Duodenal intraepithelial lymphocytosis

Dr Ian Brown

Envoi Pathology Brisbane

ianbrown@envoi.com.au

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SPECIALIST PATHOLOGISTS
inside insights

What is duodenal intraepithelial lymphocytosis?

- Intraepithelial lymphocytes (IELs) are a normal constituent of the mucosa of the luminal gastro-intestinal tract.
- CD3/CD8 positive T lymphocytes - local innate immune process and have cytotoxic function.
- Increase in IELs (**intraepithelial lymphocytosis**) can follow local or systemic immune activation
- Many immunological stimuli are responsible (**inflammatory reaction pattern**)

What is abnormal?

Site	Normal number	Abnormal
Duodenum	≤25/100 epith. cells (3µm) ≤40/100 epith. cells (7µm)	≥30/100 epith. cells (3µm) ≥40/100 epith. cells (7µm)

2 clinically relevant patterns

1. **Lymphocytosis with (~) normal villi**

2. **Lymphocytosis with villous blunting or flat mucosa**

Duodenal lymphocytosis with (~) normal villi?

How often do we see this?

- Theoretically ~2.5% duodenal biopsies
- In practice:
  - reported in 1.3–2.2% of non selected duodenal biopsies (Am J Gastroenterol 2003;(98/9):2027; J Clin Pathol 2002;55:424)
  - Some series up to 9%
- Abstract 795 USCAP 2015 Massachusetts General Hospital - 'Of the 5071 duodenal biopsies performed from 2010 to 2011, 320 **(6.3%)** were reported as DMSIL ("duodenal mucosa with normal villous architecture and slightly increased intraepithelial lymphocytes")'.
- Mayo clinic paediatric (JPGN 2013) – "Among 1290 duodenal biopsies obtained from children during the years 2000 and 2009, 56 **(4.3%)** were noted to have ''normal villous architecture with increased intraepithelial lymphocytes.''

Do we need to count the IELs?

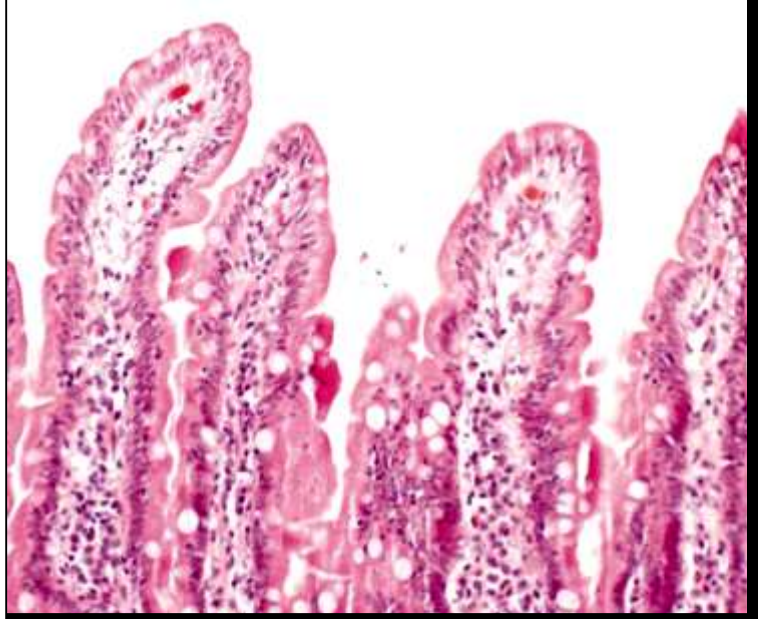
- Normal = 18-25 IEL/100 enterocytes; Abnormal is ≥30 IEL/100 enterocytes

  (J Clin Pathol 2002;55:393; Scand J Gastroenterol 2004;4:138)

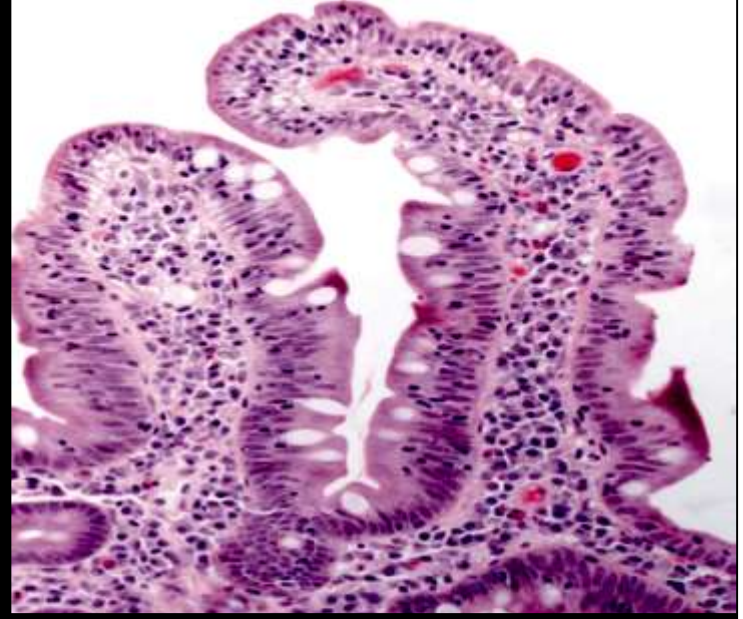
- Most pathologists use 'gestalt' assessment
- *HOWEVER* we are not as good as we think!!!
- USCAP 2015
  - Abstract 799 – over called 33% of cases
  - Abstract 795 –over called 65% of cases (inferring real IELosis count = 2.2%)
- We should try harder!!
  - Intraepithelial lymphocytosis should be reported in <2.5% of all duodenal biopsies
  - Thin sections (3µm)
- [IEL ≤ 25/100 enterocytes may miss up to 50% of potential coeliac disease]

What causes duodenal lymphocytosis with (~) normal villi?

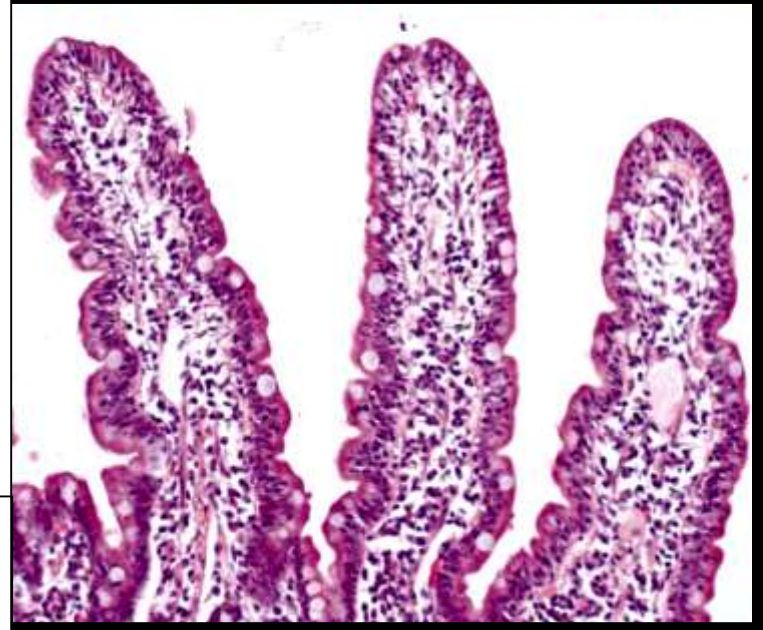
- Coeliac disease – including coeliac patients on GFD, dermatitis herpetiformis
- Infection - Viral enteritis, Helicobacter pylori infection, Giardia, Cryptosporidia, tropical sprue
- Drugs - NSAIDs, sartans, PPIs, (?SSRIs)
- Immune disease
- Bacterial overgrowth
- Idiopathic
- Other – Crohn's disease



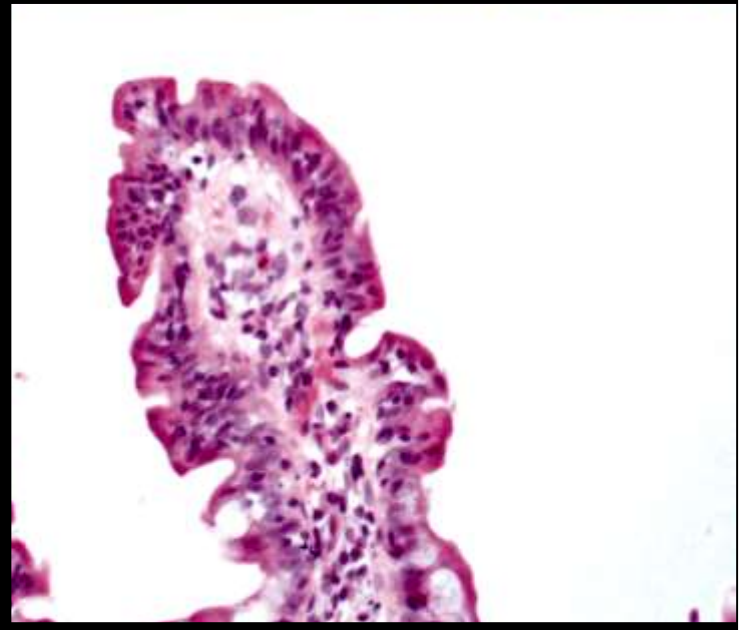
H.Pylori gastritis related



SLE related



Crohn disease related



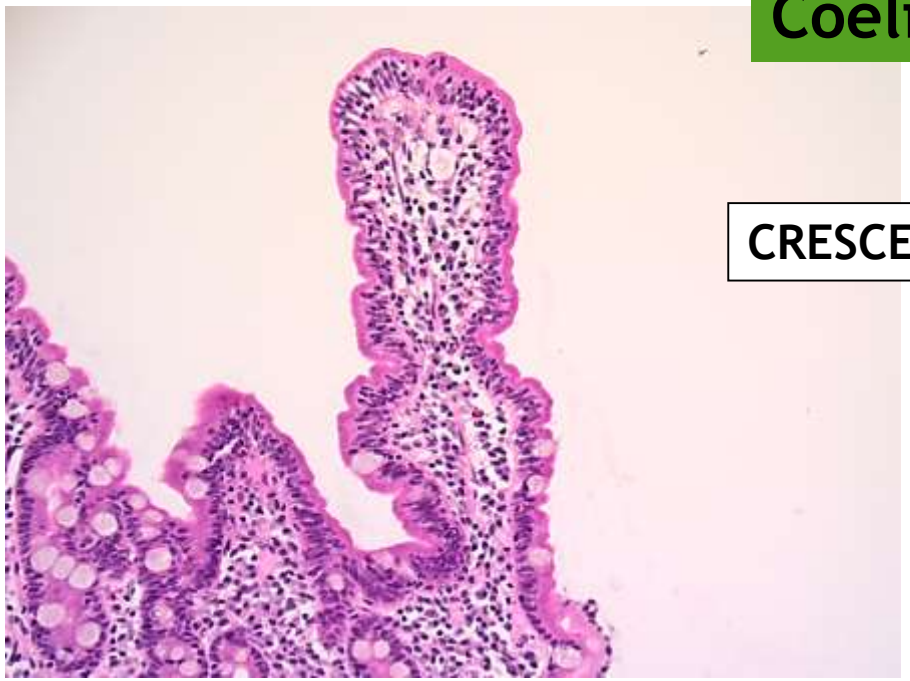
Coeliac disease

From:
Arch Pathol Lab Med.
2006;130(7):1020-5.

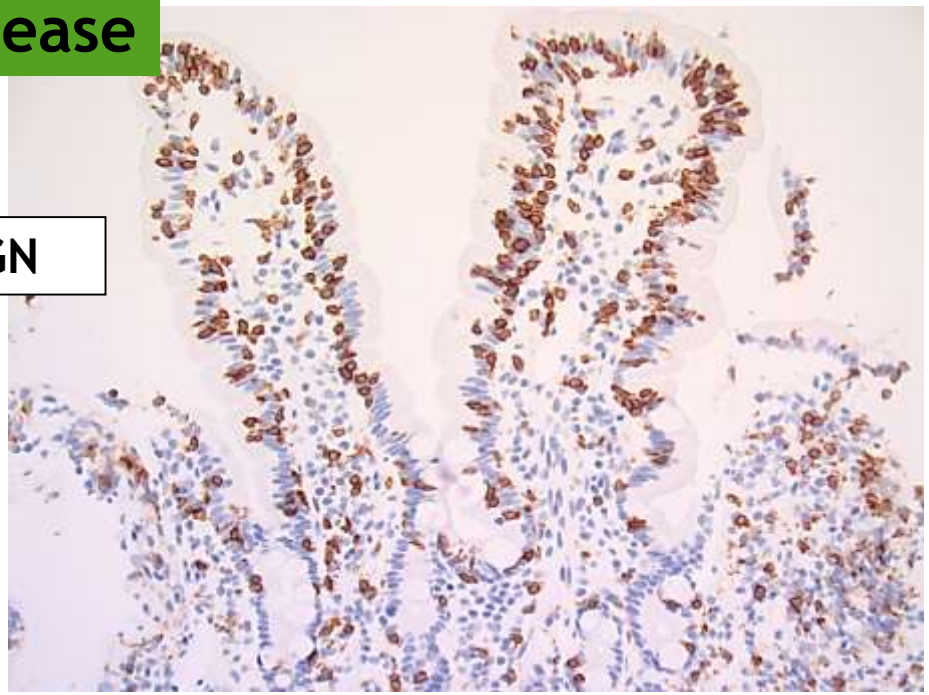
Morphological clues to the aetiology of duodenal lymphocytosis with normal villous architecture

- Really nothing!!
- Absence of crescendo sign – coeliac disease unlikely
  - May be bacterial overgrowth, medication effect
- Need clinical input

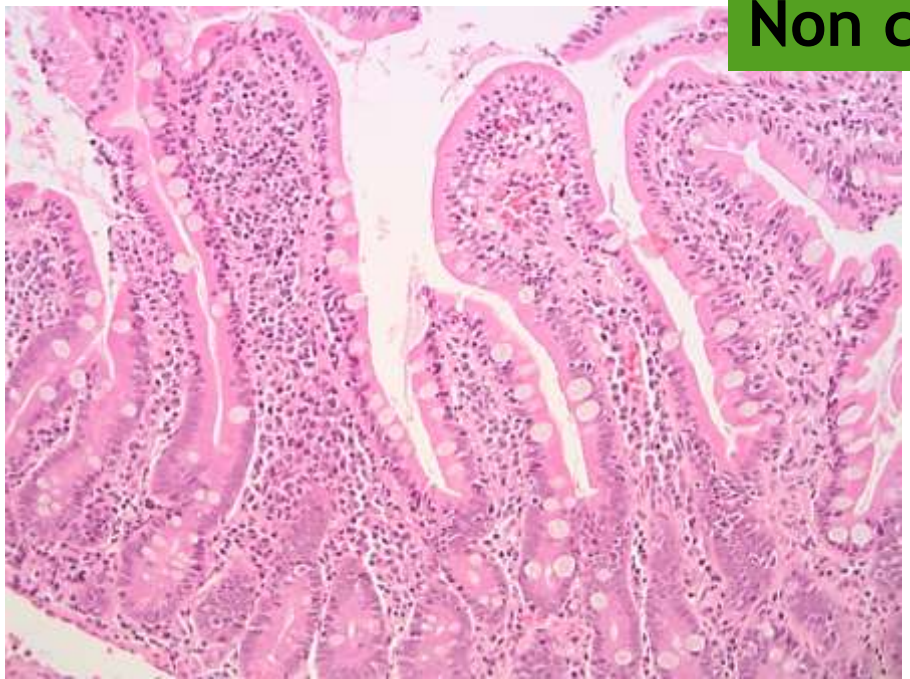
Coeliac disease

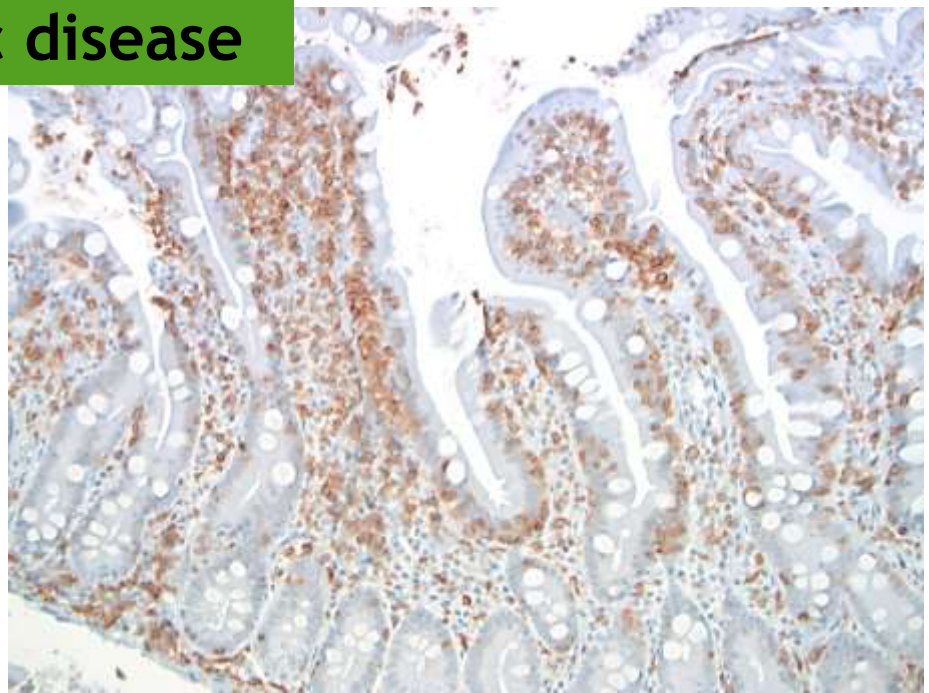


CRESCENDO SIGN

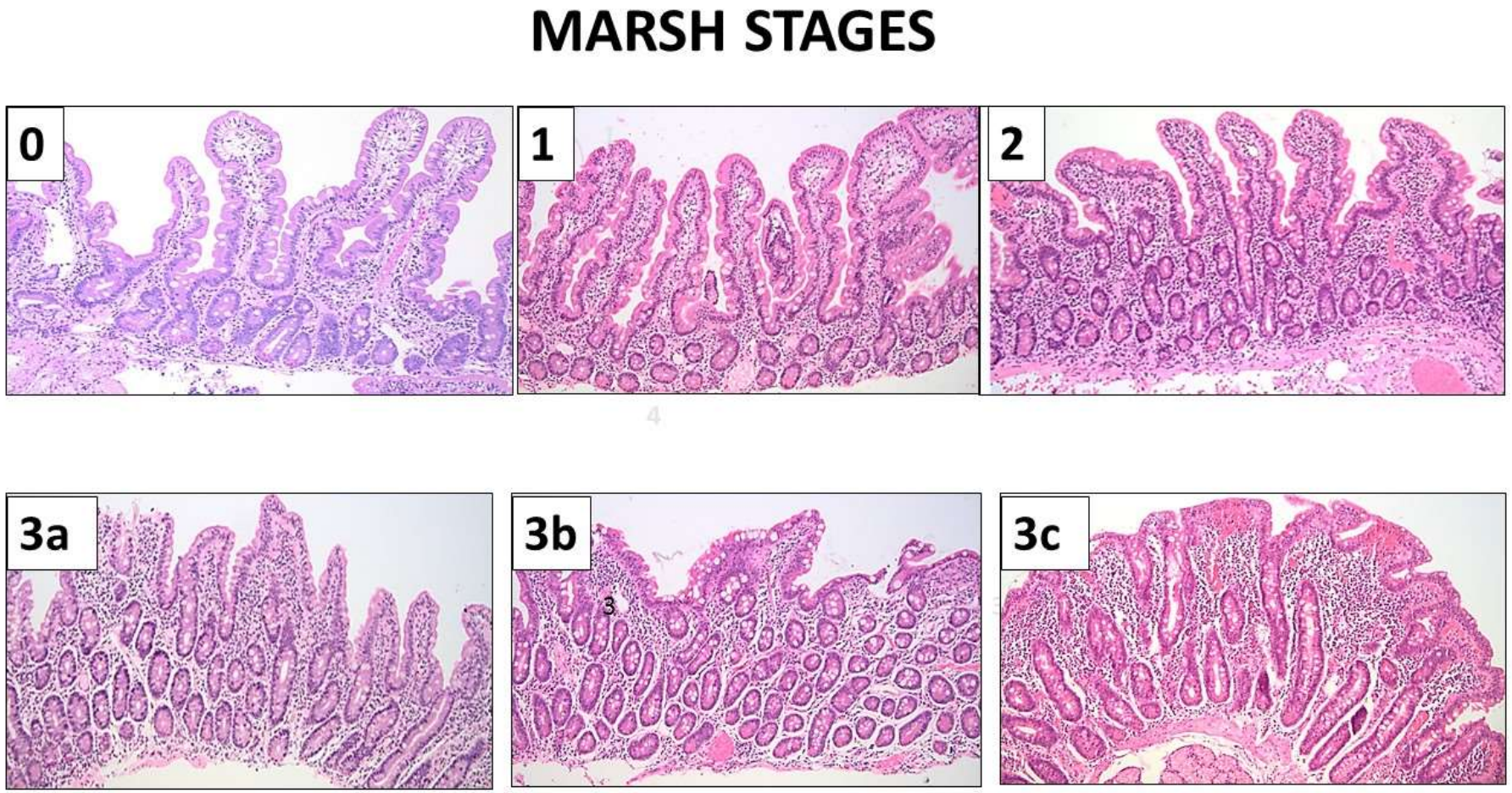


Non coeliac disease





Coeliac disease and duodenal lymphocytosis with normal villous architecture



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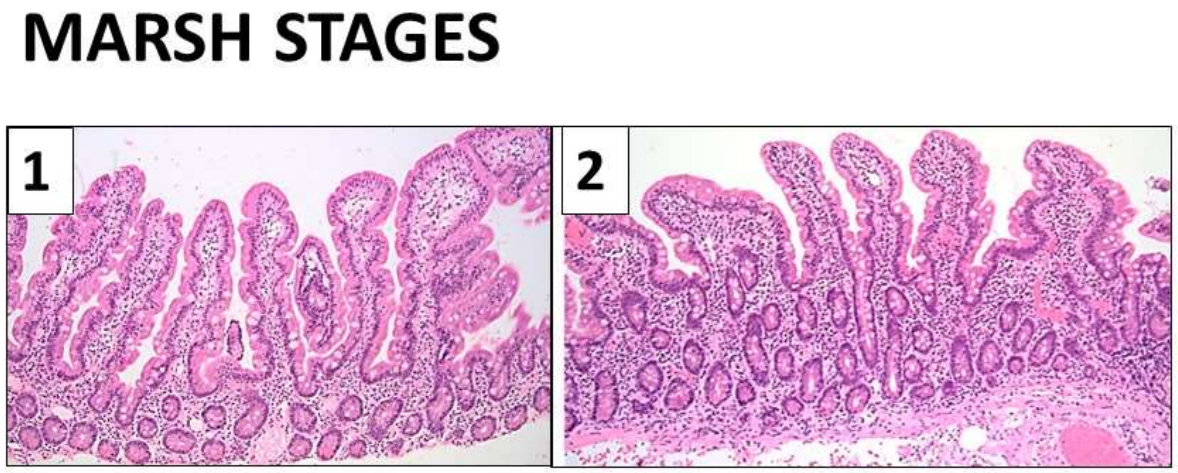


How often is duodenal lymphocytosis with normal villous architecture due to coeliac disease?

- 9% of new coeliac cases in both the Mayo clinic adult and paediatric series (Am J Gastroenterol 2003;(98/9):2027 and JPGN 2013;56: 51–55)
- Literature range 9-40%

AJG 2003 (N=47)	JPGN 2013 (N=56)	APLM 2013 (N=100)	APT 2010# (N=100)	JCG 2015# (N=215)
9%*	9%* (19% overall)	18%	16%	22%

* New diagnosis coeliac disease
# Same author/unit

Am J Gastroenterol 2003;(98/9):2027
J Ped Gastro Nutr 2013;56: 51–55
Arch Pathol Lab Med. 2013;137:1216–1219
Aliment Pharmacol Ther 2010;32:1392–1397
J Clin Gastroenterol 2015;49:477-482

Coeliac disease and duodenal lymphocytosis with normal villous architecture

- reported in 14% of duodenal biopsies from patients clinically suspected to have coeliac disease (J Clin Pathol 2008;61:1116)
  - 50% were EMA positive = coeliac disease
  - 25% were not coeliac disease

- How do we know that most cases are not latent celiac disease?
  - Long term follow up
  - Absence of HLADQ2/8 in 50% (Am J Gastroenterol. 2009;104:142, J Clin Gastro 2015;49:477)

Establishing coeliac disease as the cause of duodenal lymphocytosis with normal villous architecture

1. TTG
   - Literature reports range of 0-100% for finding EMA or TTG elevation in cases that prove to be coeliac disease
   - Probably present in 50-70% of coeliac cases (?? How well biopsy sampled)
   - TTG elevation also found in up to 17% who don't prove to be coeliac disease (JCG 2015)
   - Most have elevations ≤ 2 x normal range
   - Bottom line = high level TTG = coeliac disease; normal levels doesn't exclude it; low levels are indeterminate
2. HLA testing
   - Must carry DQ2/8
3. Gluten challenge
   - progression of lesions then response to GFD
4. Response to GFD
   - Of limited use because of the issue of non gluten food hypersensitivity

Frequency of other causes of duodenal lymphocytosis with normal villous architecture

	AJG 2003	APLM 2013	JPGN 2013	APT 2010	JCG 2015
Tropical sprue	1%	1%	—	—	—
H. pylori	—	6%	6%	14%	18%
Bacterial overgrowth	5%	3%	—	—	—
NSAIDs	14%	8%	20%	21%	14%
IBD	12%	8%	11%	2%	1%
Immune dysregulation	14%	6%	—	4%	6%
Idiopathic	7%	26%	33%	34%	11%
IBS	9%	20%	—	—	24%
Other	28%	4%	11%	9%	26%

The histology report for duodenal lymphocytosis with normal villous architecture

This is a non specific histological pattern. Approximately 10% of cases represent a histologically mild form of coeliac disease. Other common associations are infection (including gastric Helicobacter infection), autoimmune disease and a medication effect (e.g. NSAID’s).

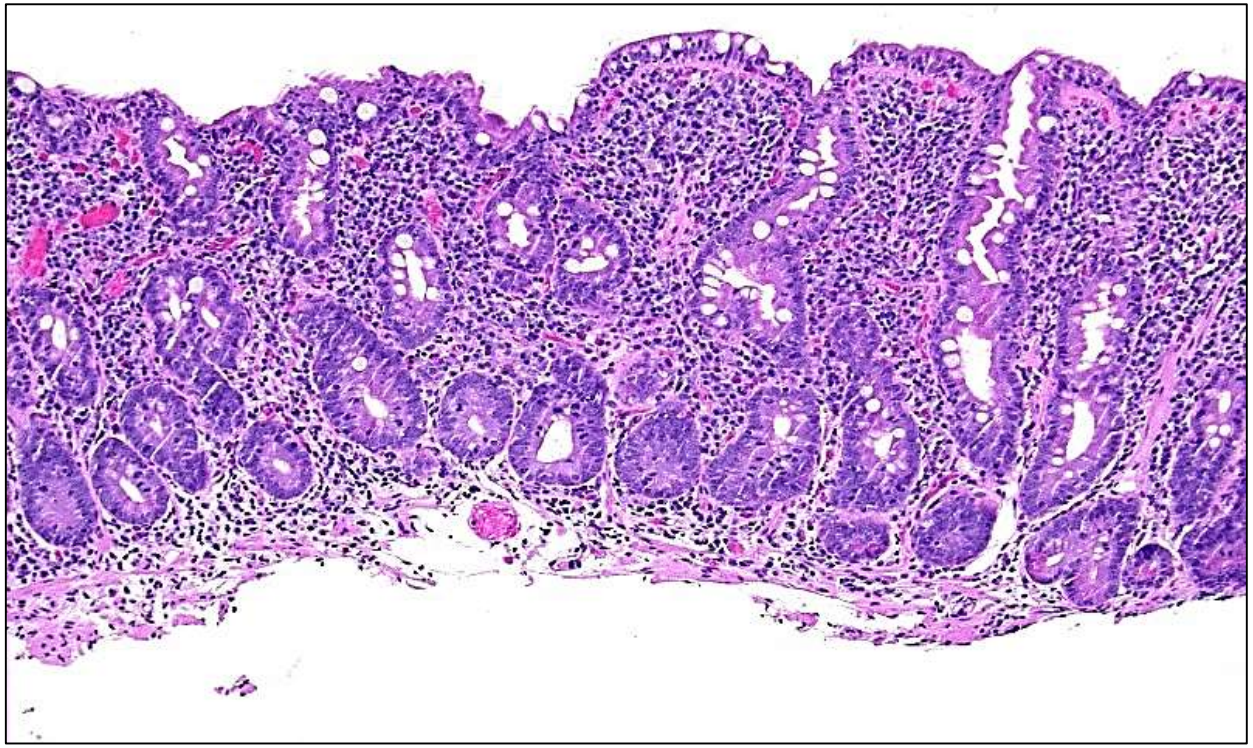
Duodenal intraepithelial lymphocytosis and villous atrophy

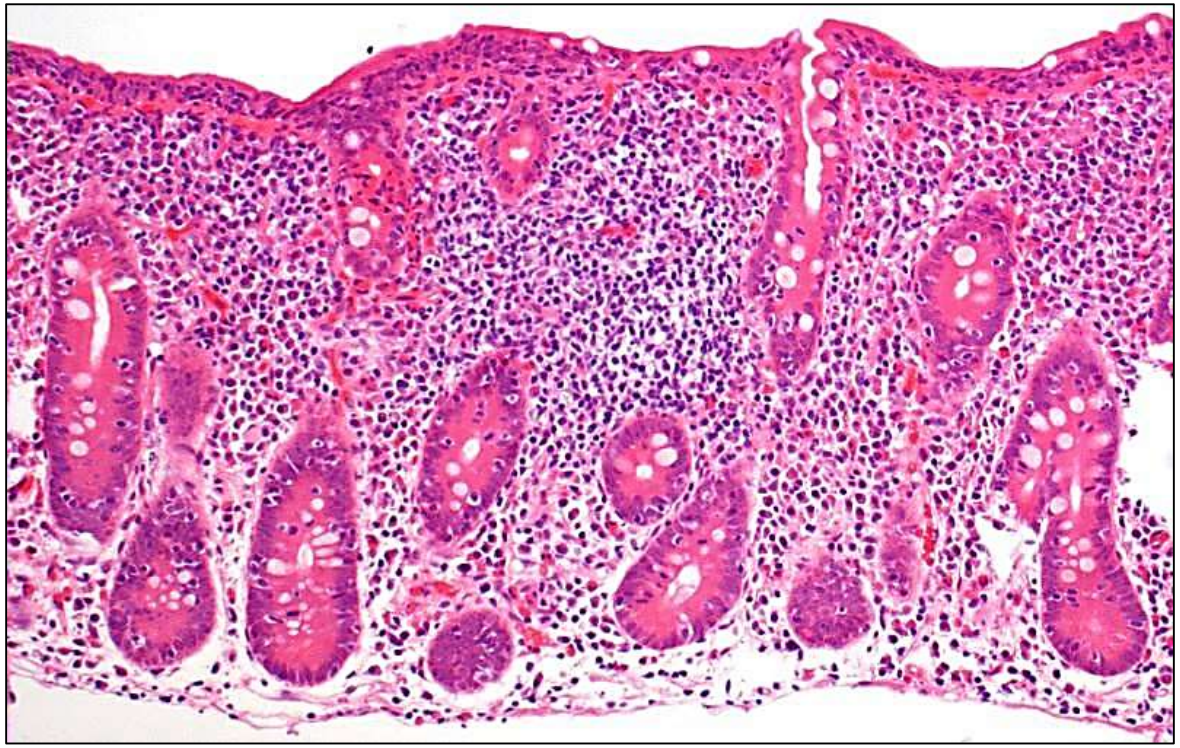
What causes duodenal intraepithelial lymphocytosis and villous atrophy?

- Coeliac disease
- Non gluten food hypersensitivity (e.g. cereals, cow's milk, soy products, fish, rice and chicken)
- Infection e.g. viral/bacterial enteritis, parasites e.g. cryptosporidia, tropical sprue
- Bacterial overgrowth
- Immune disorders e.g. IgA deficiency, Common Variable ImmunoDeficiency, Autoimmune enteropathy
- Drugs (e.g. NSAIDs, olmesartan, methotrexate, mycophenolate, biologics)
- Collagenous sprue
- Idiopathic

Paediatric	Adult
Coeliac disease	Coeliac disease
Infections – viral enteritis, parasitic	Infections – viral enteritis, parasitic AND Tropical sprue (and H.pylori)
Non gluten food hypersensitivity	Medications – Sartan family
Immunodeficiency eg IgA, CVID	Idiopathic self limited enteropathy
Autoimmune enteropathy	Immunodeficiency eg CVID
Rare syndromes eg Shwachman-Diamond syndrome	Autoimmune enteropathy

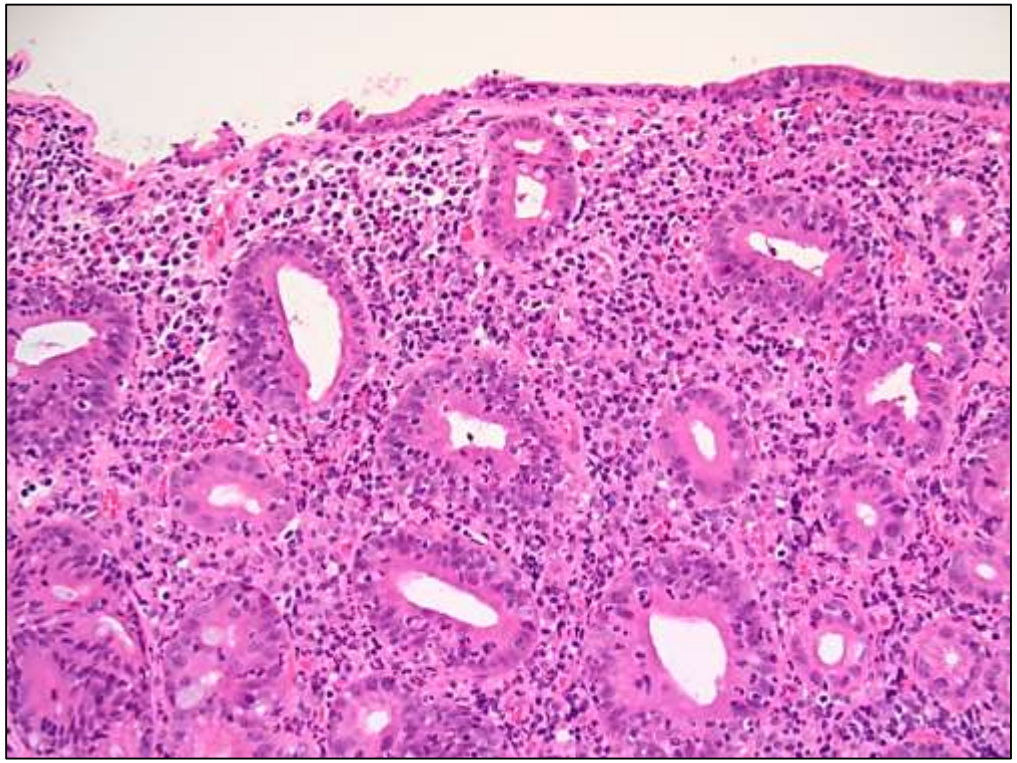
Classical histology of coeliac disease



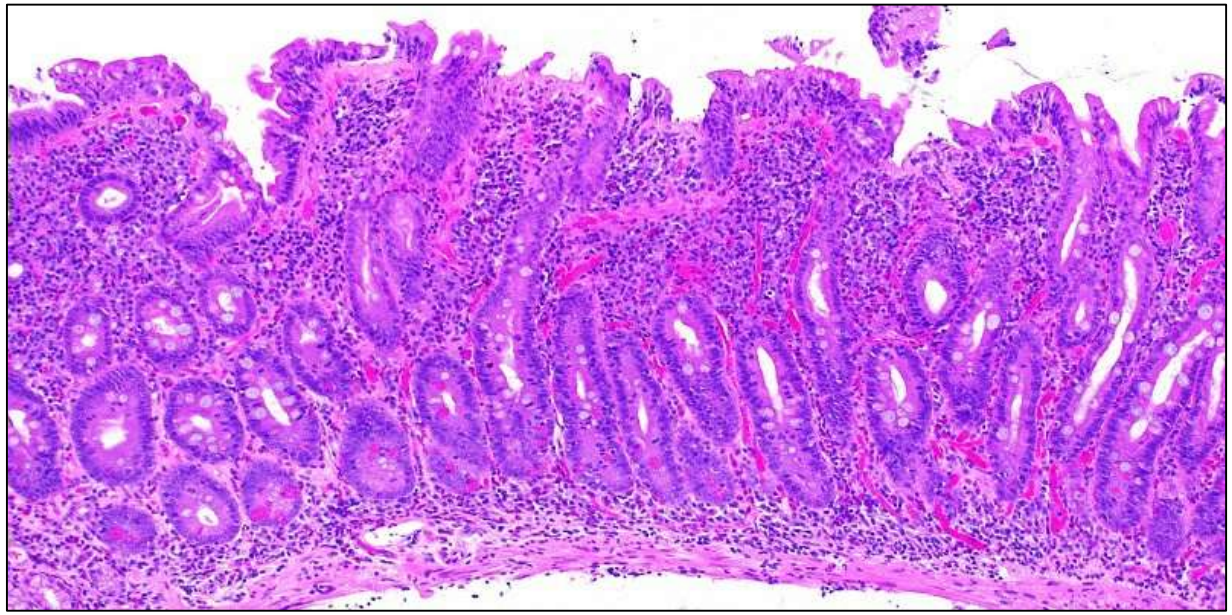


Variant features

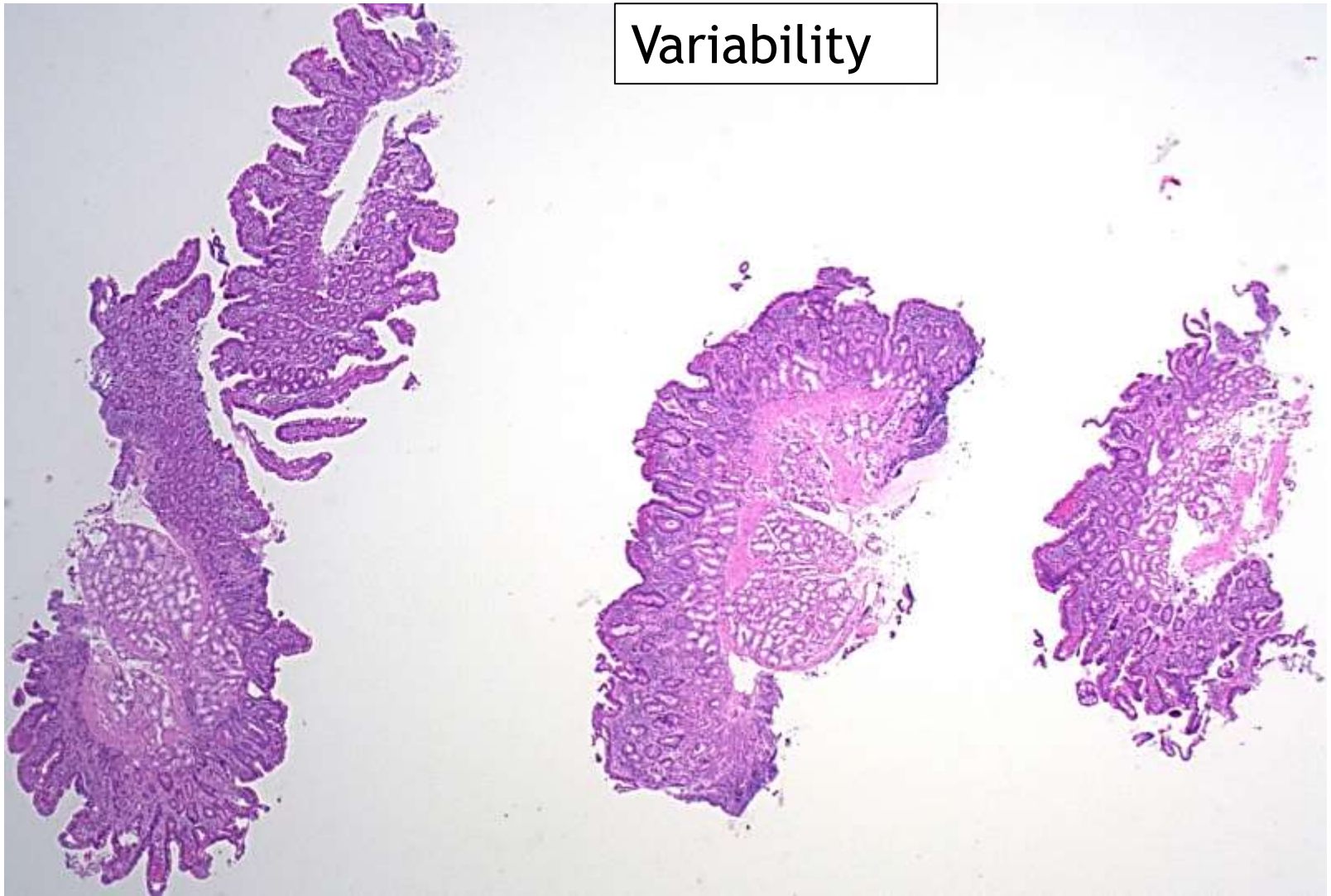
Neutrophils



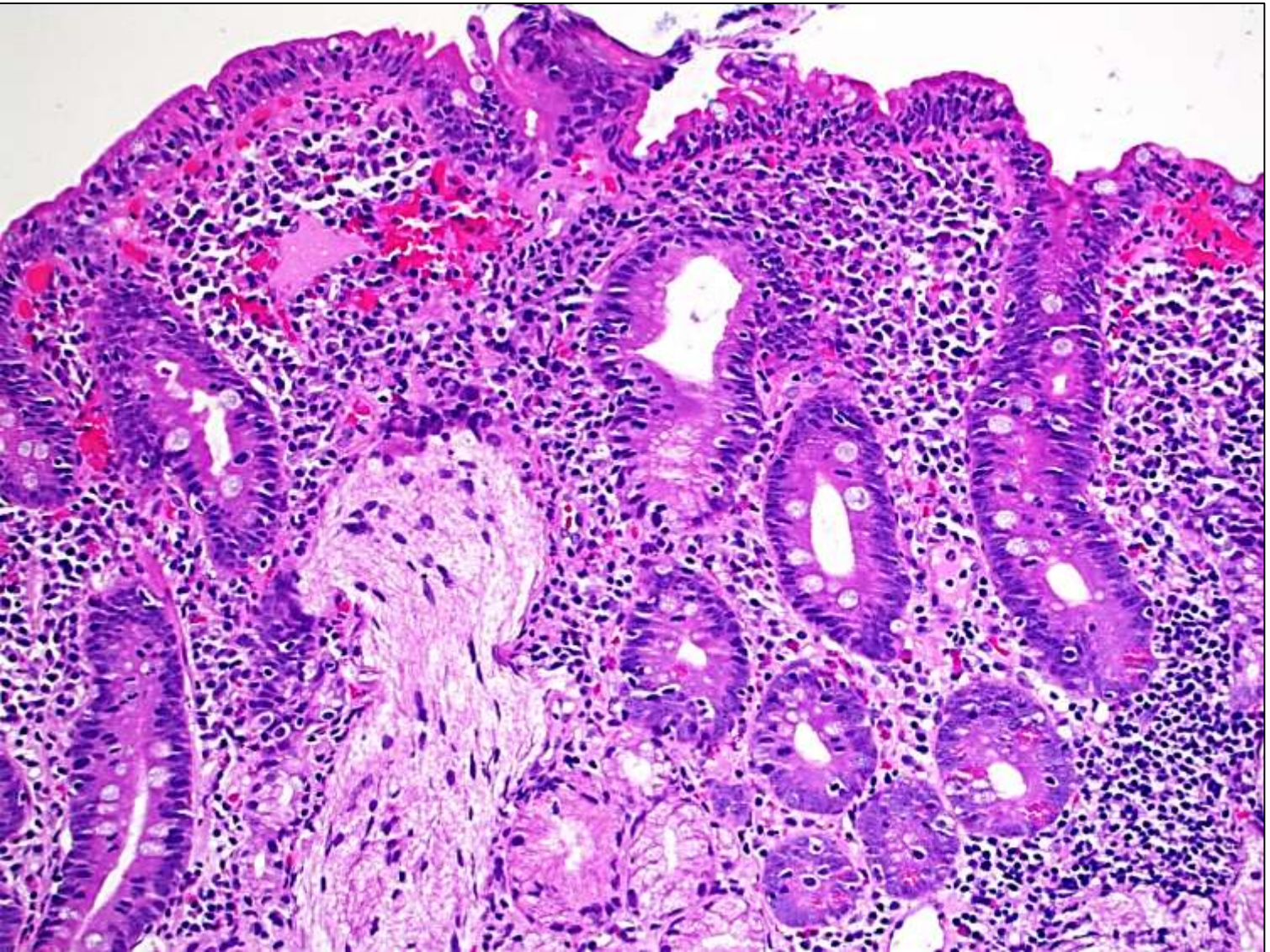
BM thickening

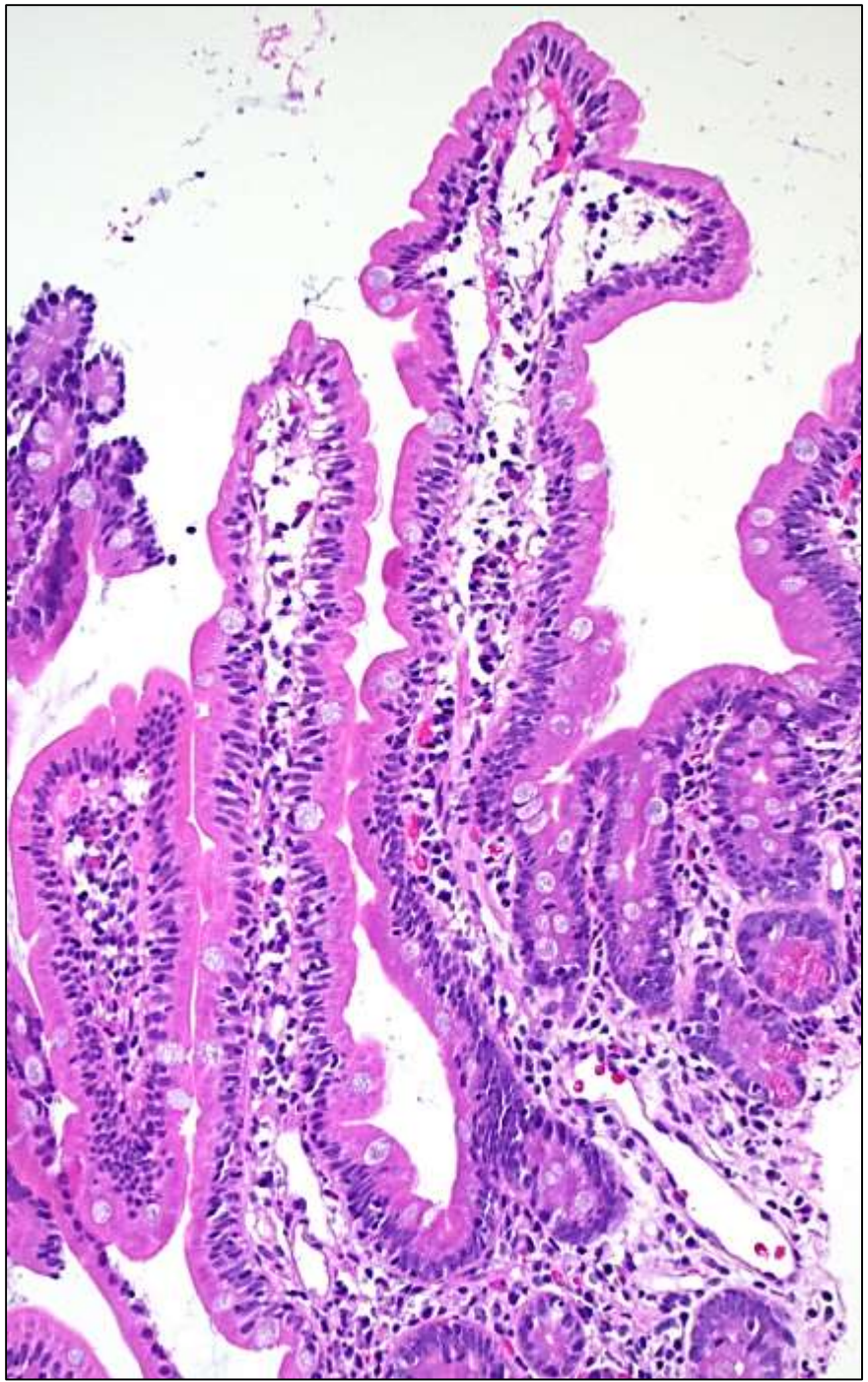


Variant features



Variant features – Bulb only disease



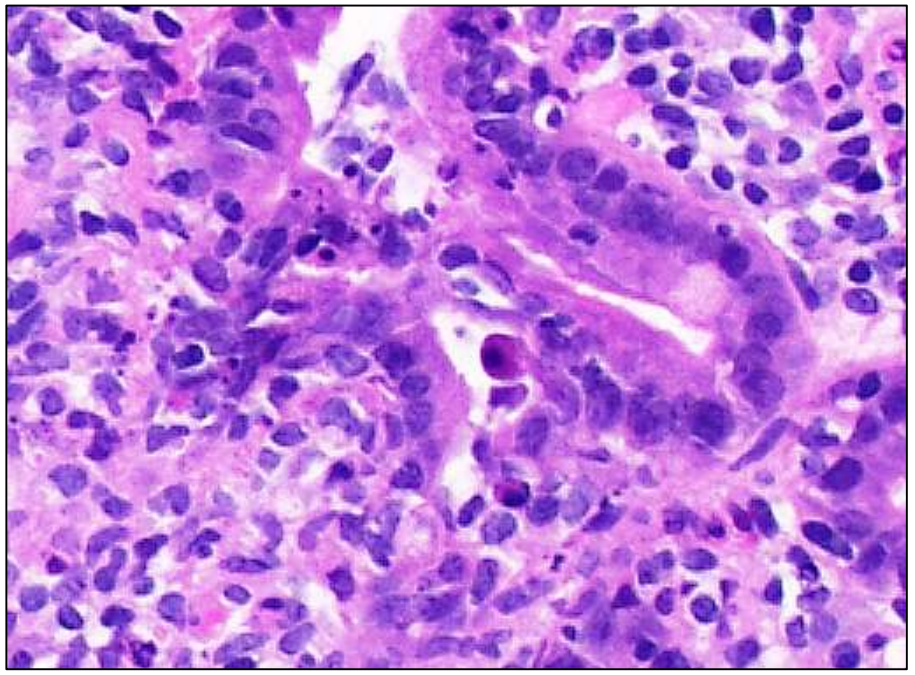


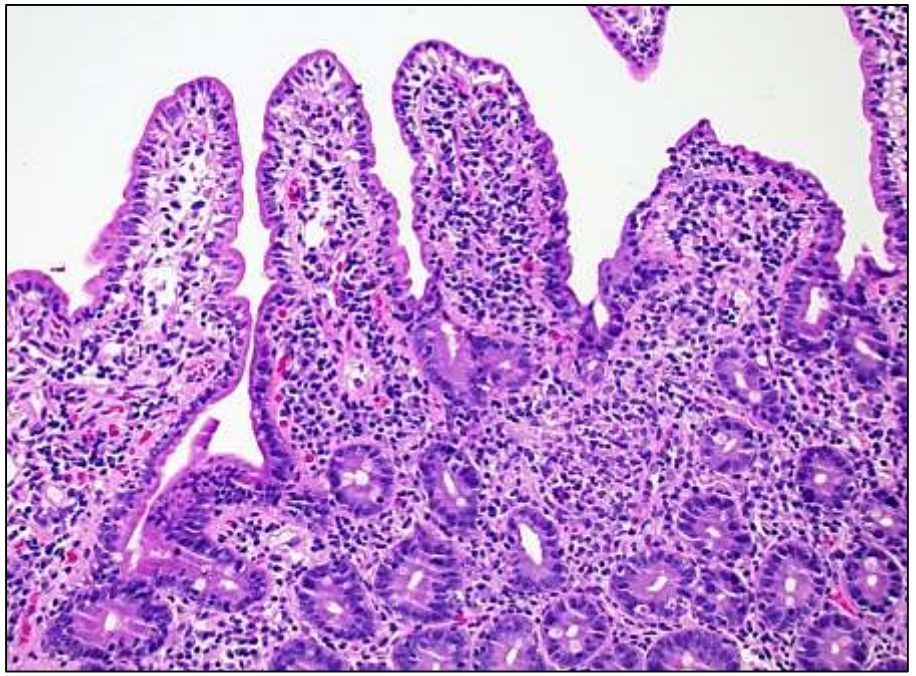
Clues that duodenal intraepithelial lymphocytosis and villous atrophy is **not** coeliac disease

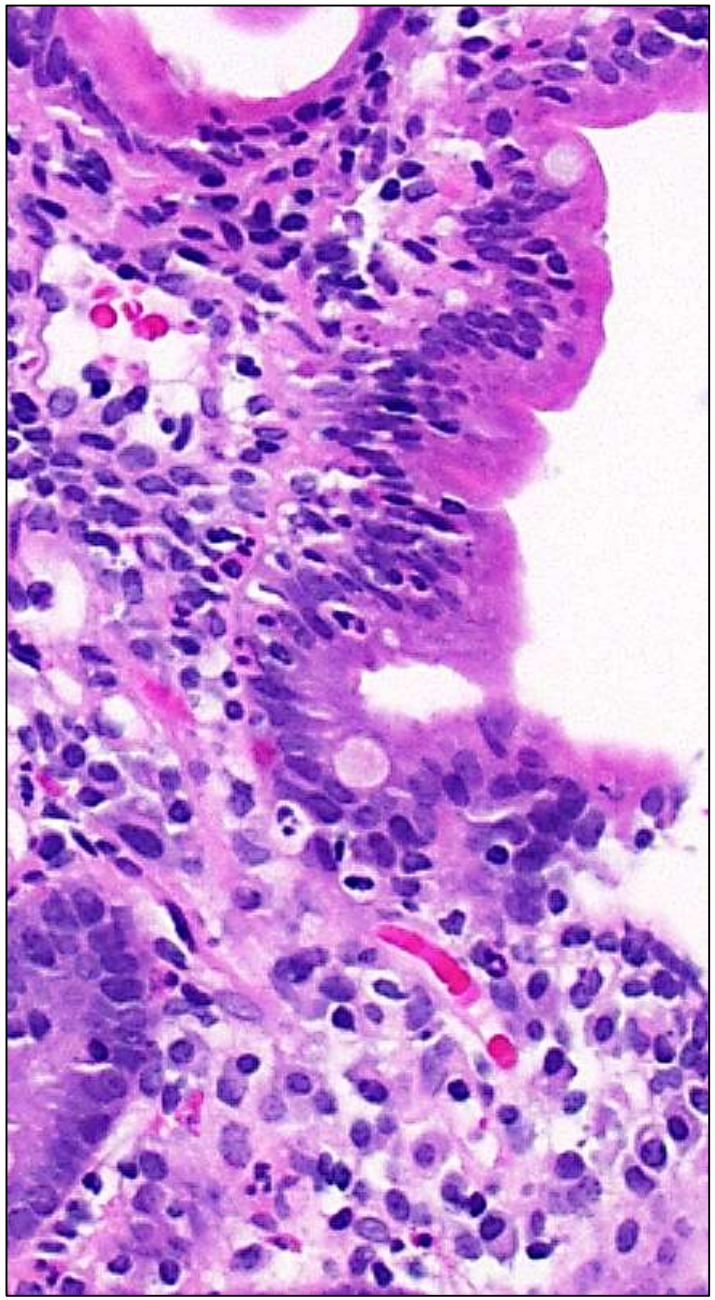
- Morphological clues – to follow
- Normal coeliac serology
- Absence of HLA DQ2/8
- Refractory disease (no response to GFD at 6/12)
- Spontaneous improvement while taking a normal diet
- Epidemiology
  - Older male
  - Low prevalence area ethnicity

Clues for infective (viral) enteritis

- Neutrophils in lamina propria and intraepithelial
- Apoptosis within epithelium
- Incomplete villous atrophy
- Intraepithelial eosinophils
- Attenuated surface epithelium with denudation
- Congestion







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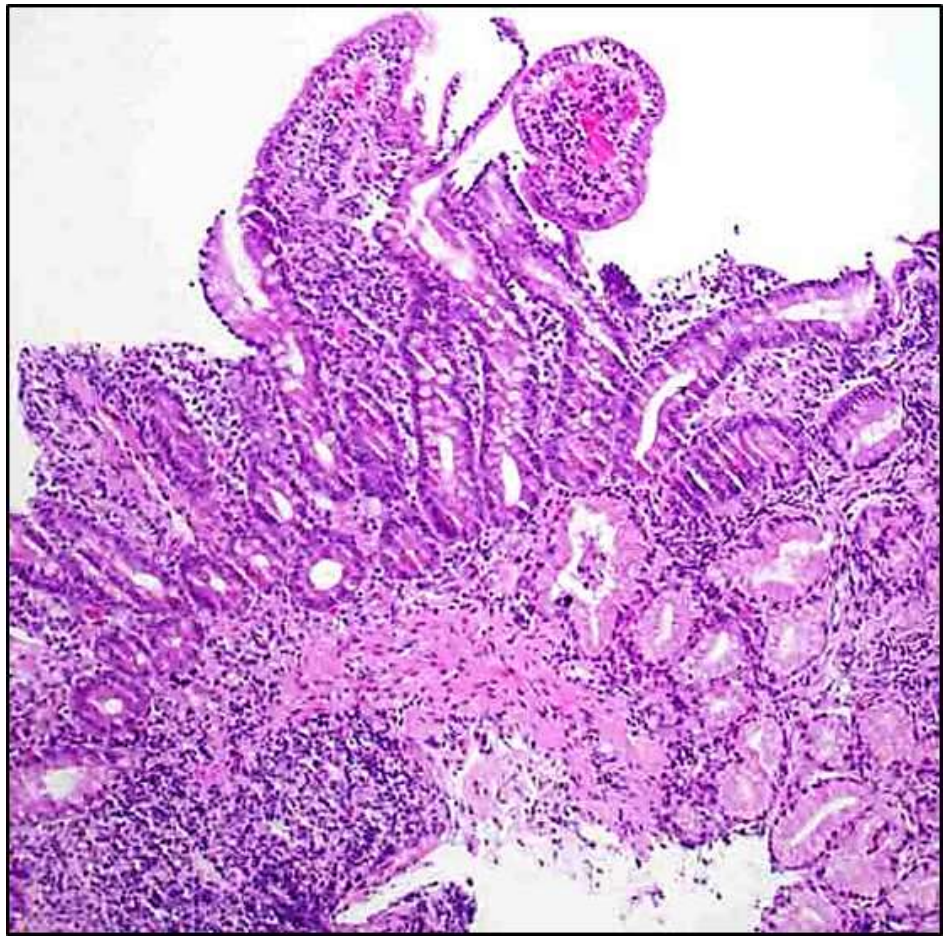
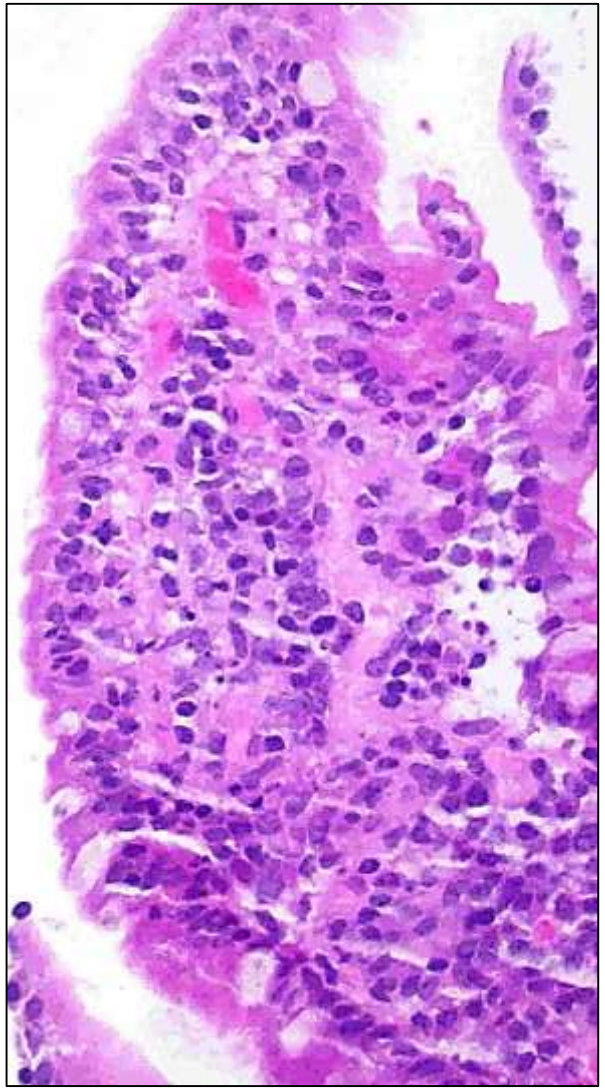
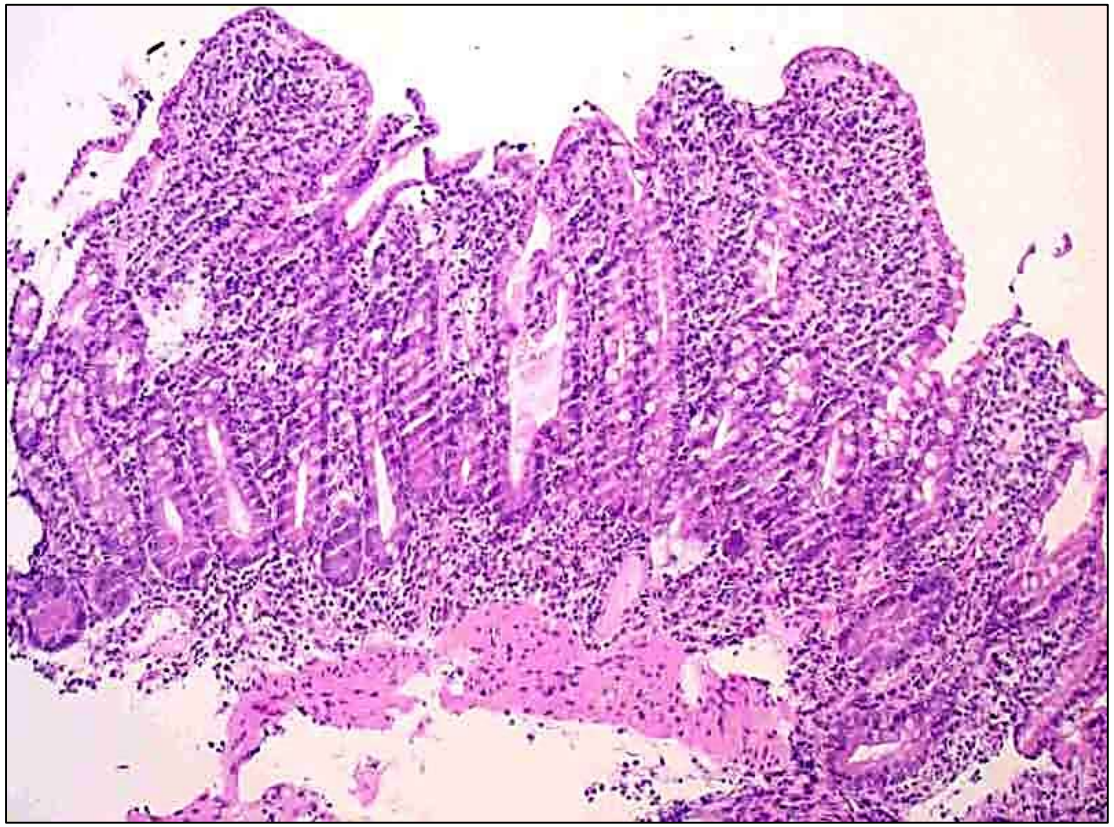
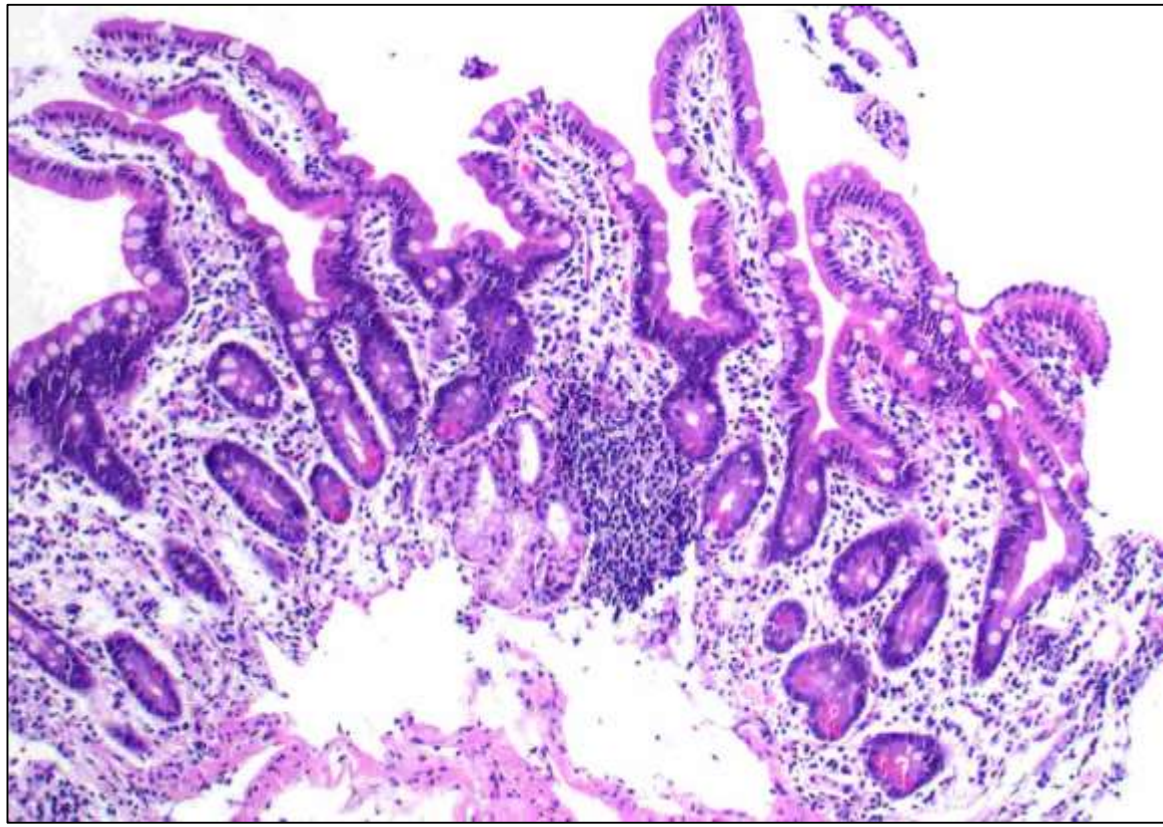




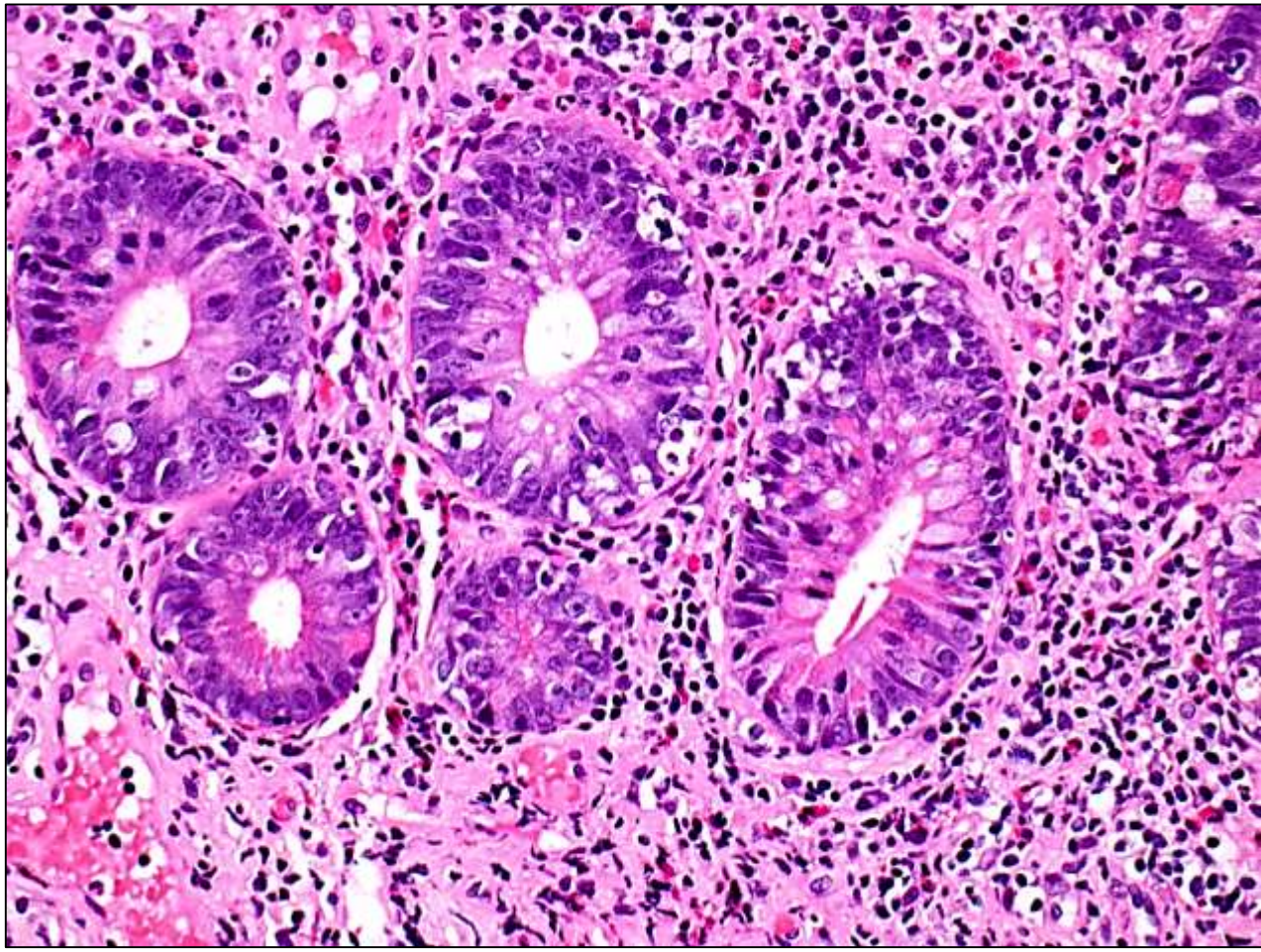
And spontaneous regression on normal diet





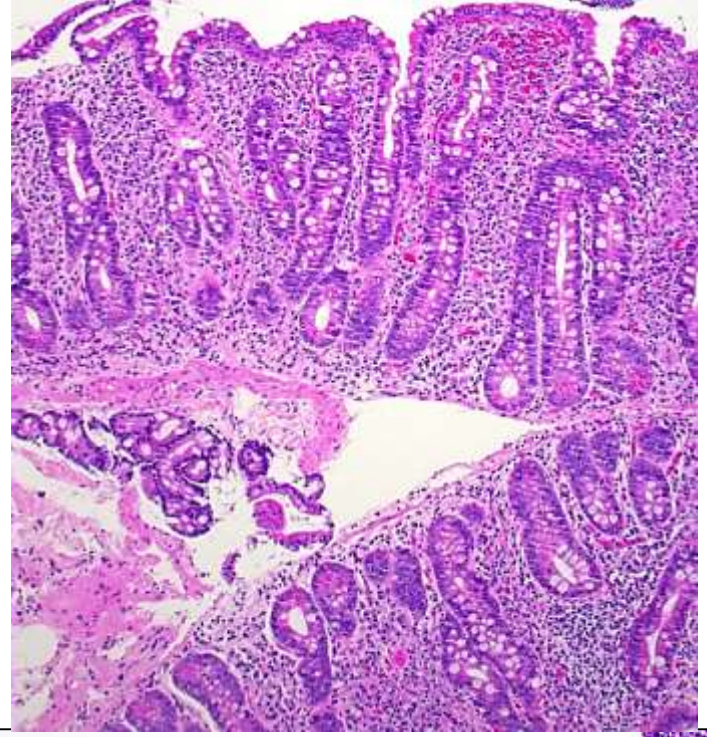
Apoptosis and duodenal intraepithelial lymphocytosis

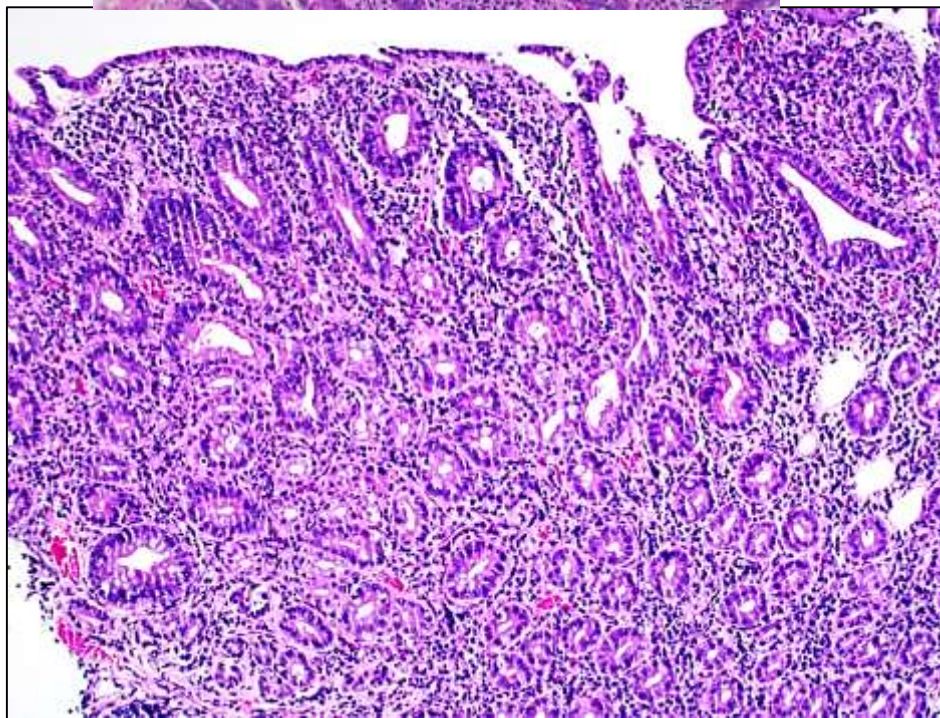
- Viral enteritis
- Medications – Sartans, biologics
- Immune disorders eg IgA deficiency, CVID and Autoimmune enteropathy



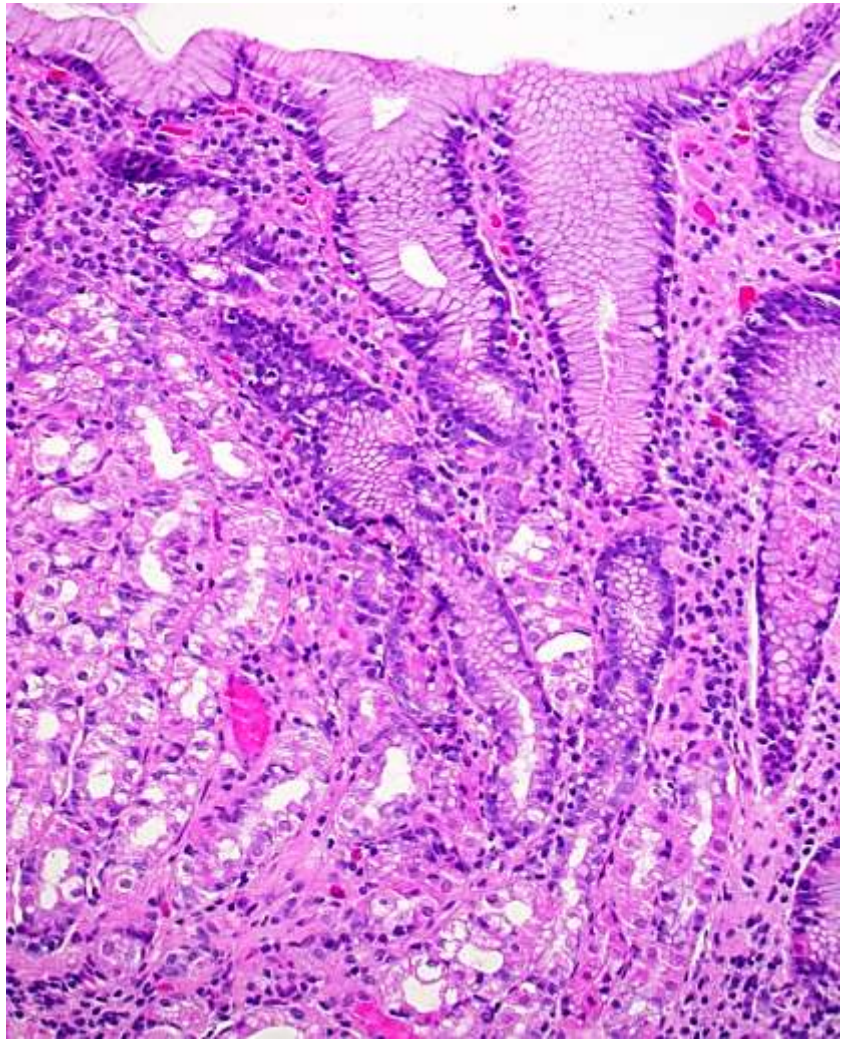
Sartan enteropathy

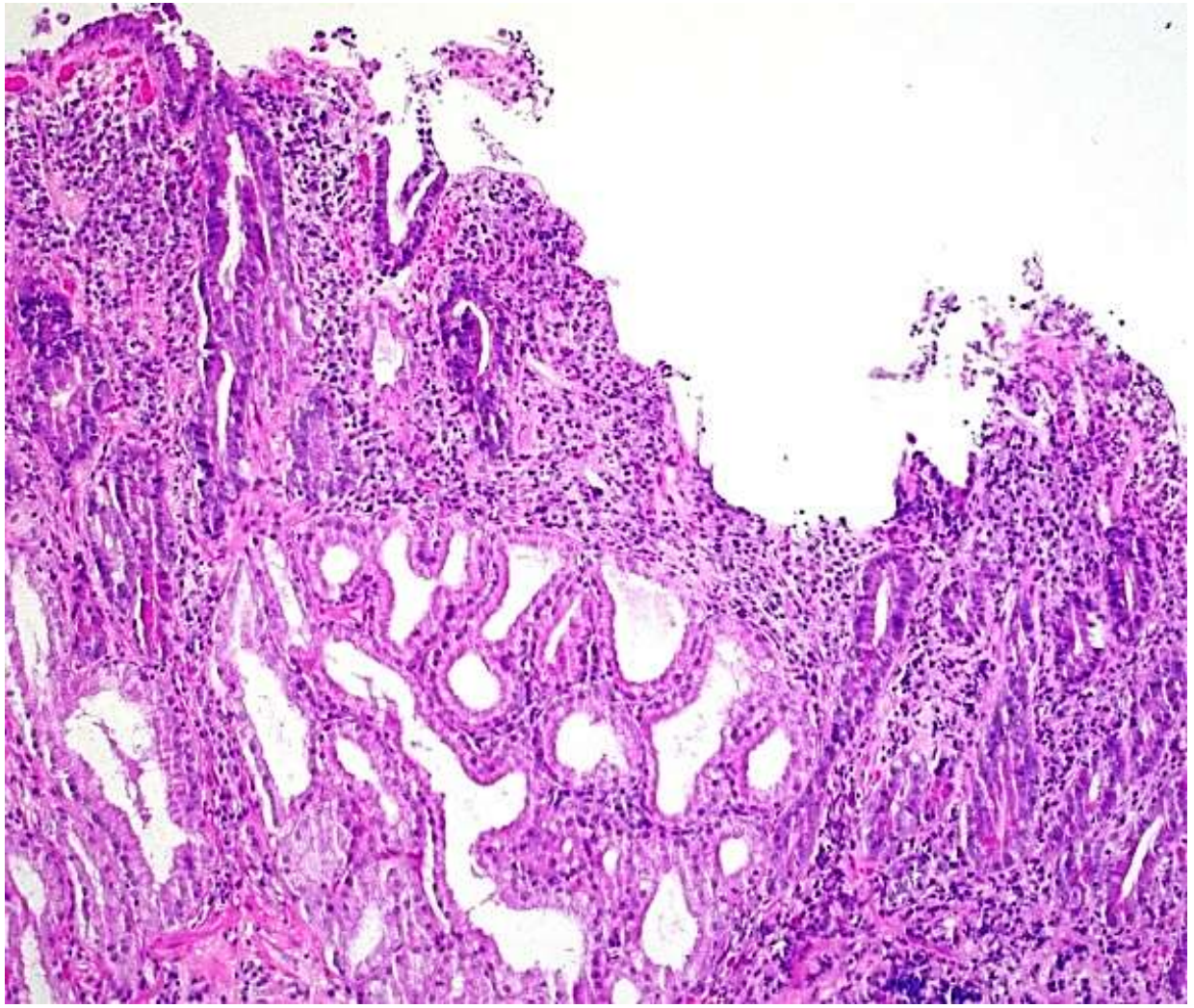
- ‘Sprue like’ enteropathy
- Less IELs than coeliac disease
- Active chronic inflammation
- May be collagenous
- Often have inflammation in other GIT sites also
  - Non-specific or lymphocytic or sometimes collagenous.
- Use of medication >1 year is typical
- Improvement on cessation of drug

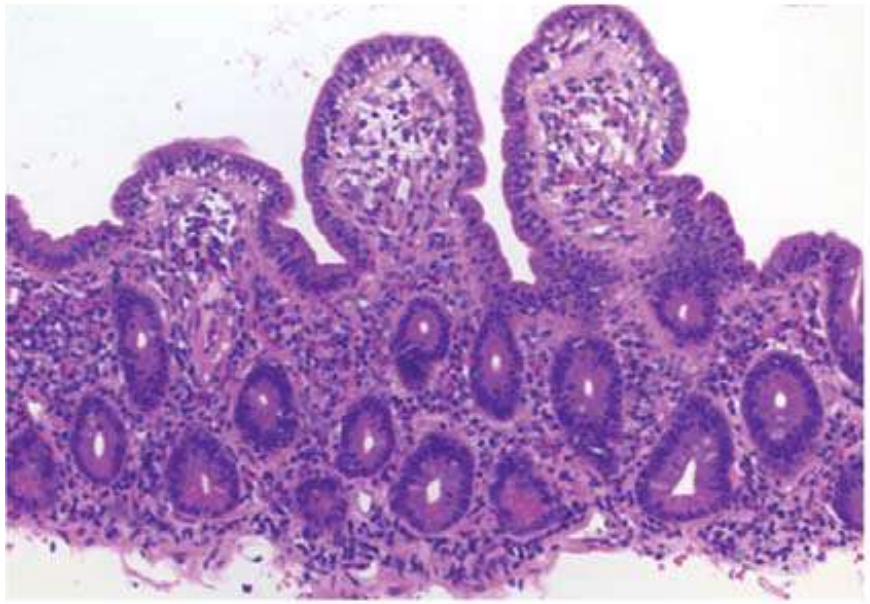


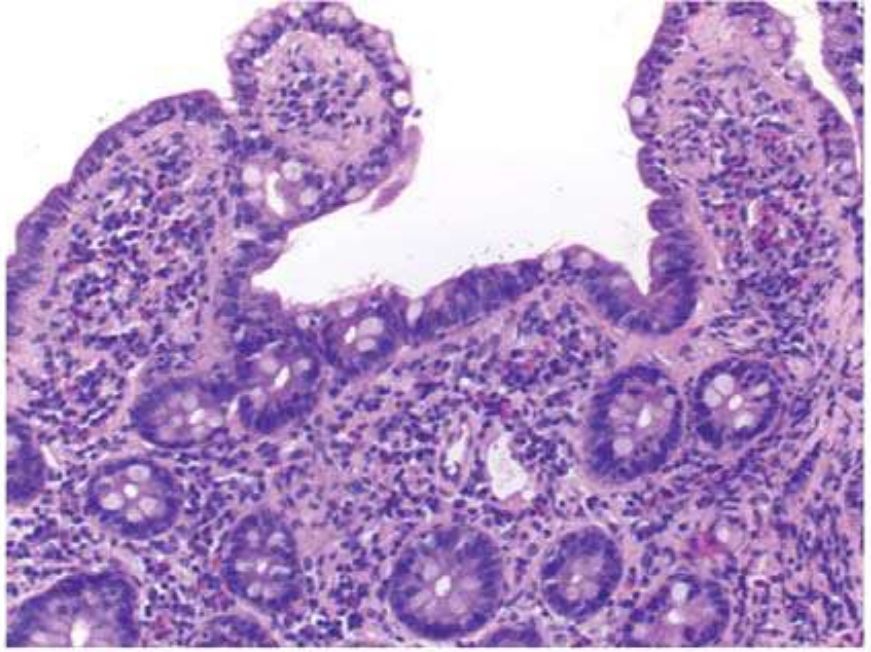


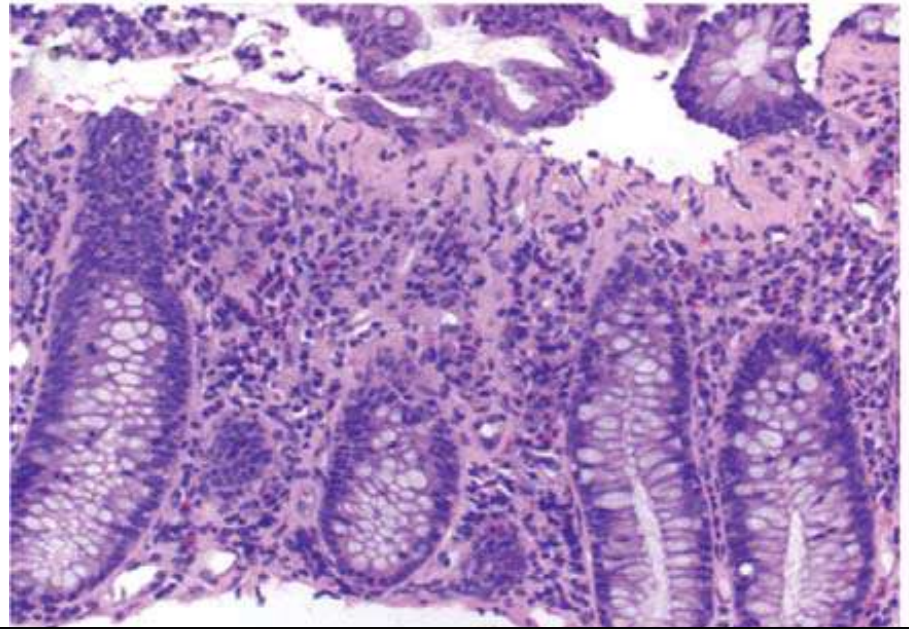
Stomach and duodenal cap in sartan induced GIT inflammation

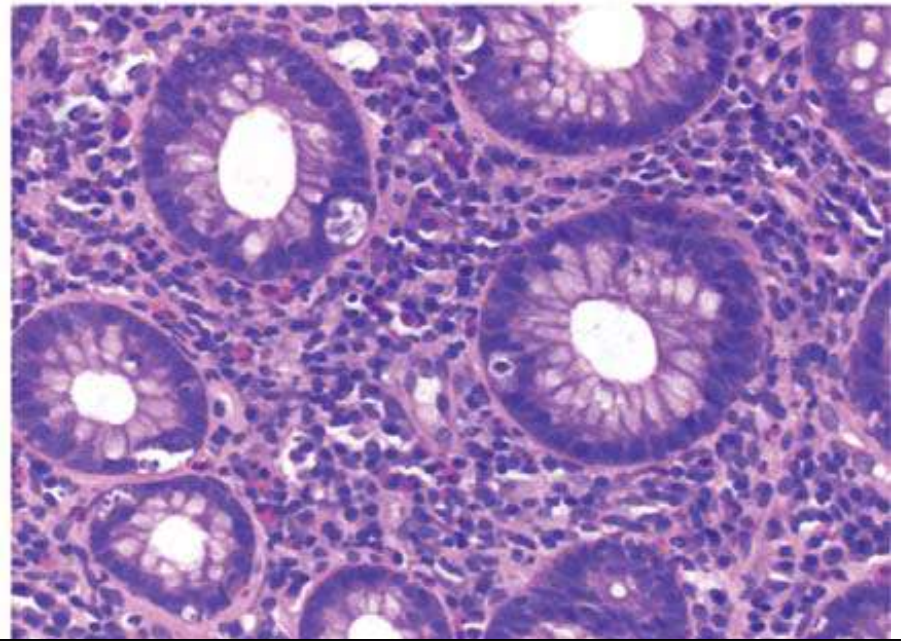








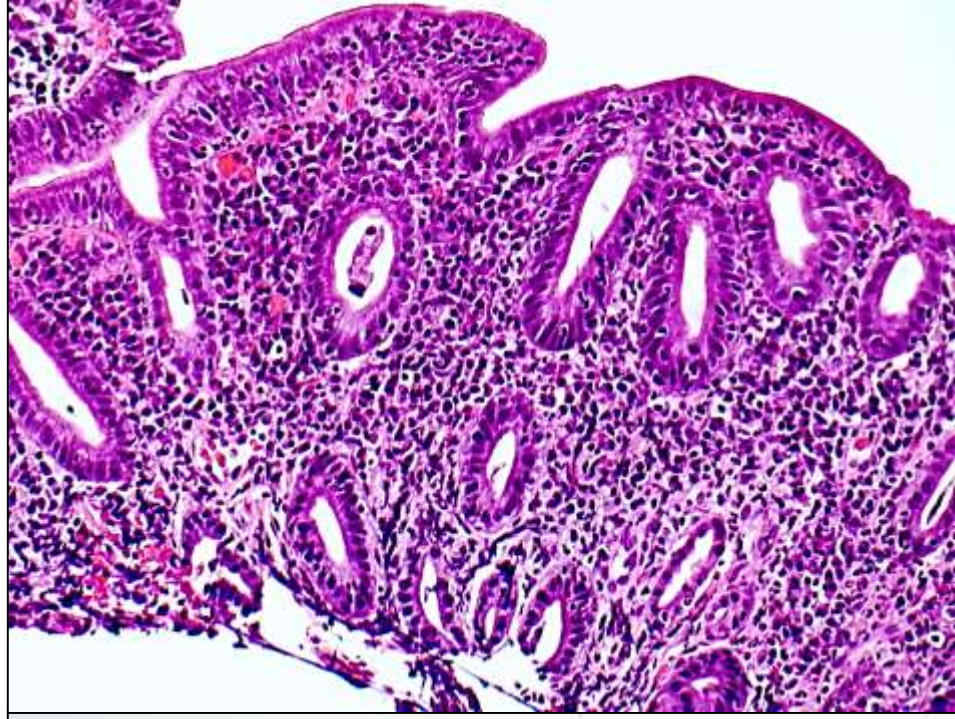


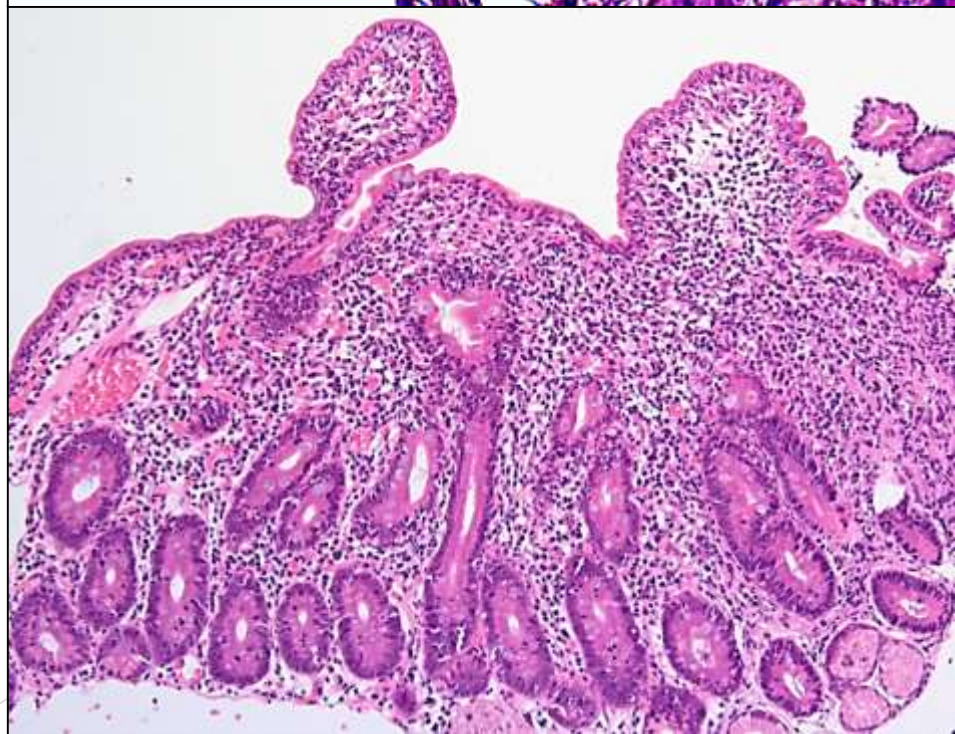


Gallivan C, Brown I. Olmesartan induced enterocolitis. Pathology. 2014;46(4):360–361.

Autoimmune enteropathy

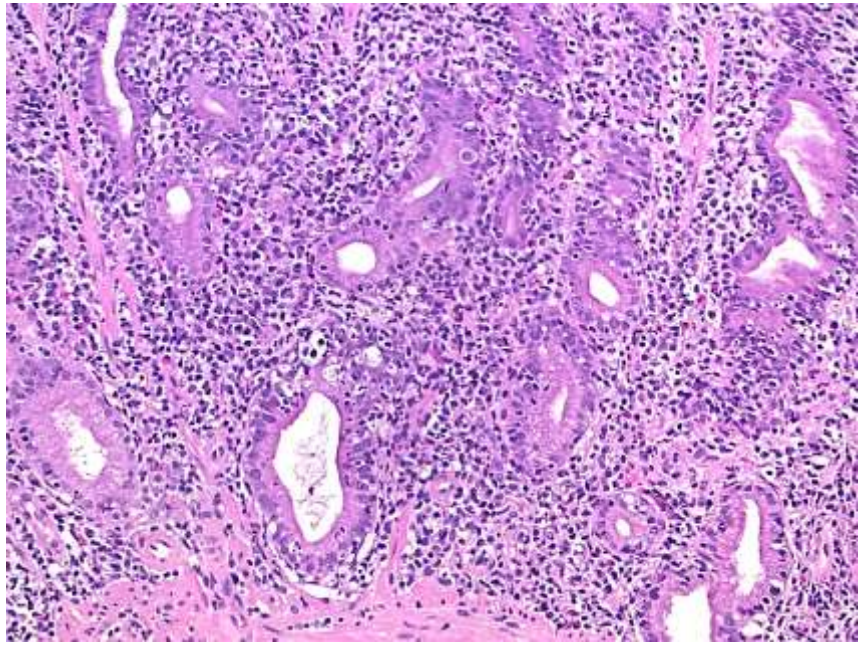
- 20% have coeliac disease like pattern
- Paediatric >> adult
- Associated autoimmune diseases or immune dysregulation diseases (e.g. IPEX)
  - Autoimmune hepatitis common
- Usually very unwell → TPN, multiple immunosuppressant's
- Anti-enterocyte antibodies – not useful

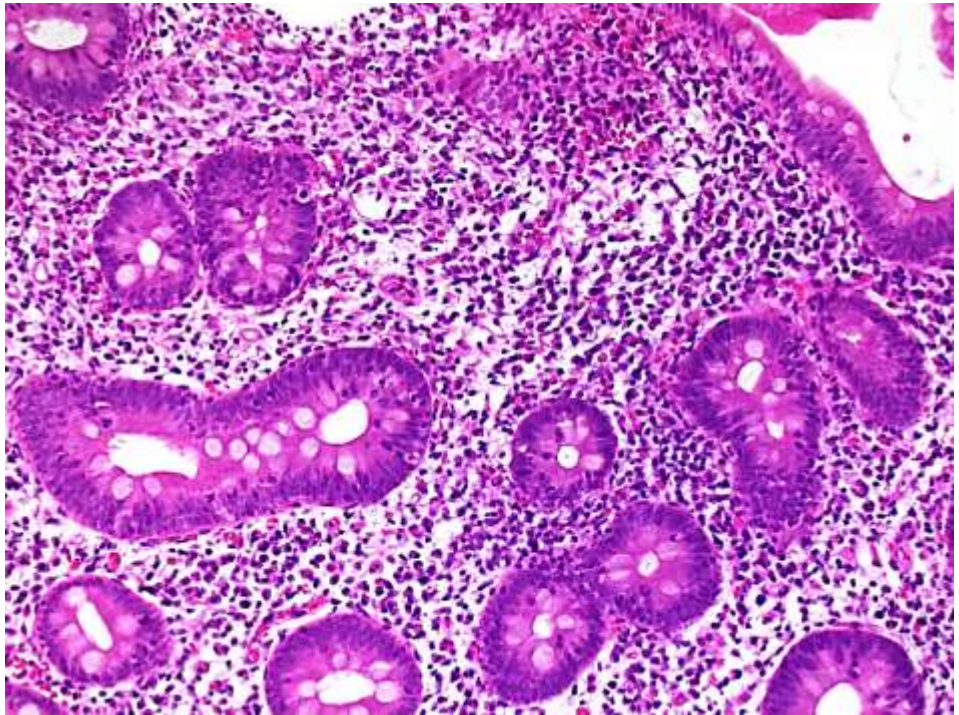


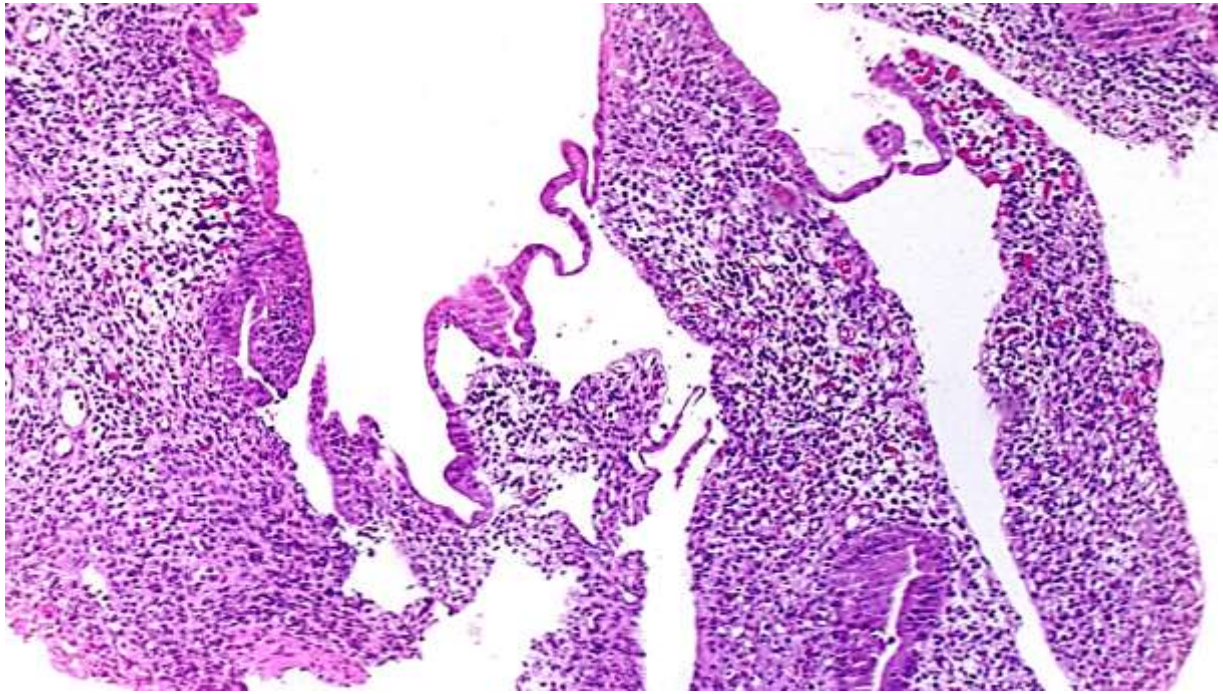


Histological clues for Autoimmune (and other immune e.g. CVID) enteropathy

- Lymphocytosis (or other inflammation) often present throughout GIT
- Apoptosis
- Florid active chronic inflammation ± erosion
- Crypt architectural disturbance
- Crypt drop out (GvHD like)

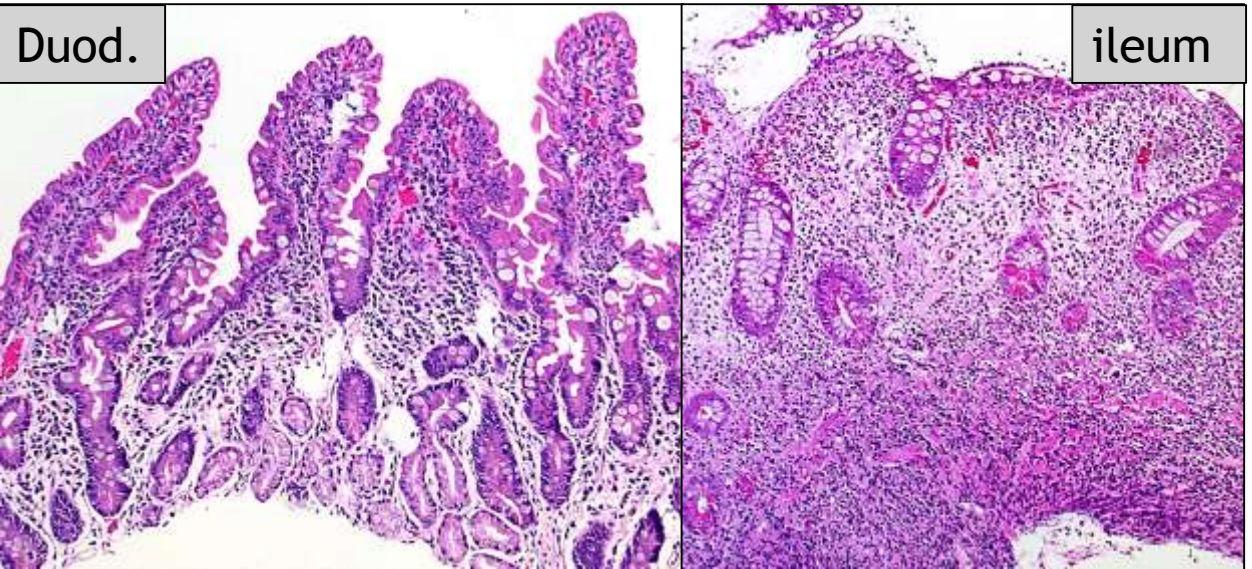


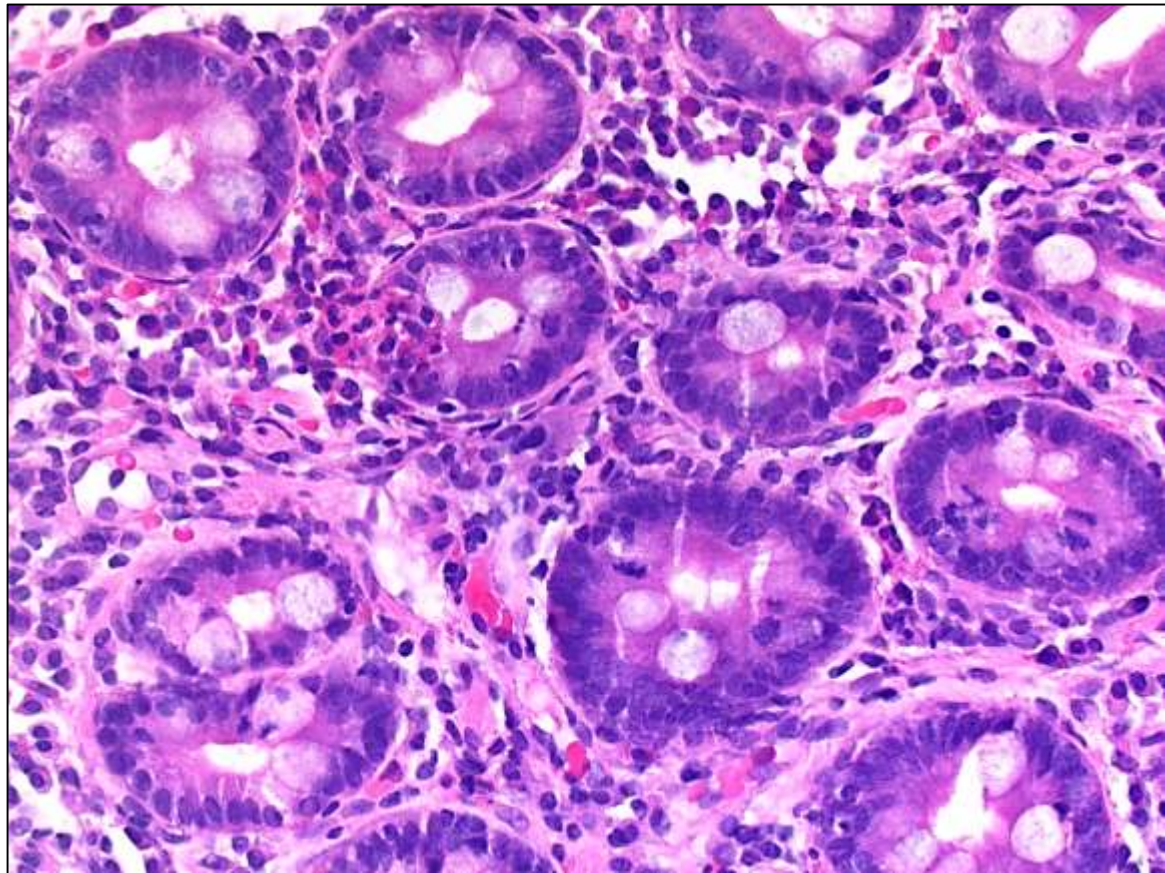




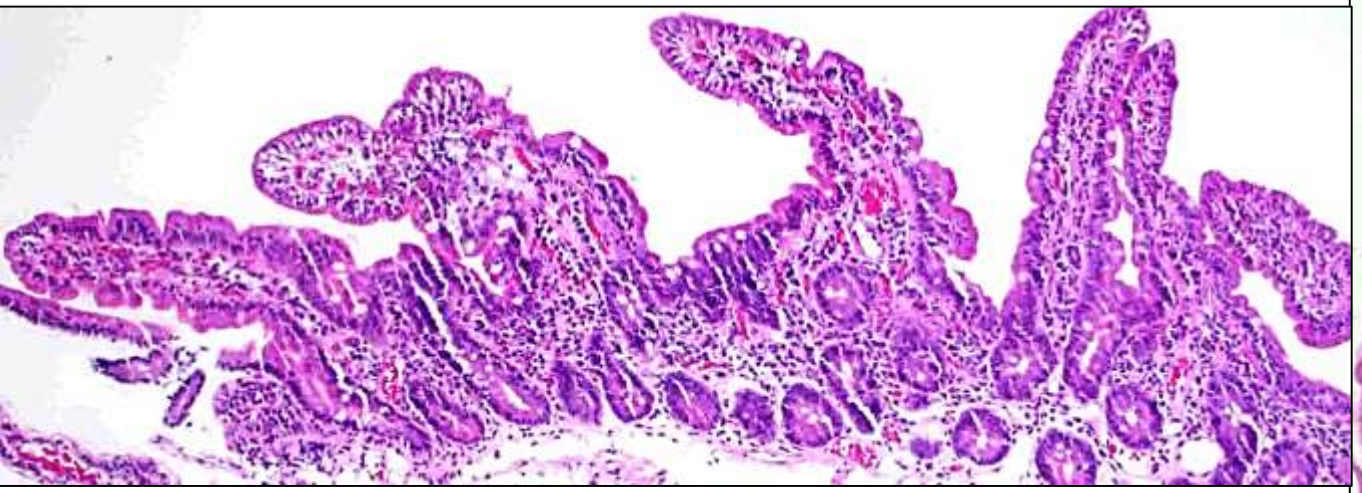
Tropical sprue – histological clues

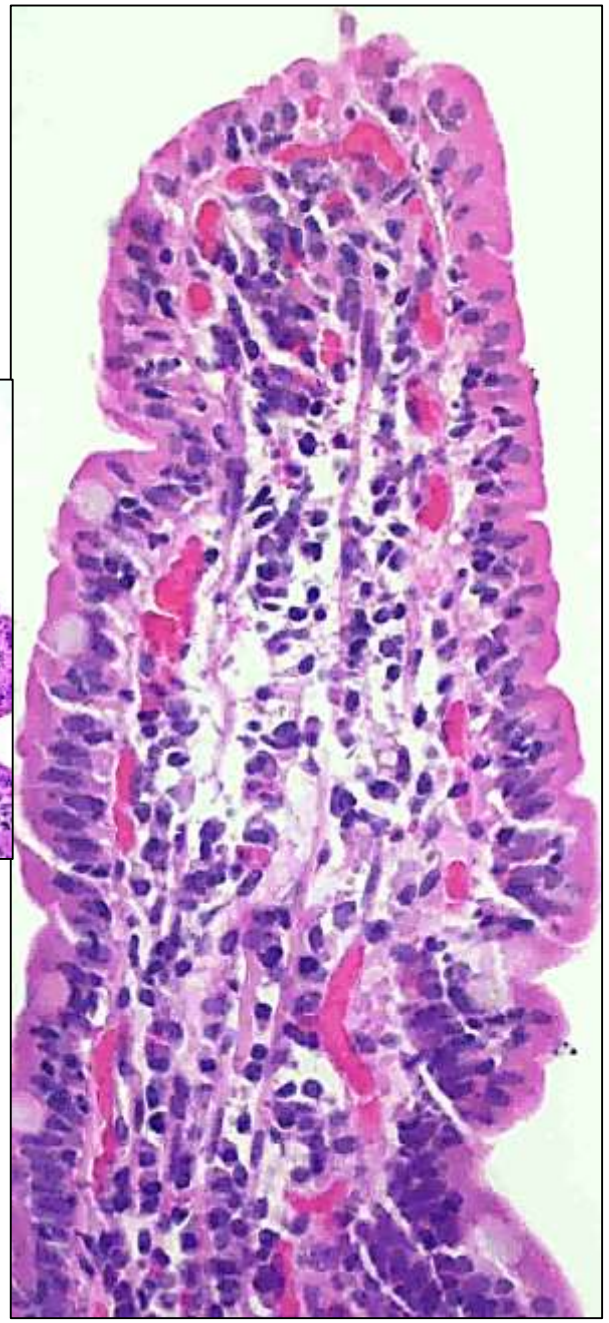
- Incomplete atrophy in duodenum
- Eosinophils in lamina propria and occasionally in crypt epithelium
- Sometimes more IELs in crypts
- Ileum > duodenum

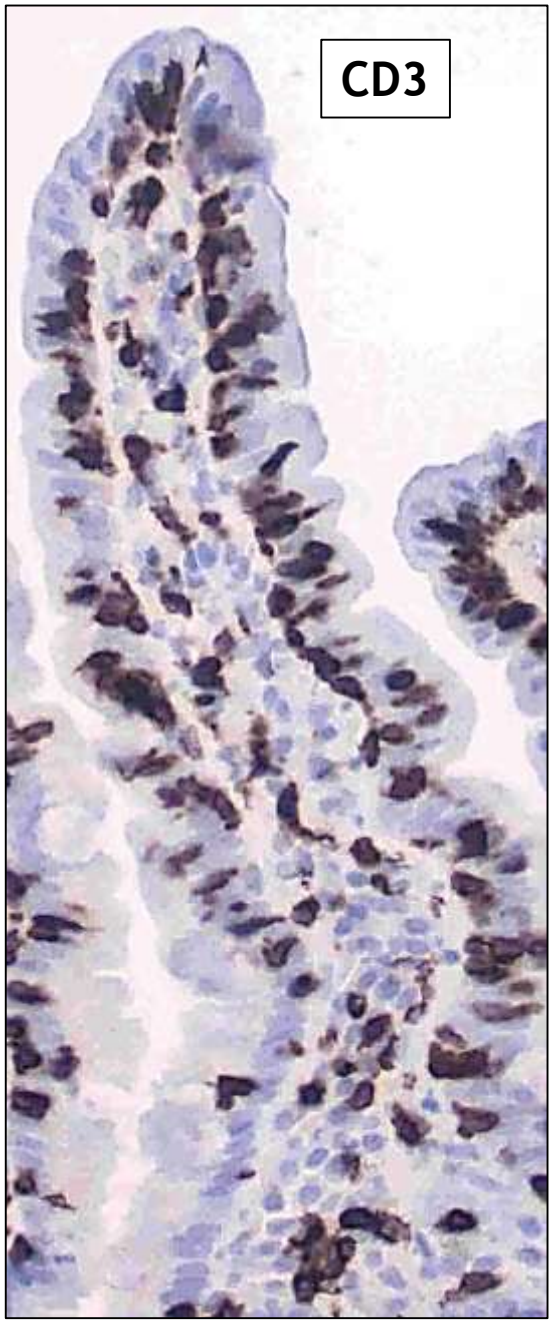




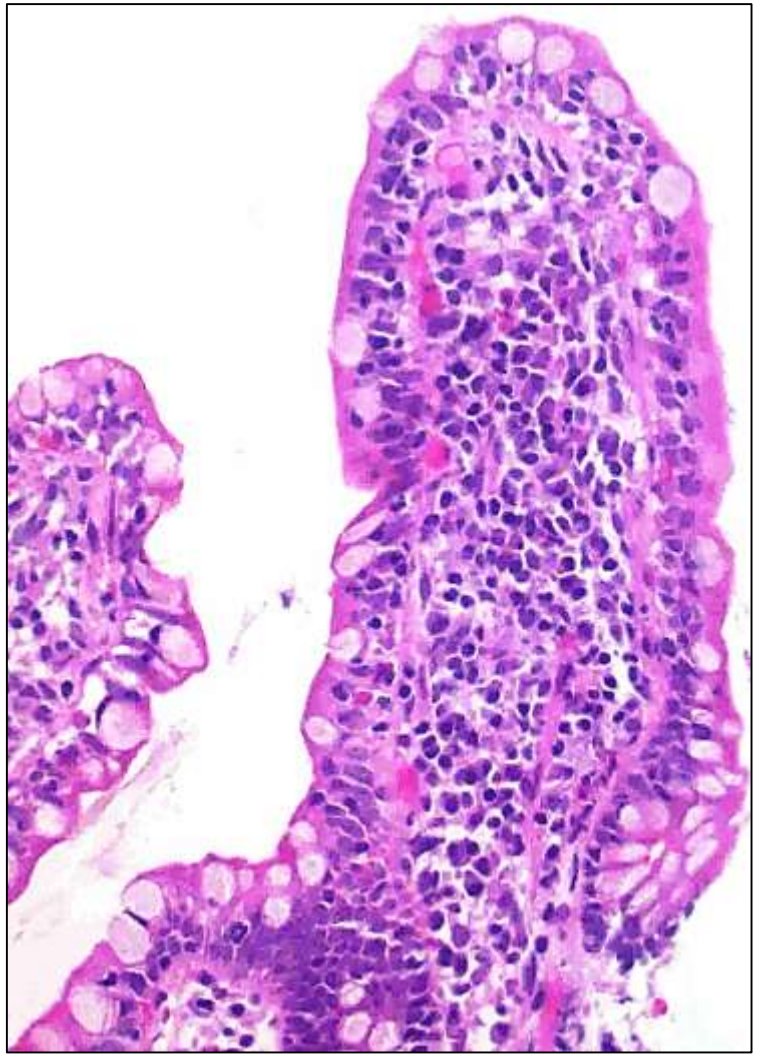
Duodenum



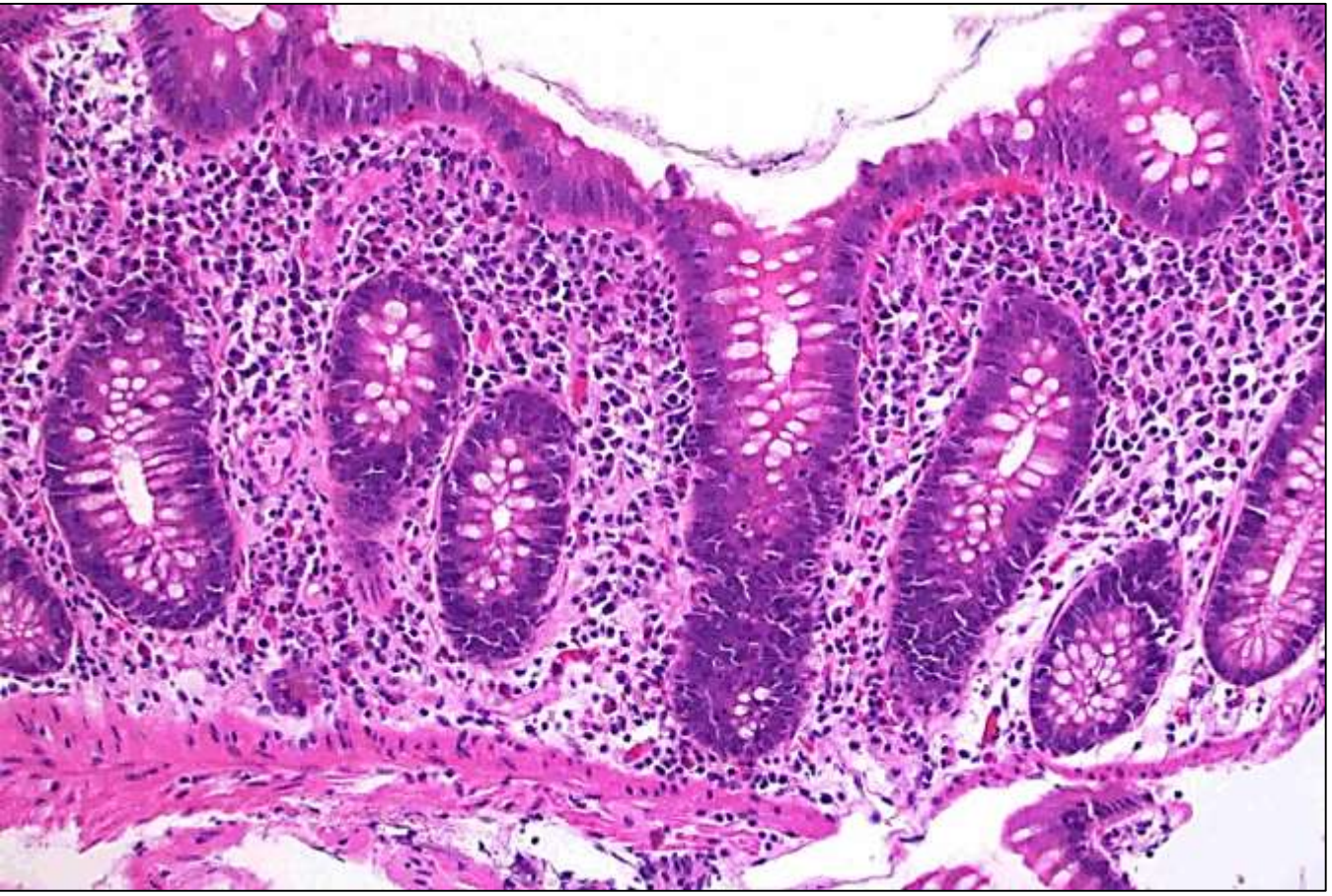




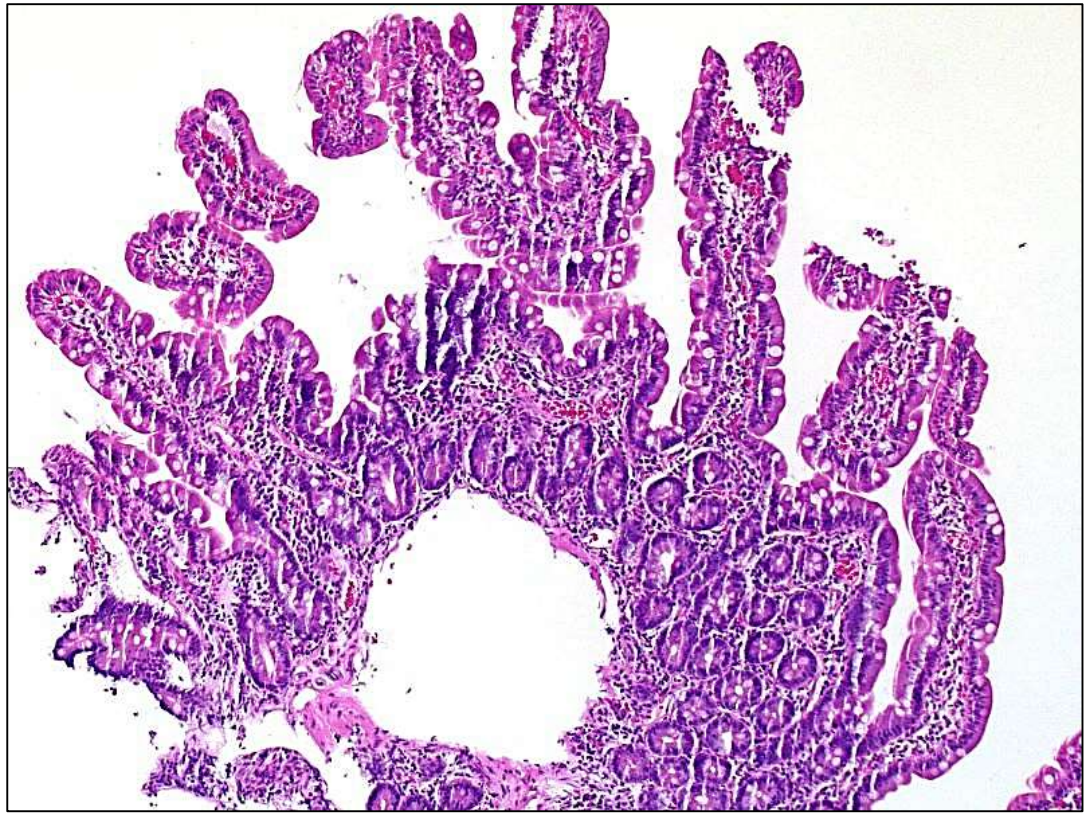
Ileum



Colon



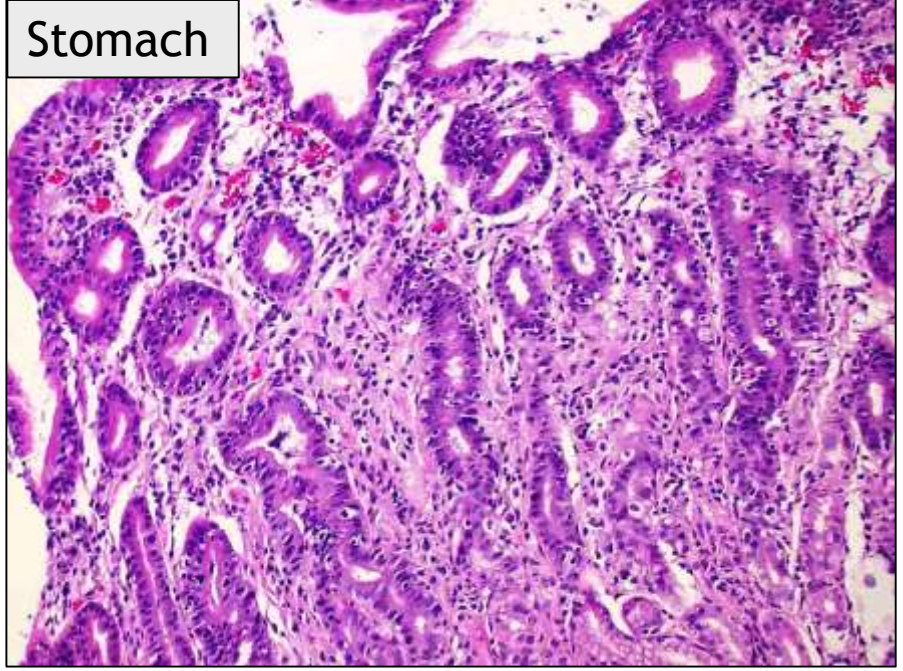
Folate and doxycycline



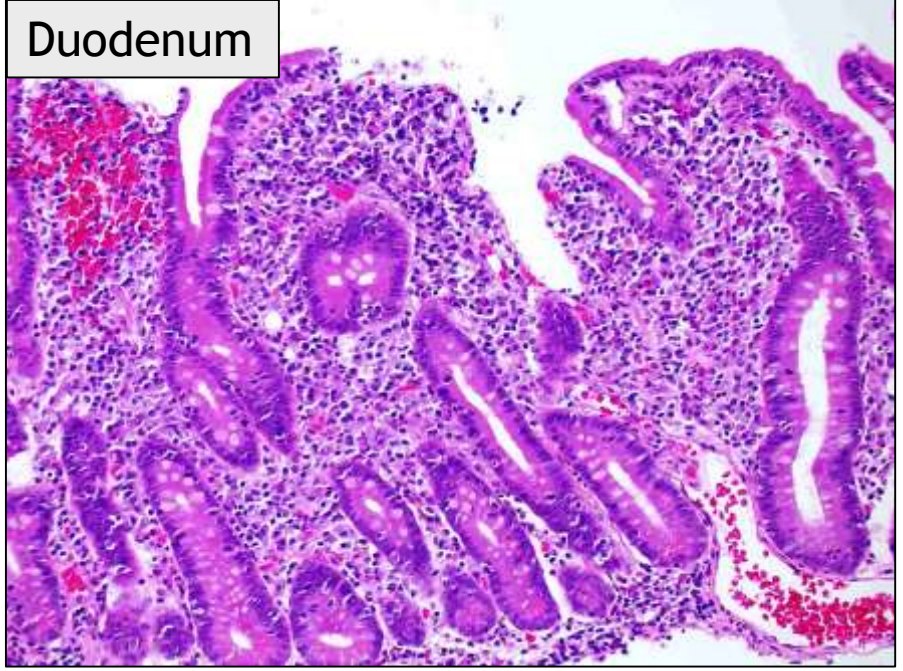
What causes pan GIT lymphocytosis

- **Coeliac disease**
  - Duodenum should be flat
  - TTG negative, no HLADQ2/8, some improvement on GFD
- **Medication** e.g. Sartans
  - Not on any regular medications
- **Immune disorder** e.g. Autoimmune enteropathy, CVID
  - Unusual age of presentation (but maybe a thymoma)
  - No history of autoimmune disorders
- **Lymphoma** (e.g. EATL)
  - B and T cell studies were normal
- **Infection** e.g. viral (maybe tropical sprue if severe)
- **Idiopathic**

Stomach



Duodenum



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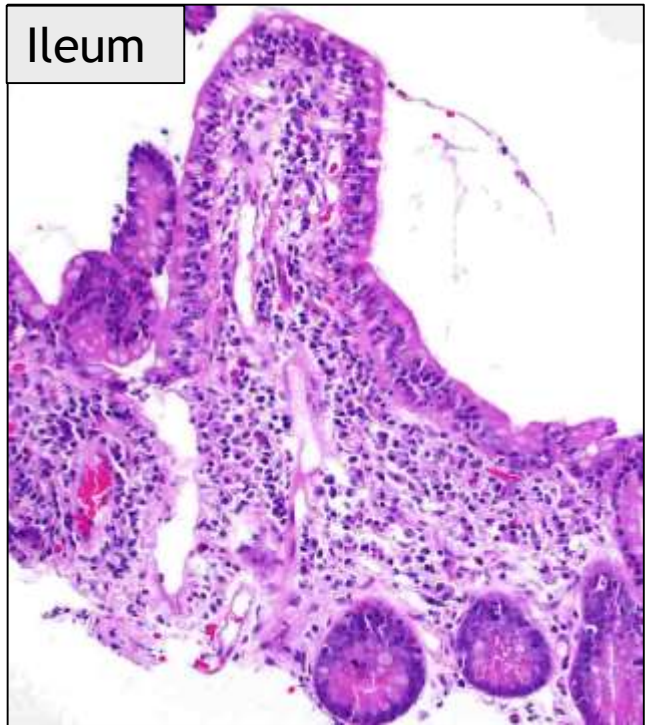
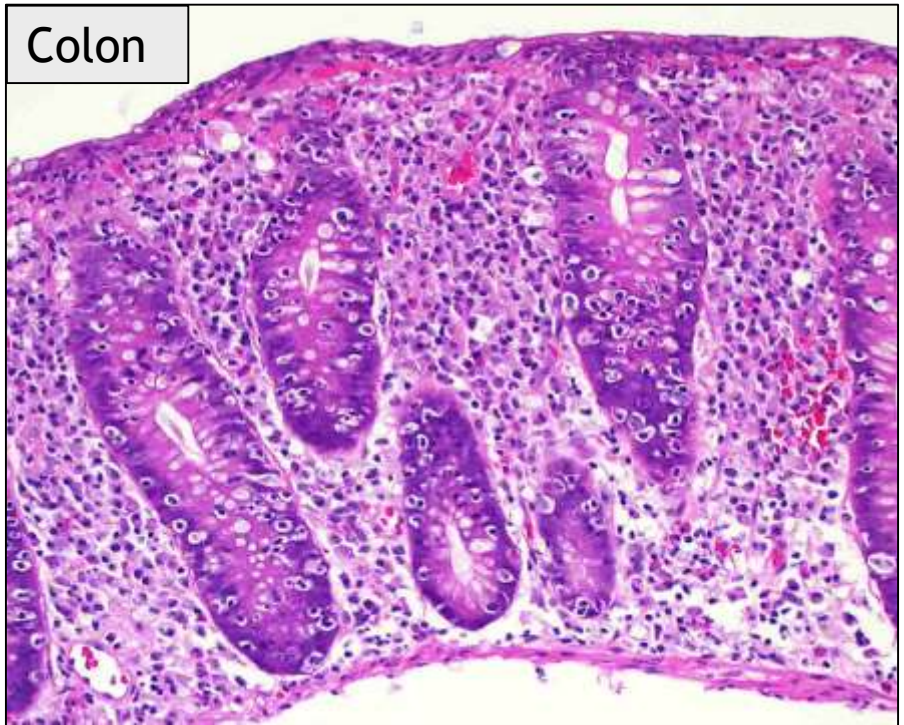


Colon



How do I report duodenal intraepithelial lymphocytosis and villous atrophy?

- No history but looks like coeliac disease
  - Coeliac disease is the most common cause of this pattern. Confirmation by serology and histological response to gluten free diet is recommended
- No history and looks atypical
  - Coeliac disease is possible however, other cause including infection, medications (e.g. sartan family) and immune disorders should also be considered. Coeliac serology and response to is recommended
- Known positive coeliac serology (high tTG)
  - Histological appearances consistent with coeliac disease

Thank you

ianbrown@envoi.com.au

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