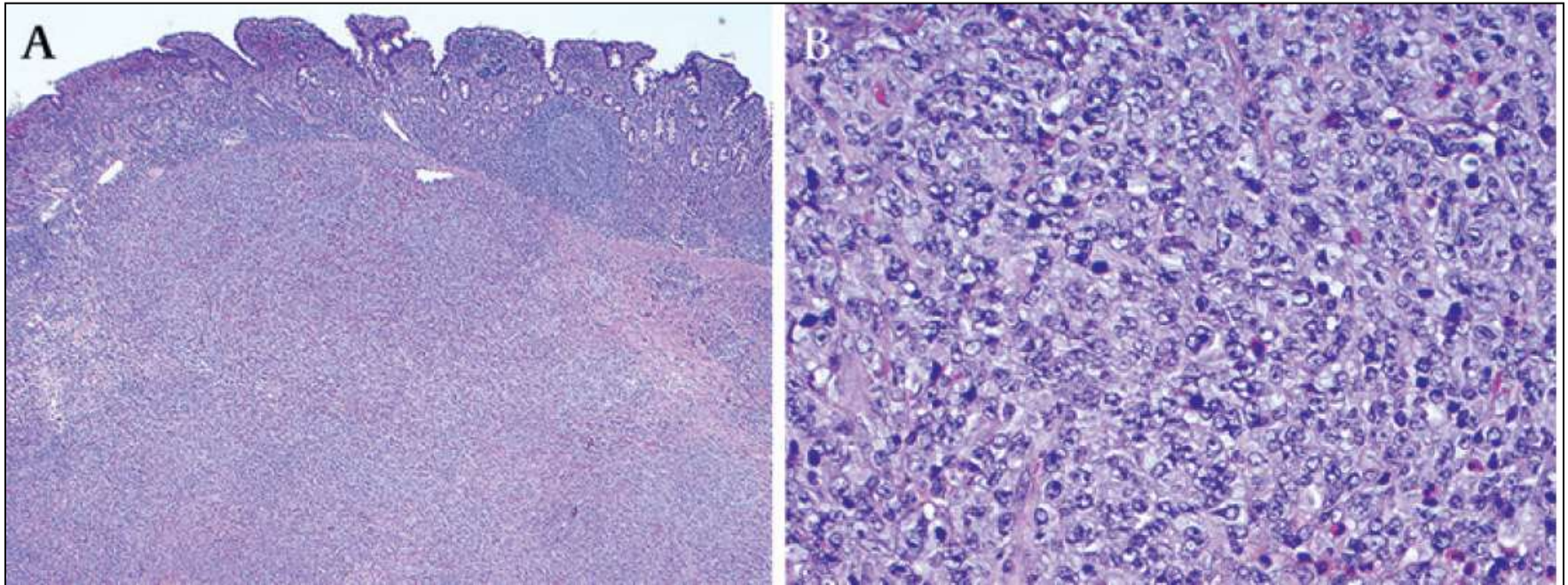
## Treatment

- **Dietary and nutritional supplementation**
- **Prednisone / Budesonide**
- **Immunosuppression?**
- **Subcutaneous IL-10: no**
- **Cladribine**
- **High-dose chemotherapy followed by ASCT**
- **Interleukine-15 blockade → promising option**
- **Surgery: only in case of complications**

# Ulcerative jejunitis



# Enteropathy-type-T-cell lymphoma



# Cladribine treatment in refractory celiac disease type II

- Open label (2-CdA)
- Period: 2000 – 2010
- n = 32 patients
- Follow-up: 31 months

	Responder (18/32)	Non-responder (14/32)
Survival 5 y.	83%	22%

- Progression to EATL= 16%



