

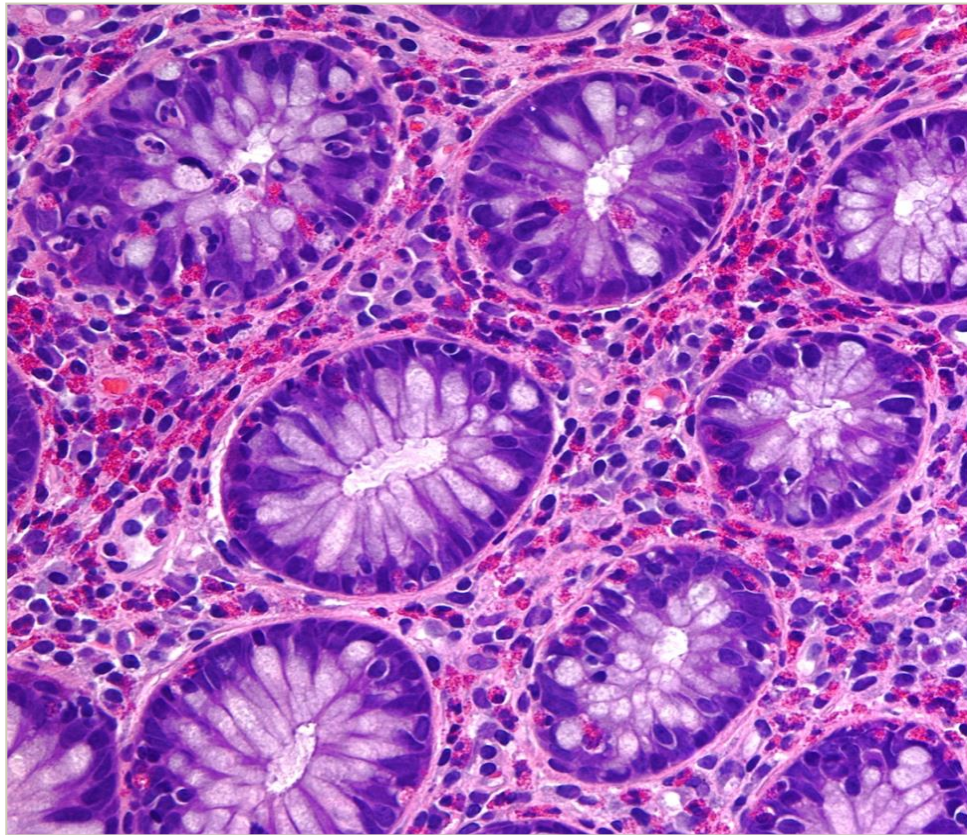


Eosinophils & Iatrogenic Pathology of the Intestines: what you need to know

Friday, November 23rd, 2018

Professor Kieran Sheahan

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St Vincent's University Hospital
University College Dublin



Classification of eosinophilic disorders of the small and large intestine

Aoife J. Mc Carthy and Kieran Sheahan

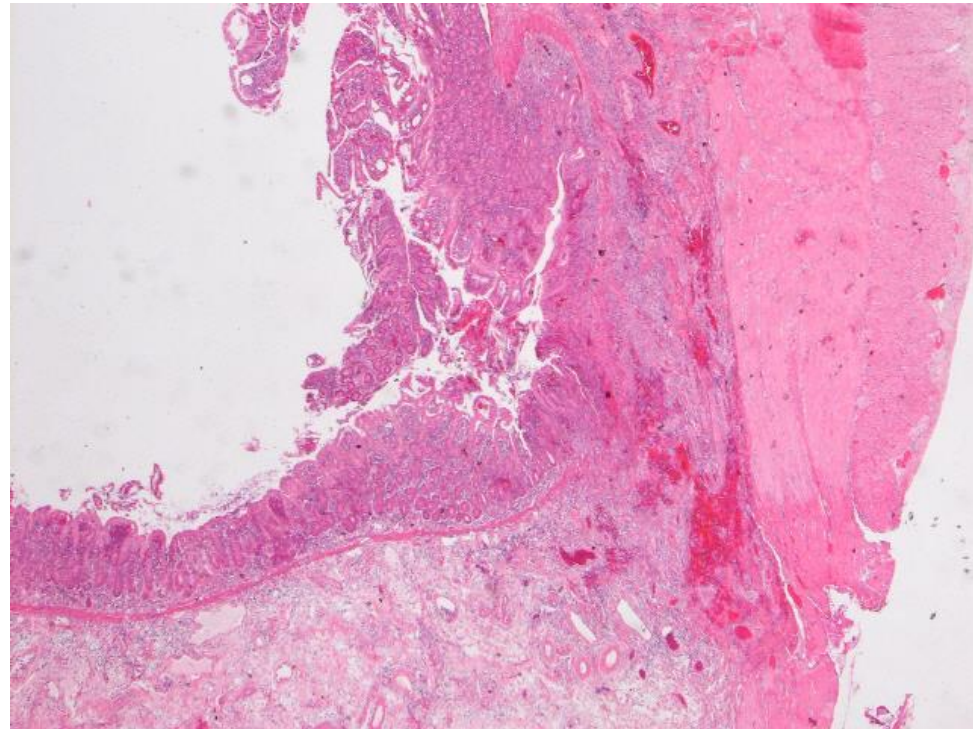
Virchows Archiv Annual Review 2018

History

- 2011
 - Abdominal pain
 - Gradual onset, severe
- CT imaging
Small bowel dilatation consistent with obstruction
 - No specific cause identified

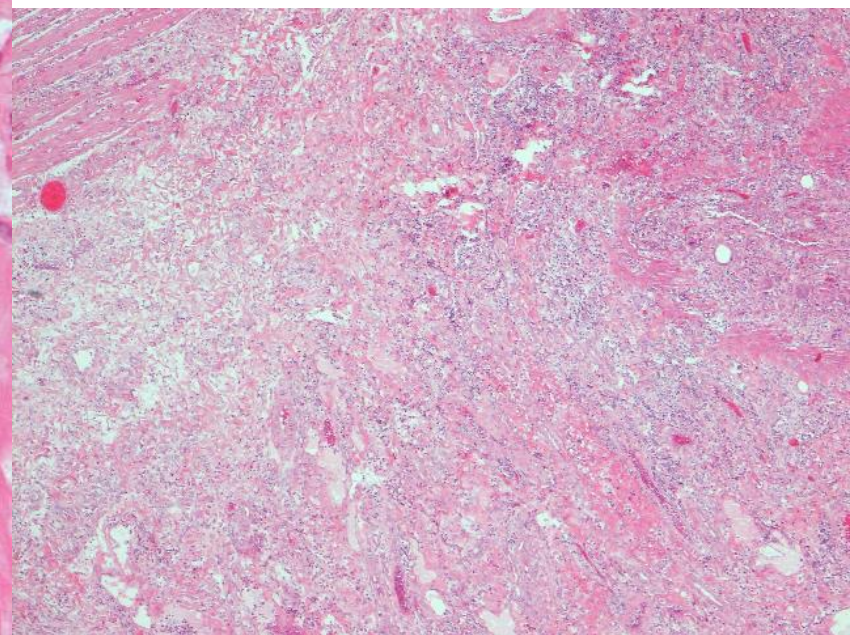
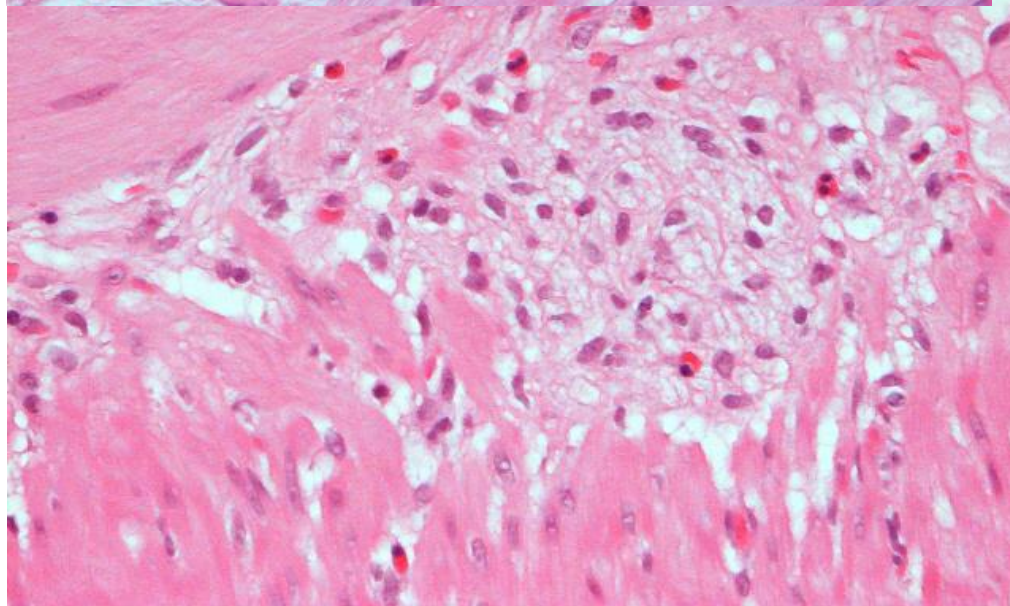
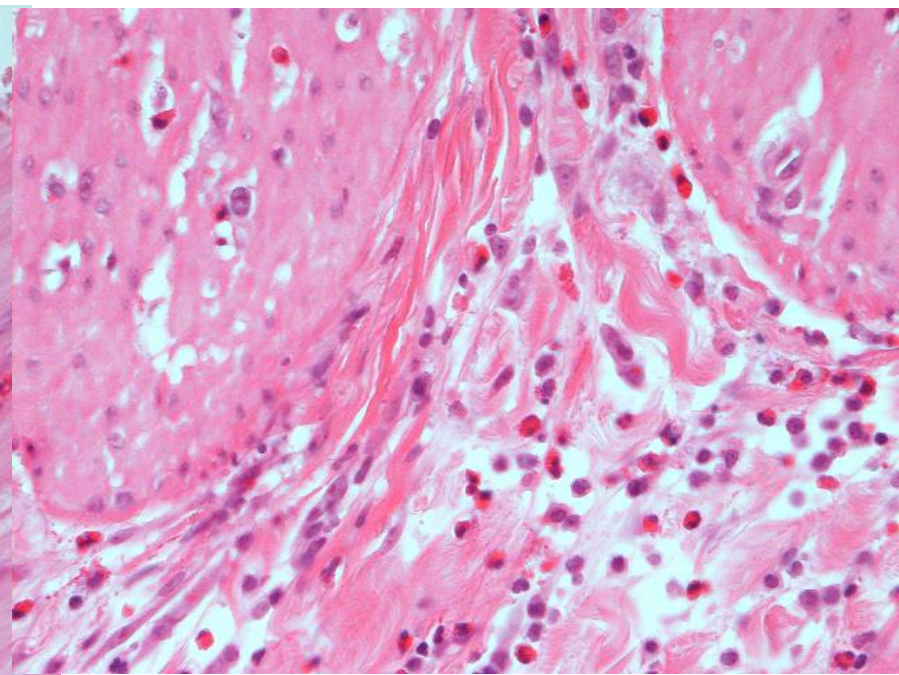
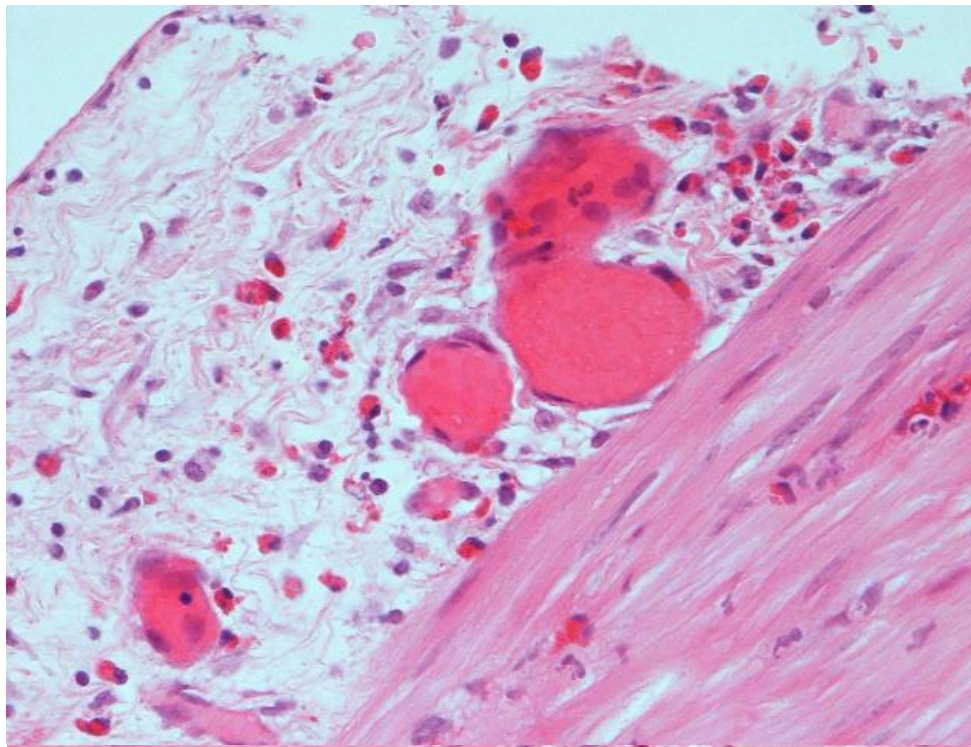
Histology

- Small bowel resection
 - Segment small bowel showing focal ulceration
 - Prominent eosinophils in muscularis propria and subserosa
 - No granulomas/lymphoid aggregates.
- DX
 - Crohn's Disease (on balance of probabilities)
- Treated with
 - Budesonide



2017

- **Nausea and vomiting**
- **Severe abdominal pain with recurrent hospital admissions**
 - **OGD**
 - D2 – mildly increased IELs, Villi normal
 - Lower oesophagus: IEE 23/HPF – reflux v EOE
 - **Colonoscopy**
 - Acute inflammatory polyp at ICV. TI and colonic biopsies normal
 - **MRI small bowel**
 - Normal
- **Review of resection**
 - Degree and pattern of eosinophil infiltrate involving MP, and subserosa favoured EGID over Crohn's Disease
- Eosinophils 0.2 check
- CRP 4
- IgE 275 (normal)
- RAST IgE
 - IgE milk 1.51 (0-0.35)
 - Class 2



OUTCOME

- TX
 - Well on an Exclusion diet
 - Montelukast (leukotriene receptor antagonist)
 - Sodium Cromoglycate(mast cell stabiliser)
 - No evidence of Crohn's Disease

Allergy- Associated Colitis in adults

- Similar to disease process as in infants
 - Cow's milk, human milk, soya
 - Exclusion diet for 2-3 years
- Allergy history
- Drug related – NSAIDS
- TI and colon>> rectum
- Clinical features are very non-specific
 - Epithelium, LP, submucosa
 - Lack of damage to epithelium

Eosinophils in GIT

- Histologically diagnosis of Eosinophilic gastrointestinal disease (EGID) remains subjective
- Number differs by up to 40 times
 - Geographic regions
 - Seasons
- Small bowel

Table 1 Normal number of eosinophils/HPF in the small intestine and suggested minimum eosinophil count/HPF for a pathological diagnosis of eosinophilic gastroenteritis

Category	Number of eosinophils/HPF	Authors
Normal number of eosinophils in the small intestine	Up to 30 eosinophils/HPF	Lowichik et al.
Suggested minimum eosinophil count for a pathological diagnosis of eosinophilic gastroenteritis	> 20 eosinophils/HPF	Uppal et al, Chen et al, Lee et al.
	> 30 eosinophils/HPF	Lowichik et al.
	> 50 eosinophils/HPF	Ingle et al.

HPF high power field

Eosinophils in Large Colon

- Up to 50 eosinophils/HPF seen in normal colon
- Higher prevalence in right colon
- Gradient from proximal to distal with second peak in rectosigmoid
- Inaccurate to apply threshold eosinophils to random colon biopsies
 - Right colon >50
 - Transverse colon >35
 - Left colon >25

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Virchows Arch
<https://doi.org/10.1007/s00428-017-2249-1>



INVITED ANNUAL REVIEW ISSUE

Classification of eosinophilic disorders of the small and large intestine

Aoife J. McCarthy^{1,2} · Kieran Sheahan^{1,2}

Clinical Presentation (EGIDS)

- Mucosal
 - Nausea, vomiting, weight loss, diarrhoea
 - Protein-losing enteropathy, malabsorption, FTT
- Muscularis Mucosa
 - Intestinal obstruction, distention
- Subserosal
 - Ascites

Work Up

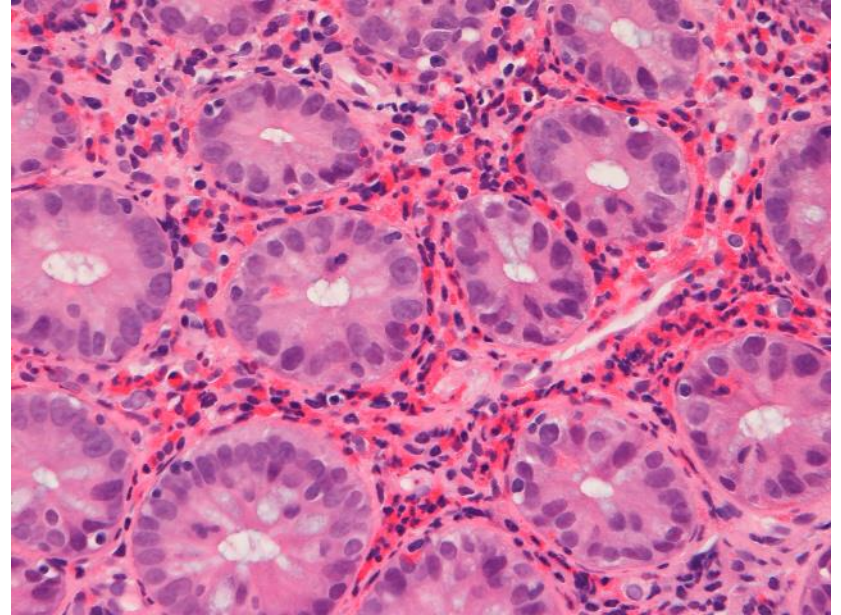
- Labs
 - Hypoalbuminaemia
 - Prolonged PT
 - Peripheral eosinophilia >500
 - IDA
 - IgE
- Stool for parasites
 - *Strongyloides* and *Toxocara* species
- Ascitic fluid sampling
- Endoscopy – mucosal
- Full Thickness R – submucosal
- Cross-sectional imaging
- Peripheral eosinophilia DDX
 - Adrenal insufficiency
 - HIV
 - Immune deficiency
 - Myeloproliferative neoplasms

Primary Eosinophilic Gastroenteritis

- 1/10,000-100,000
- Age: 20-50
- History of allergies
- +/- Serum Eosinophilia, raised IgE
- Primary
 - GI symptoms
 - GI eosinophil infiltrates
 - No other cause identified
- Stomach and proximal SB most common
- Mucosal disease 57%
 - Nausea/vomiting
 - Diarrhoea/Anaemia
- Muscularis Propria 30%
 - Intestinal obstruction
- Serosal/Subserosal 12.5%
 - Ascites
 - Intestinal obstruction
 - IgE mediated disease

Eosinophilic Colitis

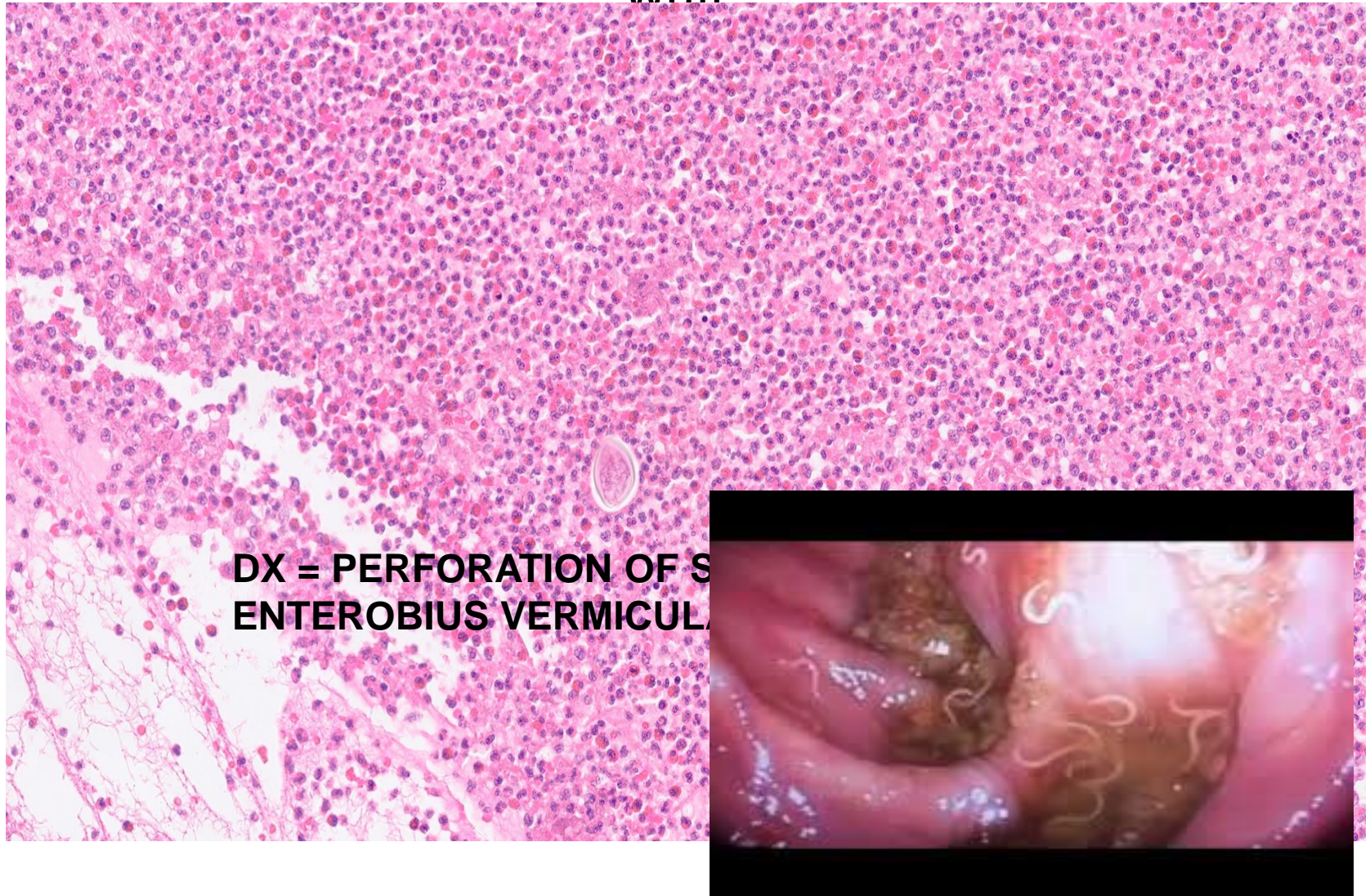
- Typically causes diarrhoea
- Mucosal injury with preserved architecture
- Transmural +/- obstruction
- Endoscopically
 - Oedematous mucosa with loss of vascular pattern
 - Patchy erythema
 - Superficial ulceration



Secondary Causes of Mucosal Eosinophilia

- Coeliac Disease
- Eosinophilis in IBD
 - Typically lymphocytes + plasma cells
 - UC – quiescent v active
 - ? Predictor of response in UC
 - CD v UC colitis
- Parasitic infections
 - Helminthic
 - Eggs/larvae/worms may not be seen
 - Regional lymphadenopathy
 - Travel history
- Drug-induced
 - NSAIDS, clozapine, AZA, rifampicin, carbamazepine
 - OLT tacrolimus
 - Radiotherapy
- Hypereosinophilia Syndrome
- Serum eosinophilia > 1550 for 6/12
 - Males, 20-50 years
 - Peripheral organ embolic events

26 year old male: Microperforation of sigmoid colon in an incisional hernia – eosinophilic abscess in colonic wall



Secondary Causes

- Connective tissue
 - band-like colonic infiltrates
- Vasculitis
- Collagenous/lymphocytic colitis
- Neoplasia
- GVHD
- Appendicitis
- Cholecystitis

Coming to a Diagnosis

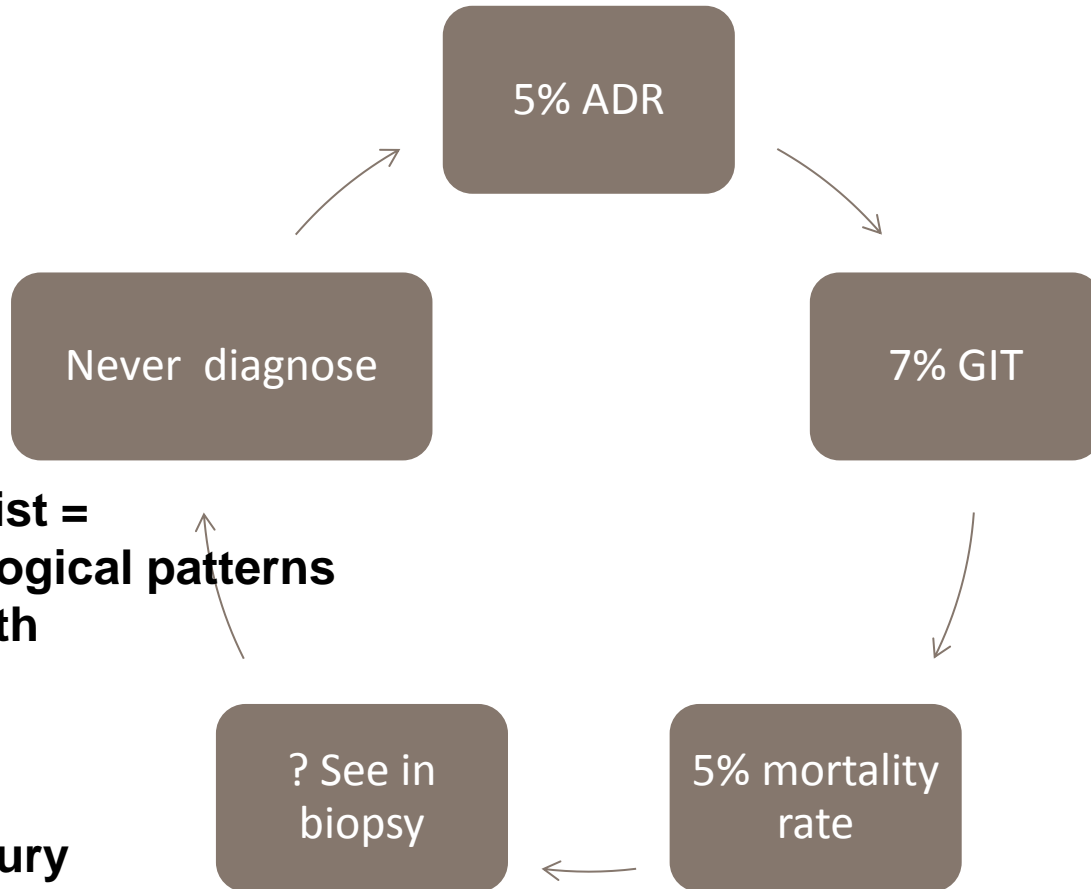
- No established criteria
 - Eosinophil quantification
 - Location of eosinophils
 - Extracellular eosinophils staining constituents – e.g free granules/degranulation
 - Absence of pathological markers of other primary disorders

Treatment Options

- Dietary
 - Elemental diet
 - 6 food elimination diet (wheat, milk, soya, nuts, eggs, & seafood)
- Glucocorticosteroids
 - Prednisolone 20-40mg/day
 - ? response at 2/52, evidence limited.
- Sodium Chromoglycate
 - preventing the release of mast cell mediators
- Ketotifen
 - H1-antihistamine and mast cell stabilizer
- Montelukast
- Leukotriene receptor antagonist

Iatrogenic gut injury is common (700 DRUGS)

5% of patients receiving drugs experience an adverse reaction



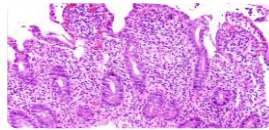
**Role of pathologist =
Recognize histological patterns**

- Associated with
- Suggestive of
- Diagnostic of

Drug-induced injury

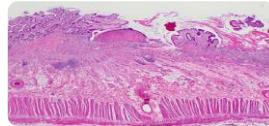
Pattern of injury & Mimics

1. Villous atrophy



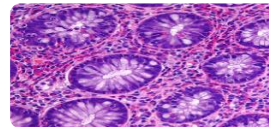
- Coeliac disease

2. Apoptotic / erosive



- Graft vs Host Disease

3. Ulcerative/colitis



- IBD



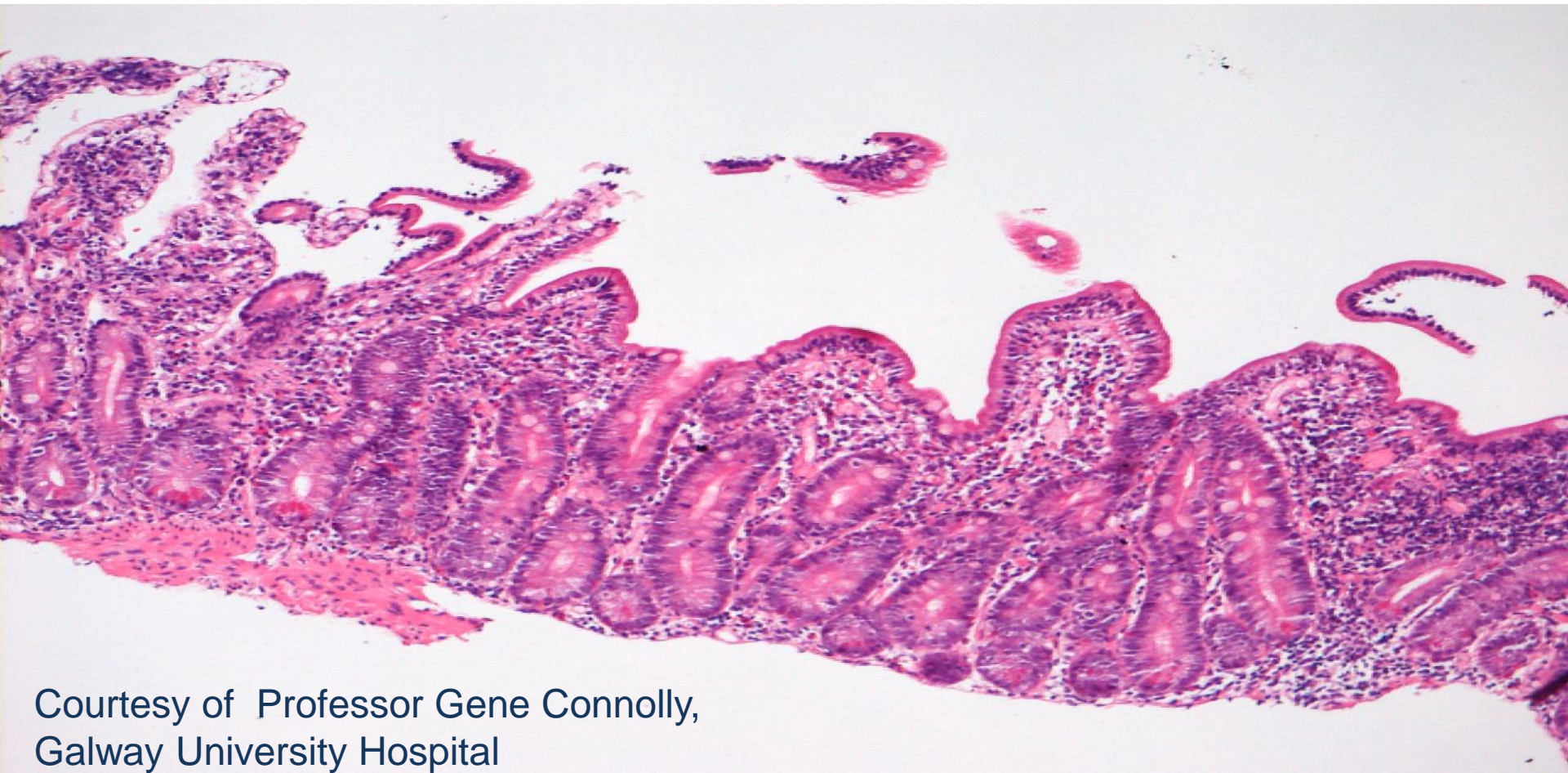
Pattern of injury & Mimics

1. Villous atrophy
 - Coeliac disease
2. Apoptotic / erosive
 - GVHD
3. Ulcerative
 - IBD



Sept 2011: 69 year old female – unwell, weight loss, signs of malnutrition

Subtotal villous atrophy, ? Coeliac Disease



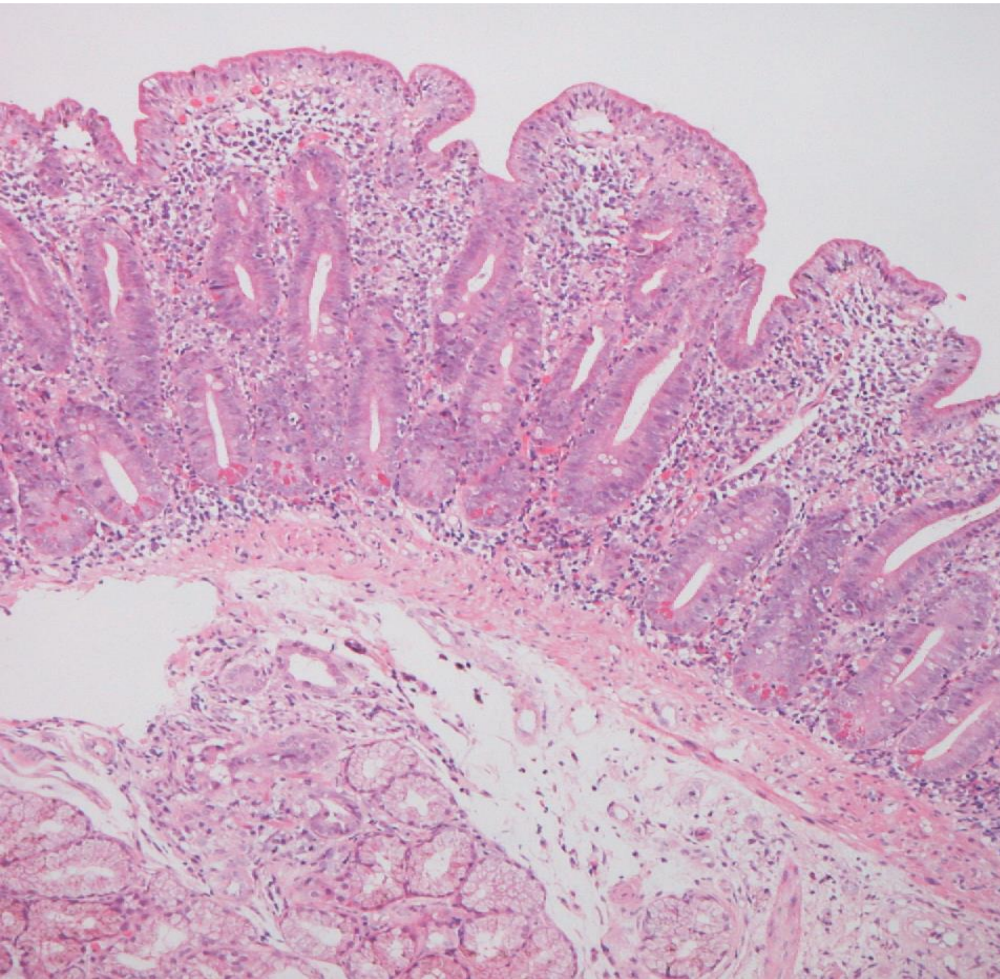
Courtesy of Professor Gene Connolly,
Galway University Hospital

No improvement on a Gluten Free Diet

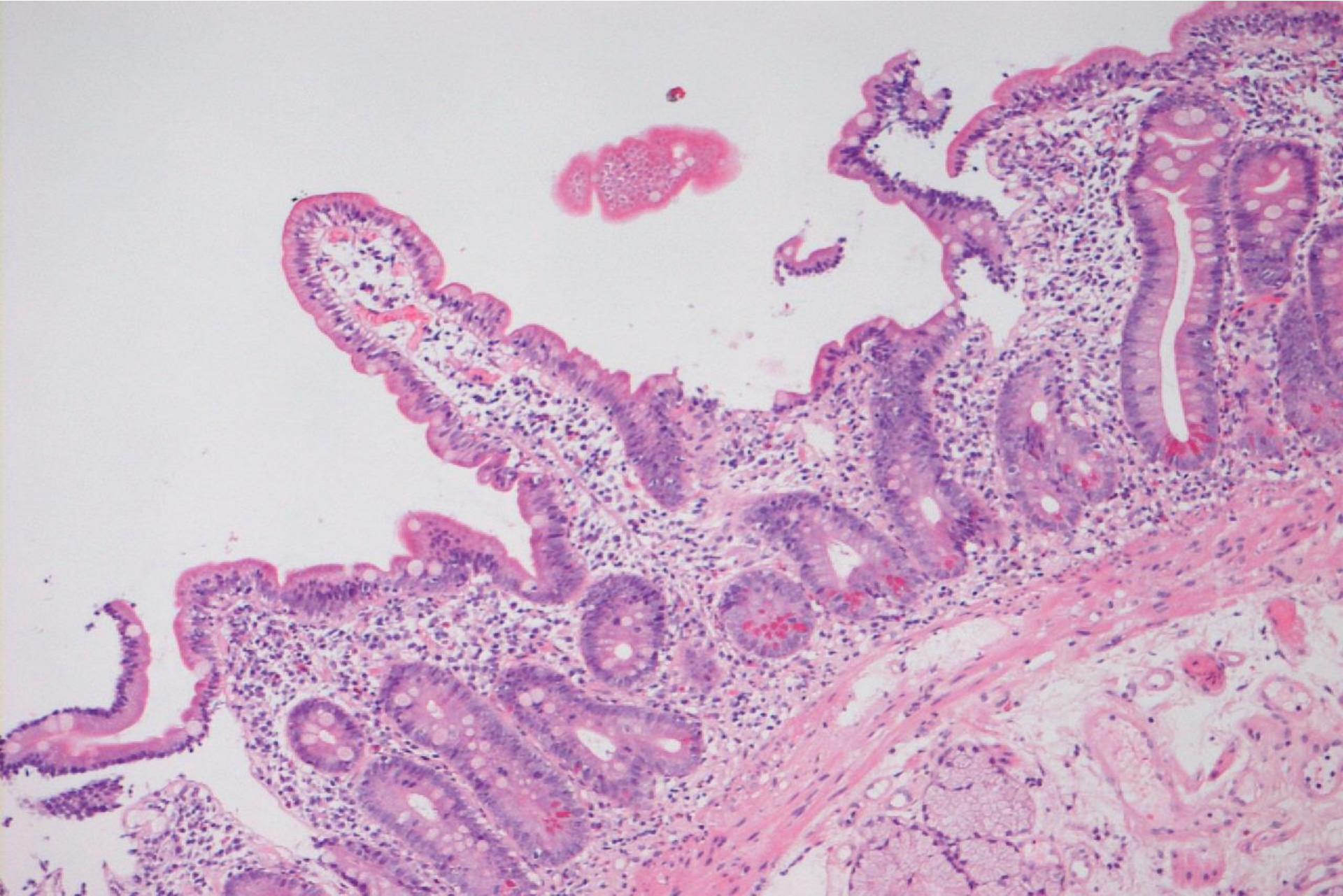
Repeat biopsy, June 2012: subtotal villous atrophy

Is this Refractory Coeliac Disease ?

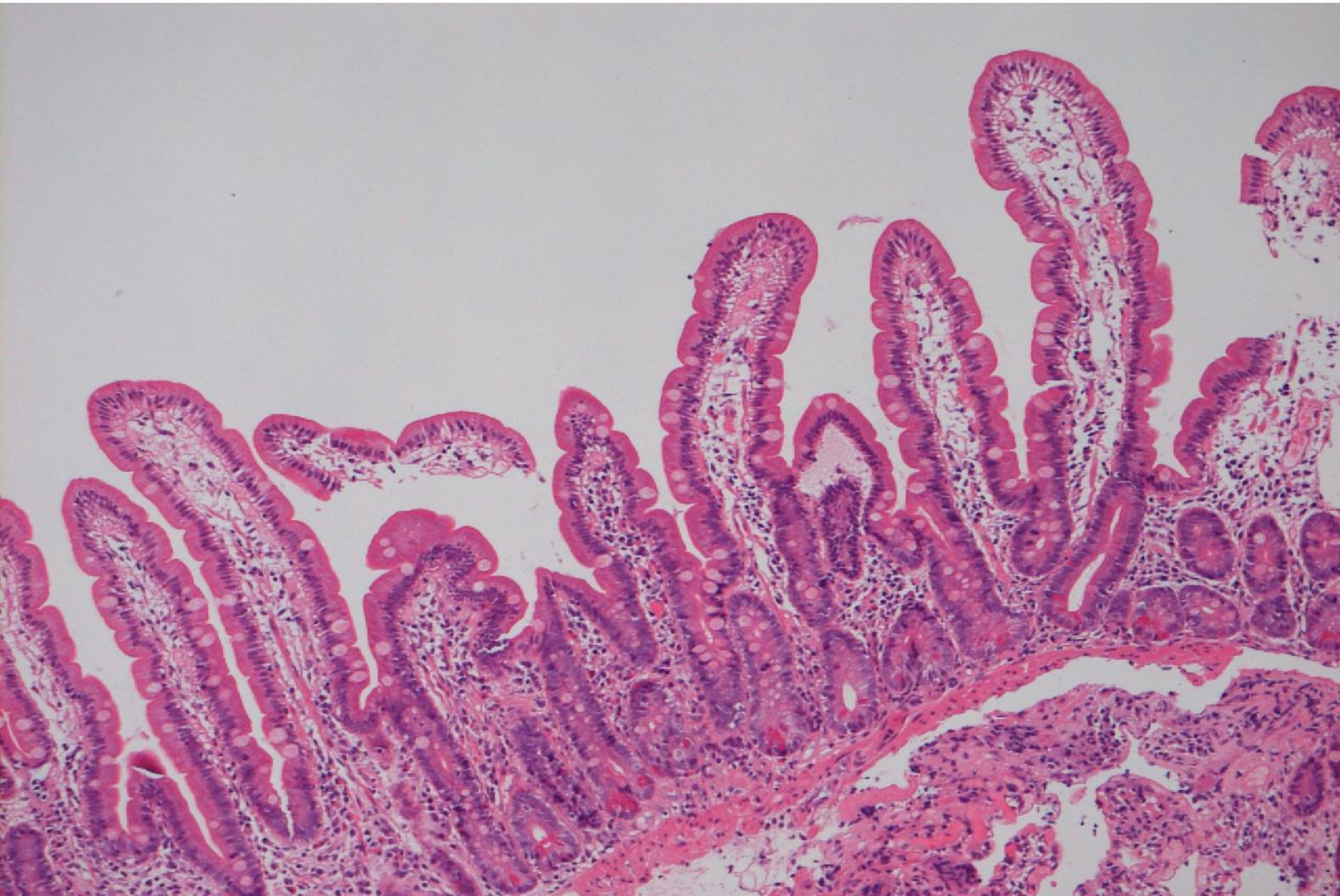
Noted to be on Olmersartan for hypertension



Off Olmesartan x 2 months: mild partial villous atrophy



Back on a Gluten-diet, Off Olmesartan x 7 months



MOST LIKELY OFFENDING AGENT

- A. Aledronate
- B. Simvastatin
- C. Lanzoprazole
- D. NSAIDS
- E. Olmersartan

Diagnosis: Severe coeliac-like enteropathy associated with Olmesartan



Angiotensin II receptor blockers (ARBs)

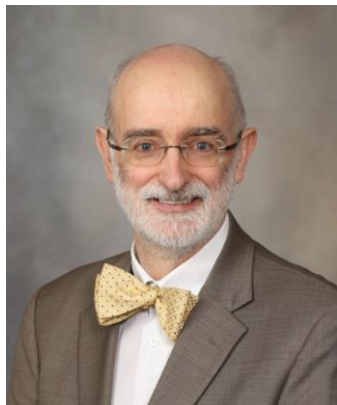
ARBs Hypertension Medicines
ARBs block the angiotensin receptors that constrict the blood vessel, thus ARBs relaxes blood vessels and lower blood pressure.



- New drug class for treatment of hypertension & cardiac failure & protection from diabetic nephropathy (since 2002)

At least 8 clinically available (azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan)

ORIGINAL ARTICLE



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

- Chronic diarrhoea (> 4 weeks) while taking olmesartan
- Cause of enteropathy not established after diagnostic evaluation – often very ill & all required admission
- Clinical improvement after discontinuation
- Also microscopic colitis & lymphocytic gastritis +/-collagen

Olmesartan causes symptoms & signs of coeliac disease

Limited number of literature citations on topic

- In 2012, approx. 10.6 million prescriptions for approx. 2 million patients
- In this era of poly-pharmacy, be vigilant of drug adverse effects (absolute incidence is RARE, < 1/1,000)



Pattern of injury & Mimics

1. Villous atrophy
 - Coeliac disease
2. Apoptotic / erosive
 - GVHD
3. Ulcerative
 - IBD



PC & Background



- Severe diarrhoea (x 20/day)
- Tacrolimus 3mg BD
- Mycophenolate Mofetil 500mg BD
- Prednisolone 5mg OD
- Calcichew D3
- Ulcerative colitis
- Ileoanal pouch anastomosis
- Primary sclerosing cholangitis
- Orthotopic liver transplant

Pouch and pre pouch ileum on Admission



Name:

Ref: Age:
D.O.Birth:

07-17-2017
20 59 12

547529

0:04:14.91
DeG: 2: 7.8

Physician:
Comment:



Name:

Ref: Age:
D.O.Birth:

07-17-2017
20 59 12

547529

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DeG: 2: 7.8

Physician:
Comment:



What would you do next?



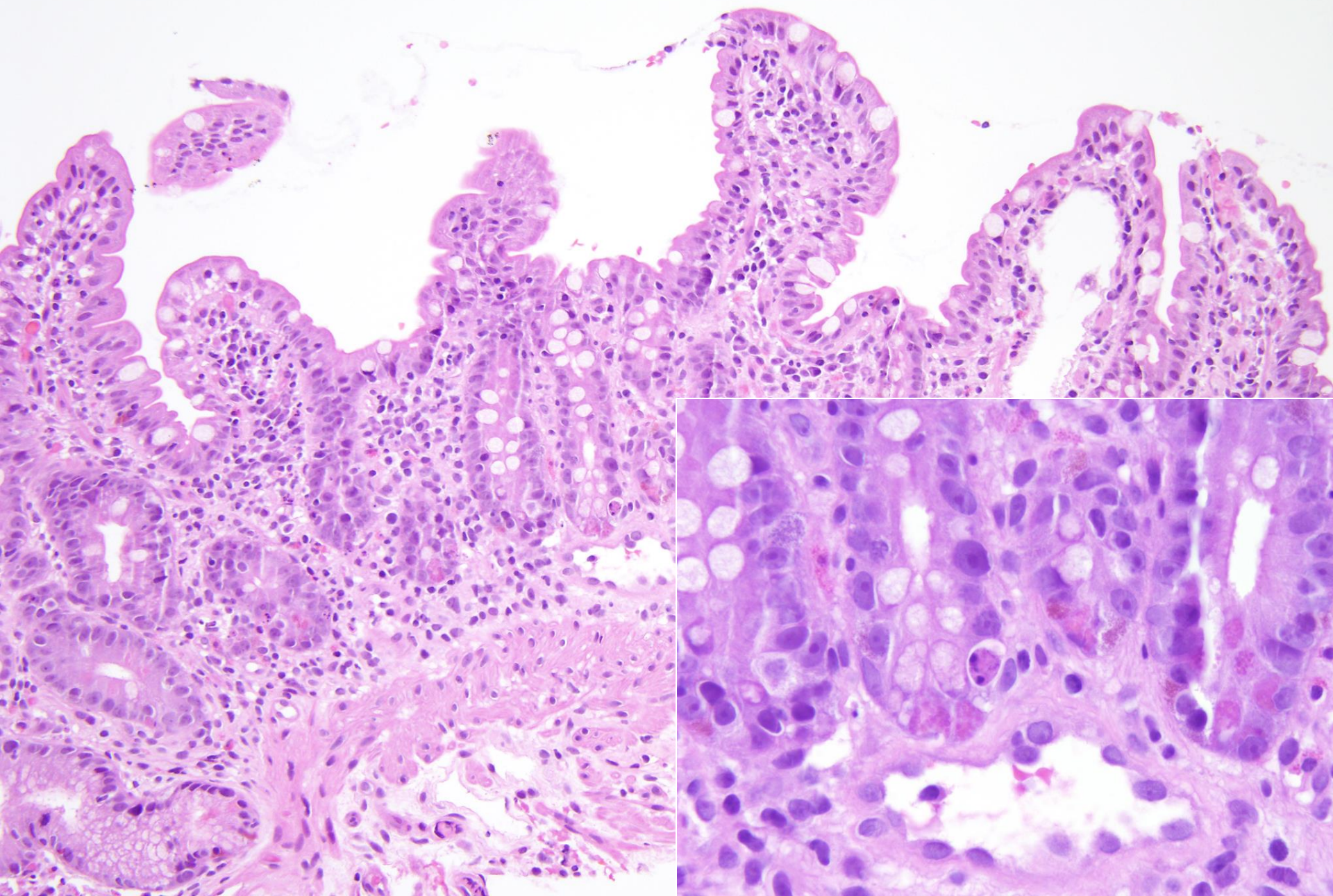
Differential Diagnosis

- ☞ Pouchitis
- ☞ Crohn's disease
- ☞ Viral enteropathy
- ☞ Drug-induced enteropathy

Investigations (all negative)

- ☞ Stool C&S, C. diff
- ☞ Full CMV workup
 - ☞ serum, stool, histology
 - ☞ CMV negative pre transplant
- ☞ HSV PCR
 - ☞ IgG positive pre transplant
- ☞ MR Enterography

Mycophenolate-associated injury to small intestine (enteropathy)



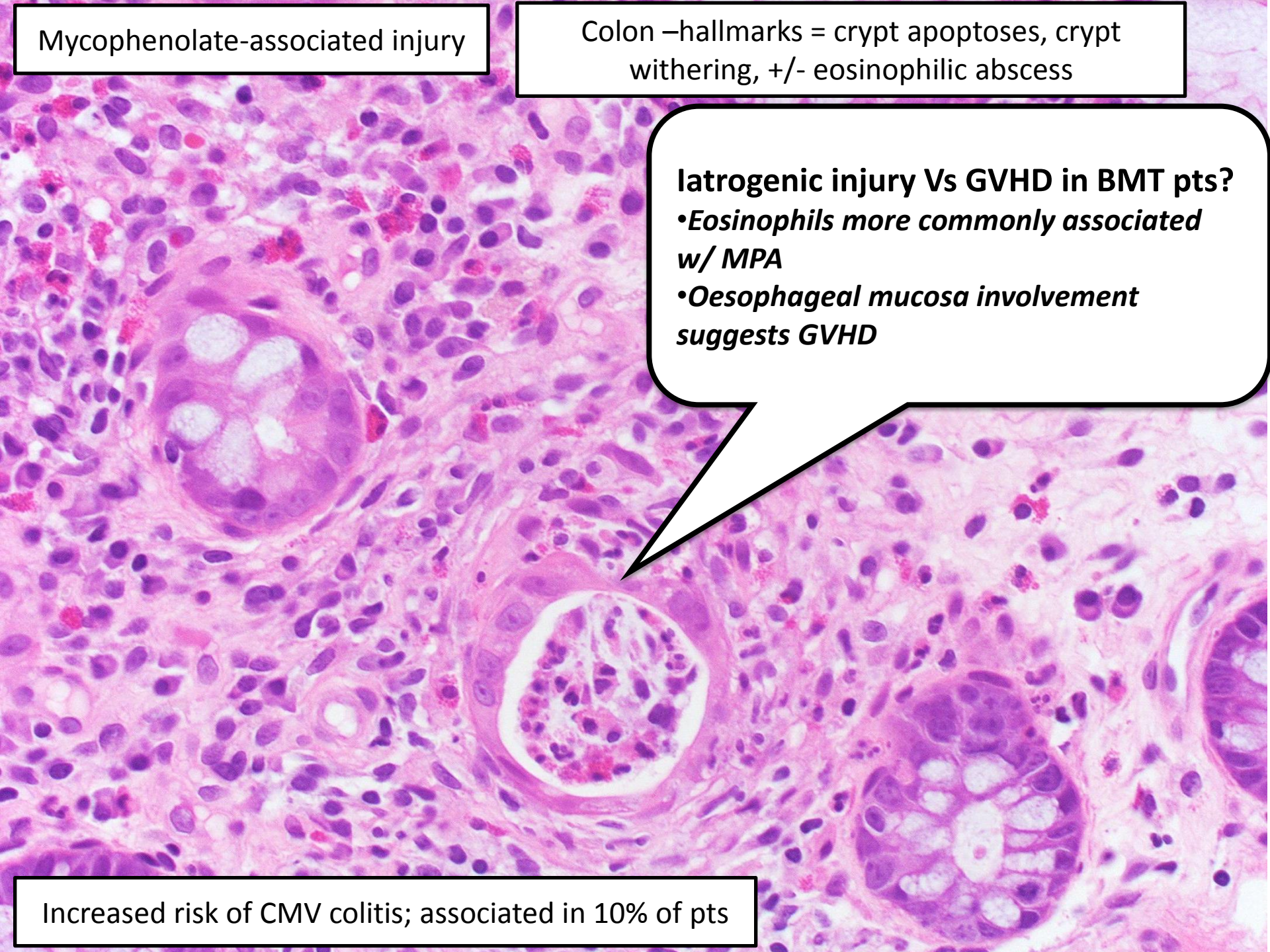
Mycophenolate-associated injury

Colon –hallmarks = crypt apoptoses, crypt withering, +/- eosinophilic abscess

Iatrogenic injury Vs GVHD in BMT pts?

- *Eosinophils more commonly associated w/ MPA*
- *Oesophageal mucosa involvement suggests GVHD*

Increased risk of CMV colitis; associated in 10% of pts



Outcome



- ❧ Mycophenolate Mofetil was discontinued
- ❧ Diarrhoea settled completely
- ❧ Discharged home

Mycophenolic Acid (MPA)

Mycophenolate mofetil (CellCept[®])

Mycophenolate sodium (Myofortic[®])

Used in Allograft rejection, GVHD, Autoimmune conditions

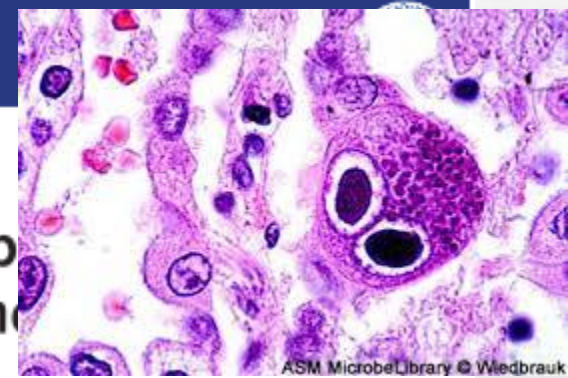
GVHD-like alterations throughout the GIT

Active oesophagitis with ulceration or erosion

Chemical gastropathy; focal active gastritis

Crohn's-like damage in the duodenum

Cryptitis, crypt withering & distortion, reparative changes & increased neuroendocrine cells



Coeliac-like duodenal pathology in orthotop transplant patients on mycophenolic acid th

Maura B Cotter,¹ Ahmed AbuShanab,² Raphael Merriman,² Aiden McCormick² & Kieran Sheahan^{1,2}

¹Departments of Histopathology, ²Hepatology, and Centre for Colorectal Disease, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland.

- ⌘ A retrospective review of OLT patients who had OGD and D2 biopsies over a 19 year period
- ⌘ 152 D2 biopsies. 5% had coeliac type changes
- ⌘ Discontinuation or reduction of MPA was associated with improvement of symptoms within 1-3 weeks.

Mycophenolate-associated injury

Colon

Iatrogenic injury Vs GVHD in Bone Marrow Transplant patients

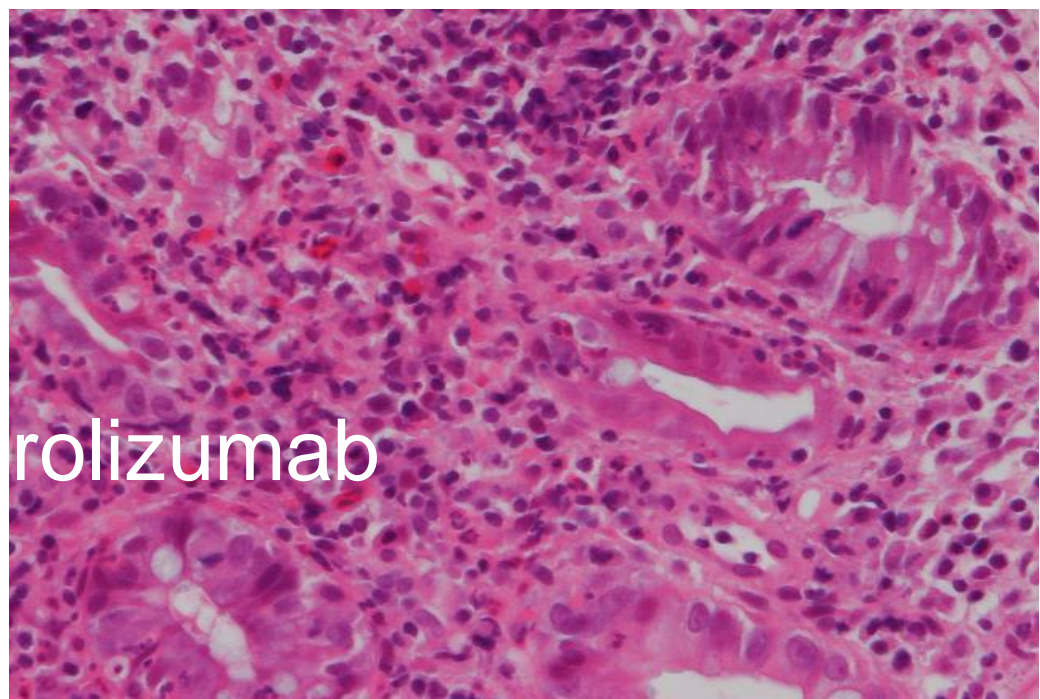
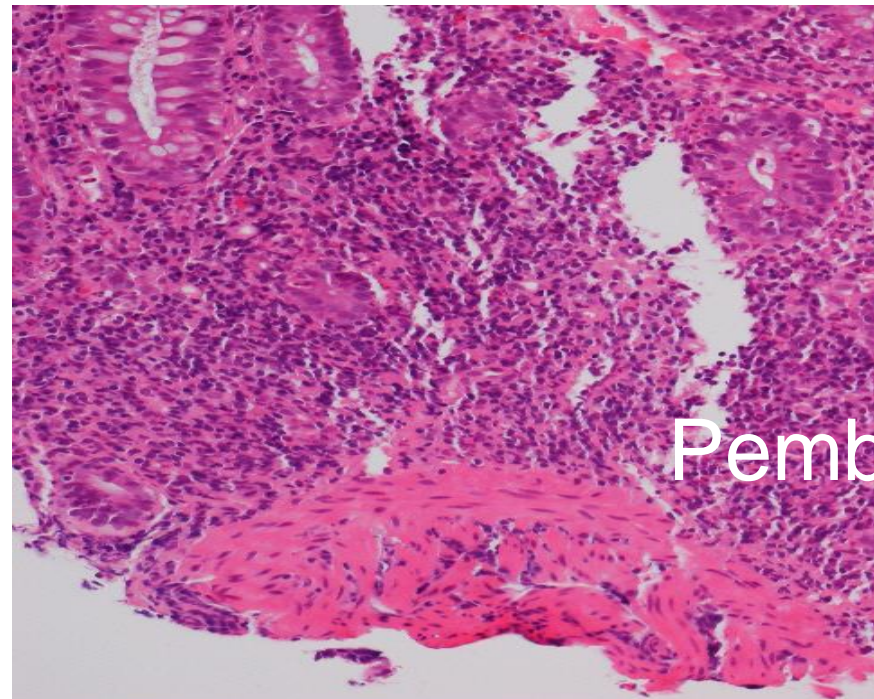
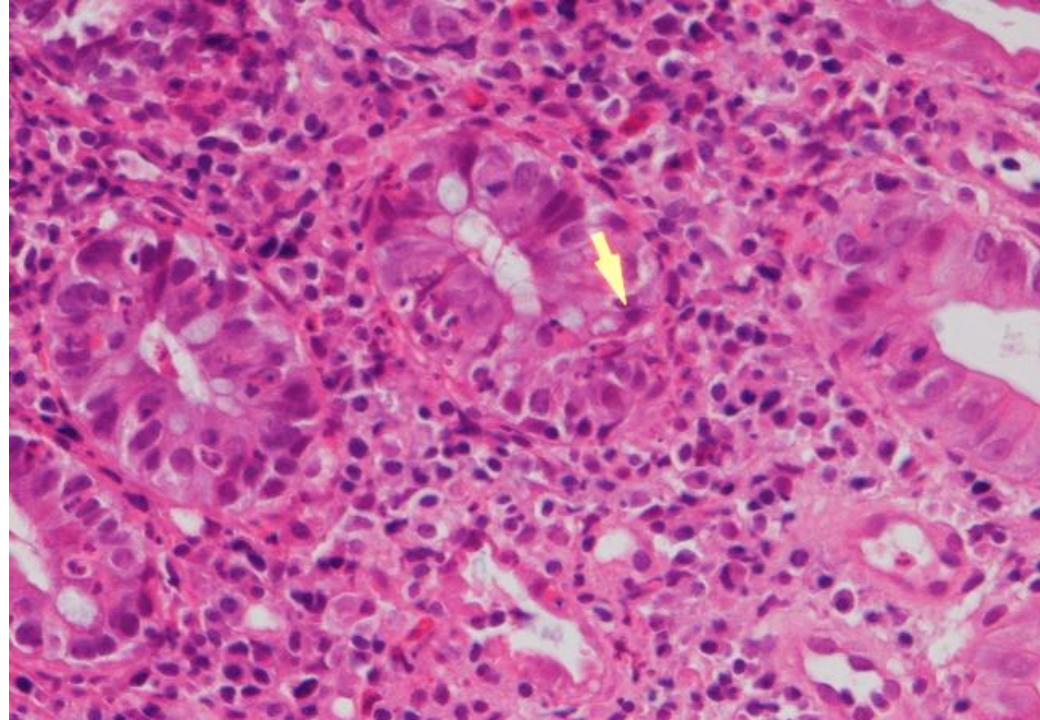
- *Eosinophils more commonly associated w/ MPA*
- *Oesophageal mucosa involvement suggests GVHD*

Increased risk of CMV colitis; associated in 10% of patients

61 year old female
Stage IV lung
adenocarcinoma

PDL-1 biomarker
positive. Prescribed
new oncological
agent.

Bloody diarrhoea.
Proctitis to 15cm

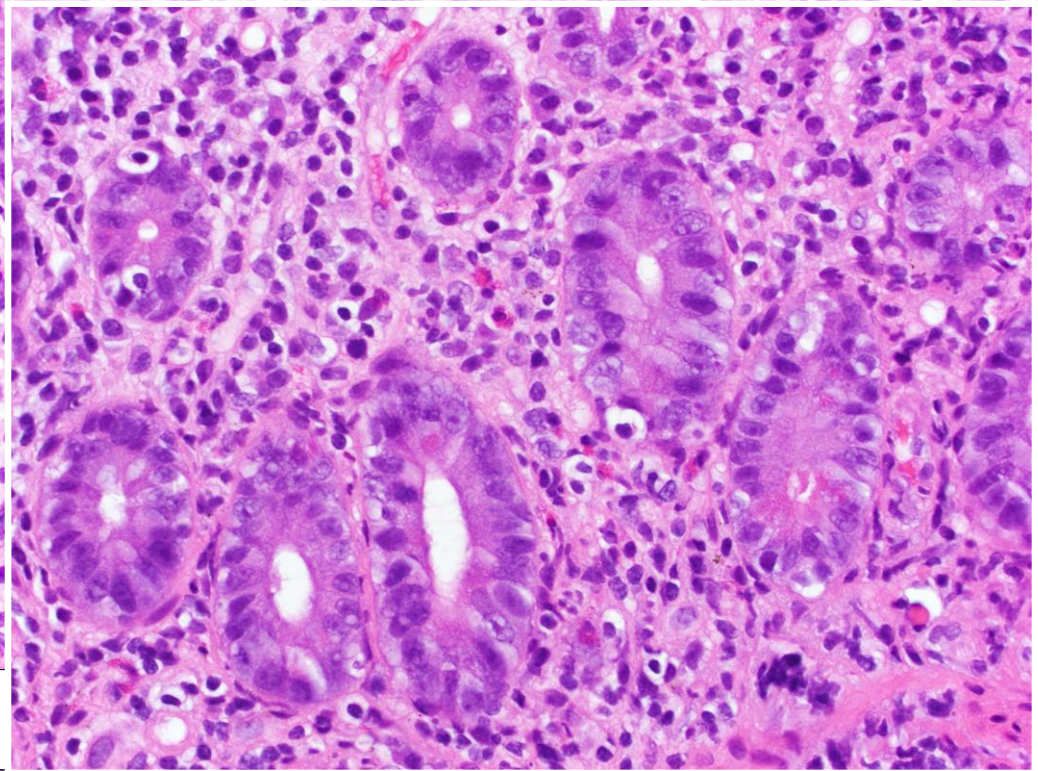
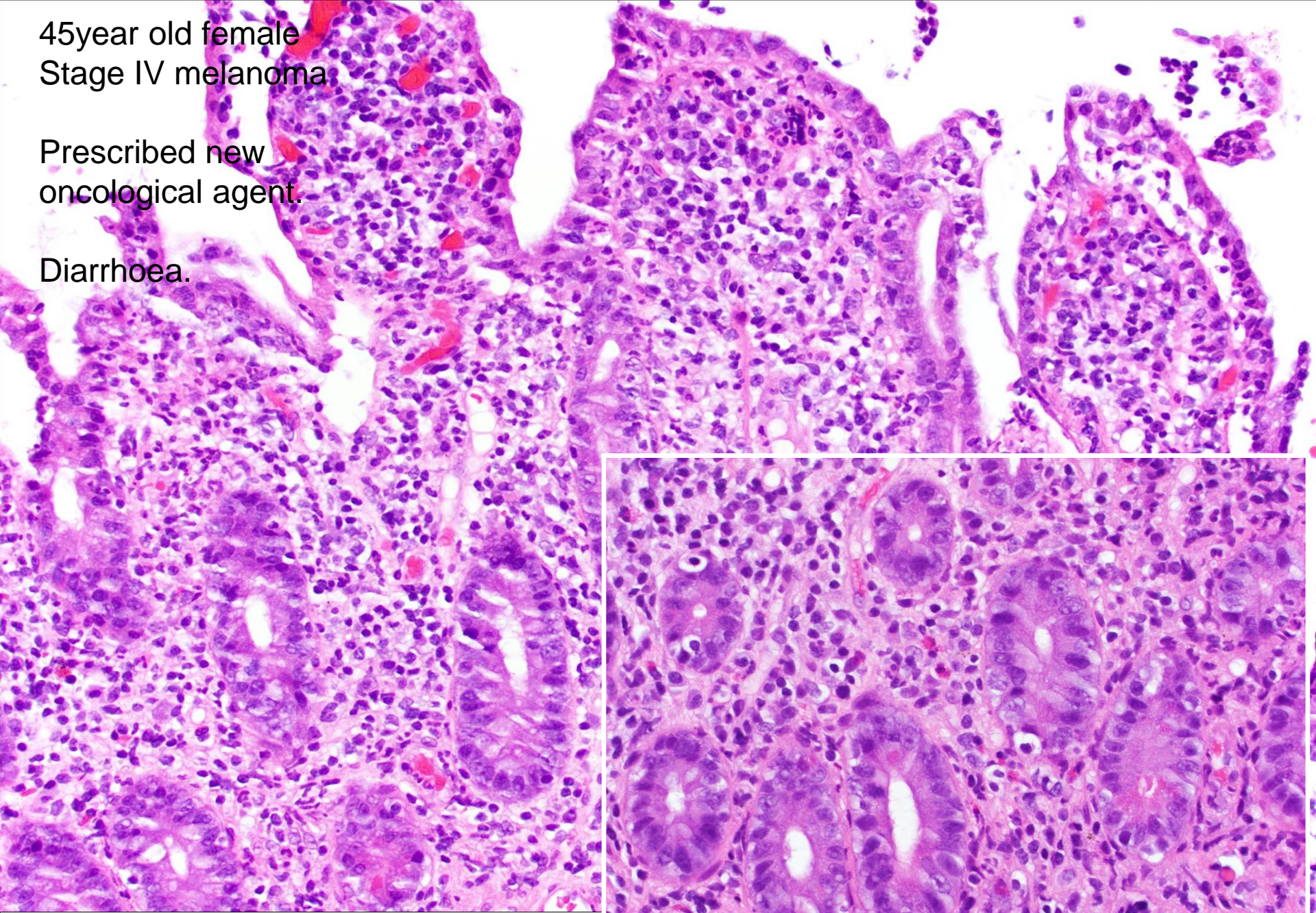


Pembrolizumab

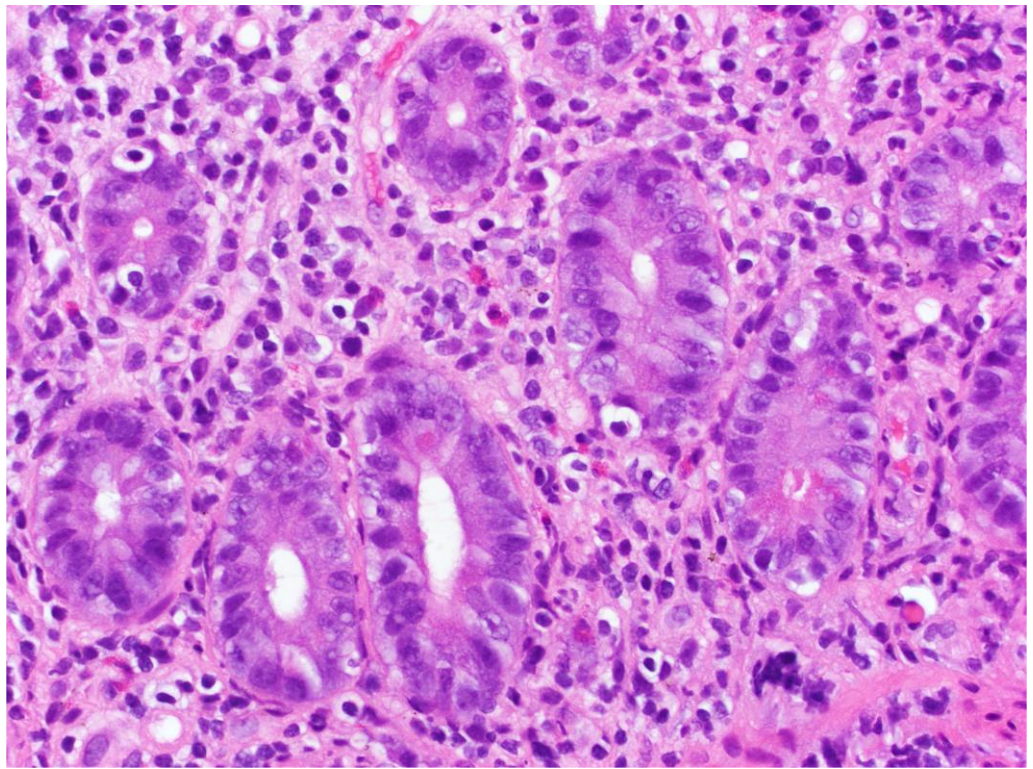
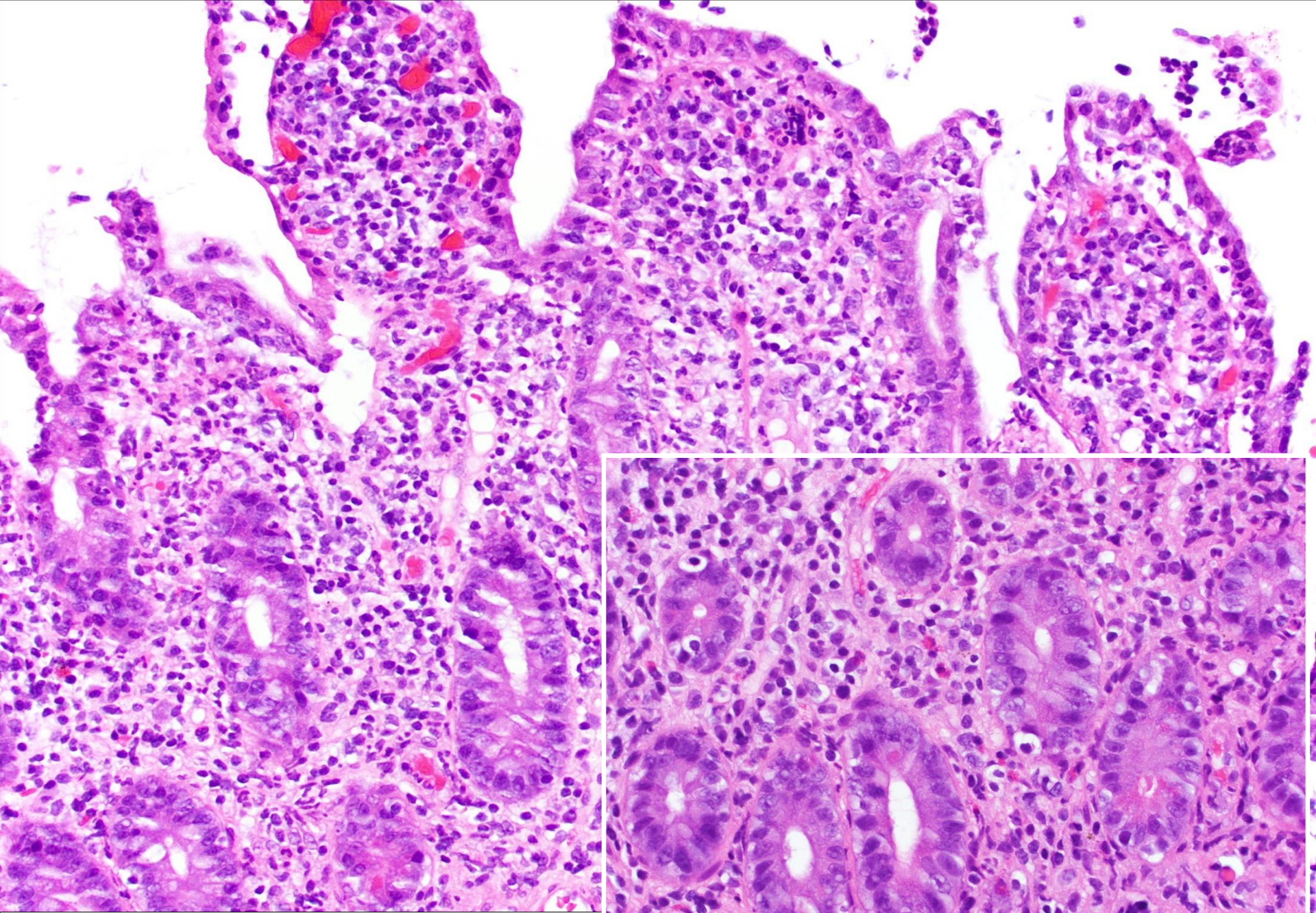
45year old female
Stage IV melanoma

Prescribed new
oncological agent.

Diarrhoea.

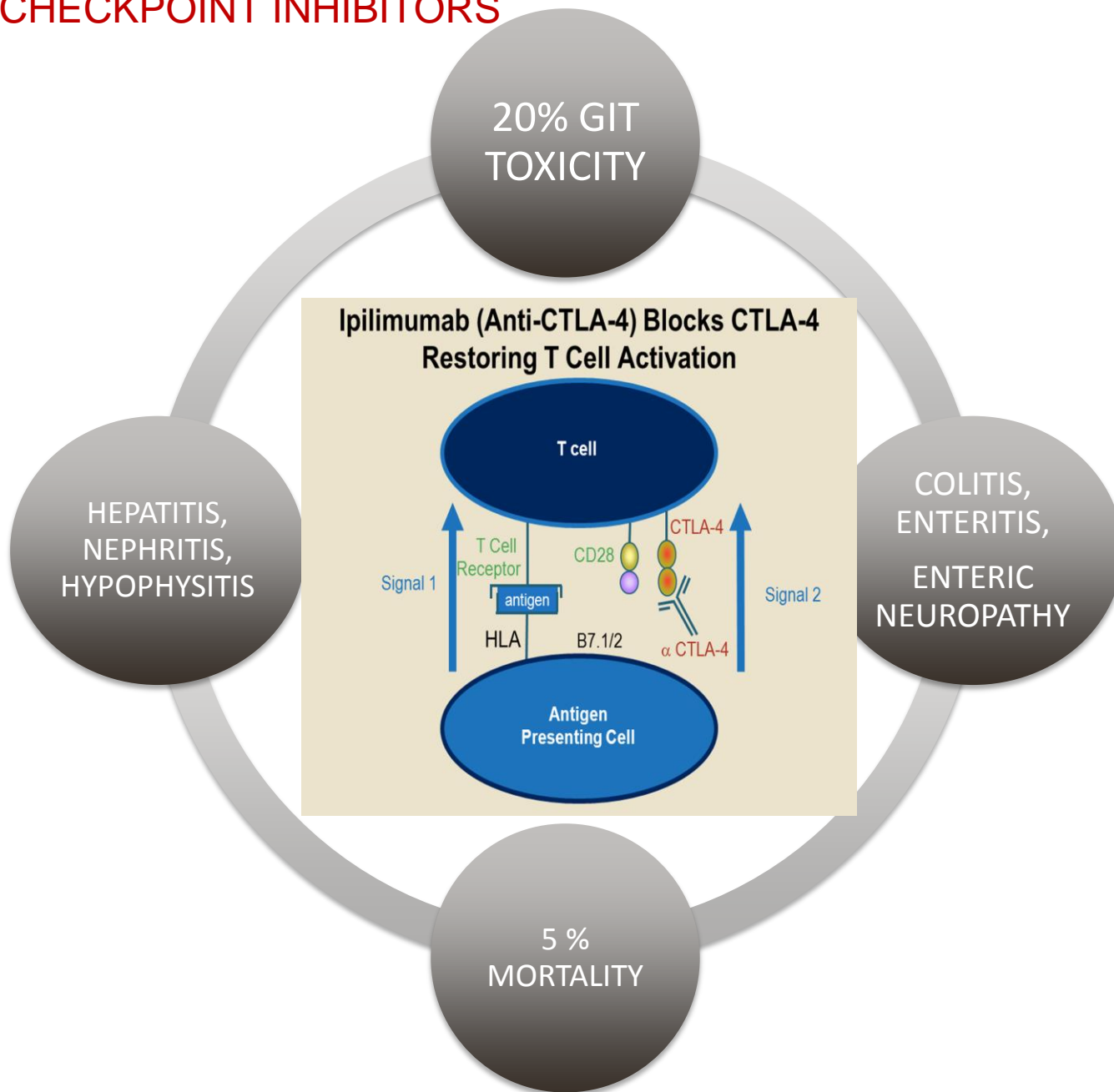


CTLA-4 monoclonal antibody (ipilimumab)
small intestine

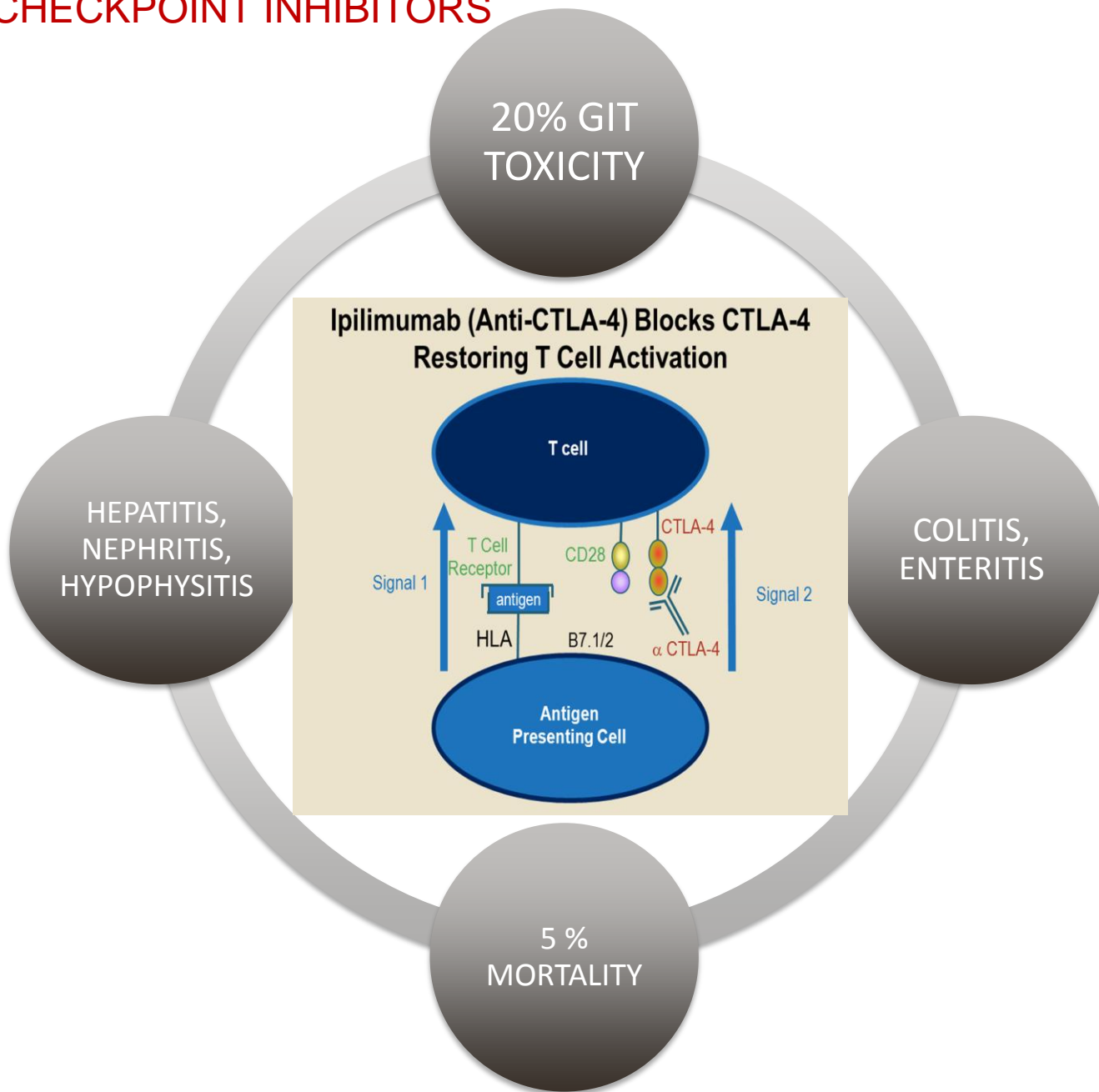


CTLA-4 monoclonal antibody (ipilimumab)
small intestine

IMMUNE CHECKPOINT INHIBITORS



IMMUNE CHECKPOINT INHIBITORS



PD-1 inhibitor gastroenterocolitis: case series and appraisal of ‘immunomodulatory gastroenterocolitis’

Raul S Gonzalez,¹ Safia N Salaria,² Caitlin D Bohannon,³ Aaron R Huber,¹ Michael M Feely⁴ & Chanjuan Shi²

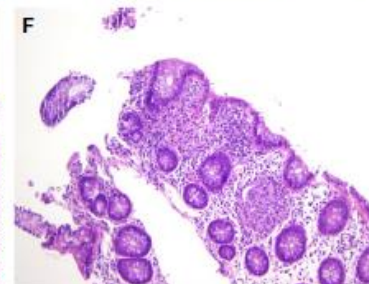
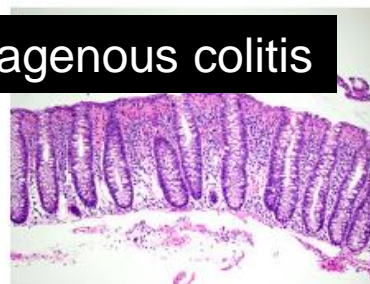
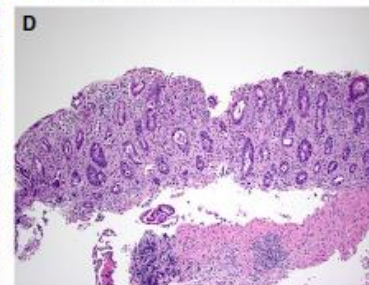
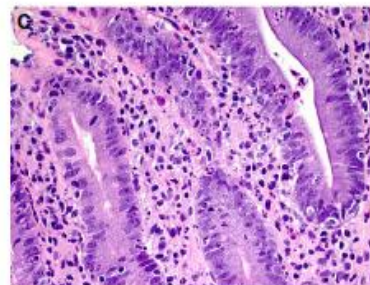
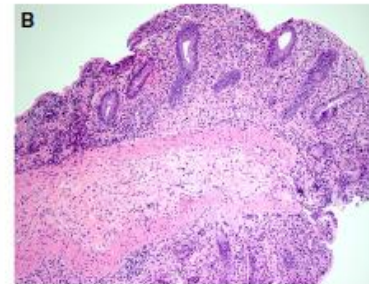
¹*Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY,*

²*Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN,*

³*Immunology and Pathogenesis Branch, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA. and*

⁴*Department of Pathology, Immunology, and Laboratory*

Figure 1. Typical and atypical findings in patients with gastroenterocolitis secondary to a programmed cell death protein 1 (PD-1) inhibitor. **A,** Erythema and granularity of the colon were evident macroscopically in this patient taking a PD-1 inhibitor. **B,** This colonic biopsy shows lamina propria expansion, crypt distortion and crypt abscesses. **C,** Cryptitis and pronounced epithelial reactive change, including prominent nucleoli, are visible at higher power. There is a mild increase in crypt apoptosis above baseline, a feature seen in approximately half of colon biopsies. **D,** Changes resembling ischaemic colitis were seen in three specimens. **E,** Changes resembling collagenous colitis were seen in one specimen. **F,** Crypt rupture with responding histiocytes was a distinctive but uncommon feature, seen in five of the 34 biopsies available for review. In this colon biopsy, the histiocytes are arranged tightly, forming granulomas.



UC

NSAIDs-effect

Collagenous colitis

Crohn's

Enterocolitis due to immune checkpoint inhibitors: a systematic review

Emilie Soularue,^{1,2} Patricia Lepage,³ Jean Frederic Colombel,⁴ Clelia Coutzac,⁵ David Faleck,⁴ Lysiane Marthey,¹ Michael Collins,^{1,2} Nathalie Chaput,^{5,6} Caroline Robert,^{2,7} Franck Carbonnel^{1,2}

Table 1 Risk factors of enterocolitis due to immune checkpoint inhibitors

Risk factors		References
Type of ICI	Combotherapy>anti-CTLA-4>anti-PD-1	Tandon <i>et al</i> ⁹
Dose of ICI	Dose-dependant toxicity with anti-CTLA-4	Ascierto <i>et al</i> ¹¹
NSAIDs use	Suggested with anti-CTLA-4	Marthey <i>et al</i> ²⁵
Pre-existing IBD	About 30% risk of relapse with anti-CTLA-4; not reported with anti-PD-1	Johnson <i>et al</i> ¹² Kähler <i>et al</i> ¹³ Menzies <i>et al</i> ¹⁵
Microbiota	Baseline microbiota enriched in Firmicutes and poor in Bacteroidetes with anti-CTLA-4	Chaput <i>et al</i> ⁸⁴
Tumour histology	Increased risk in melanoma as compared with NSCLC and RCC with anti-PD-1	Khoja <i>et al</i> ⁷ Wang <i>et al</i> ⁸

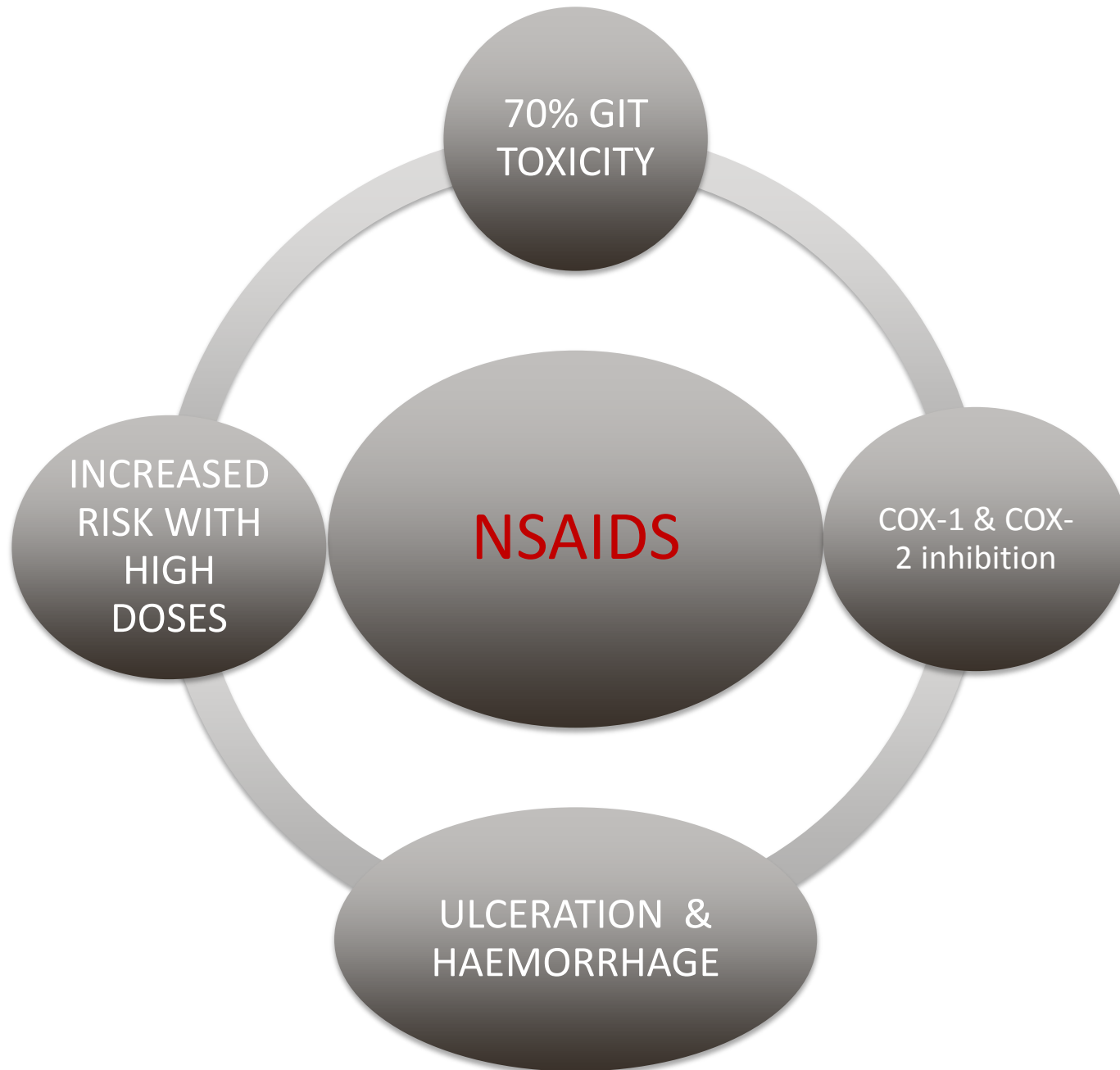
CTLA-4, cytotoxic T-lymphocyte-associated protein-4; ICI, immune checkpoint inhibitor; NSAID, non-steroidal anti-inflammatory drug; NSCLC, non-small cell lung carcinoma; PD-1, programmed death-1; RCC, renal cell carcinoma.

To cite: Soularue E, Lepage P, Colombel JF, *et al*. *Gut* 2018;**67**:2056–2067.

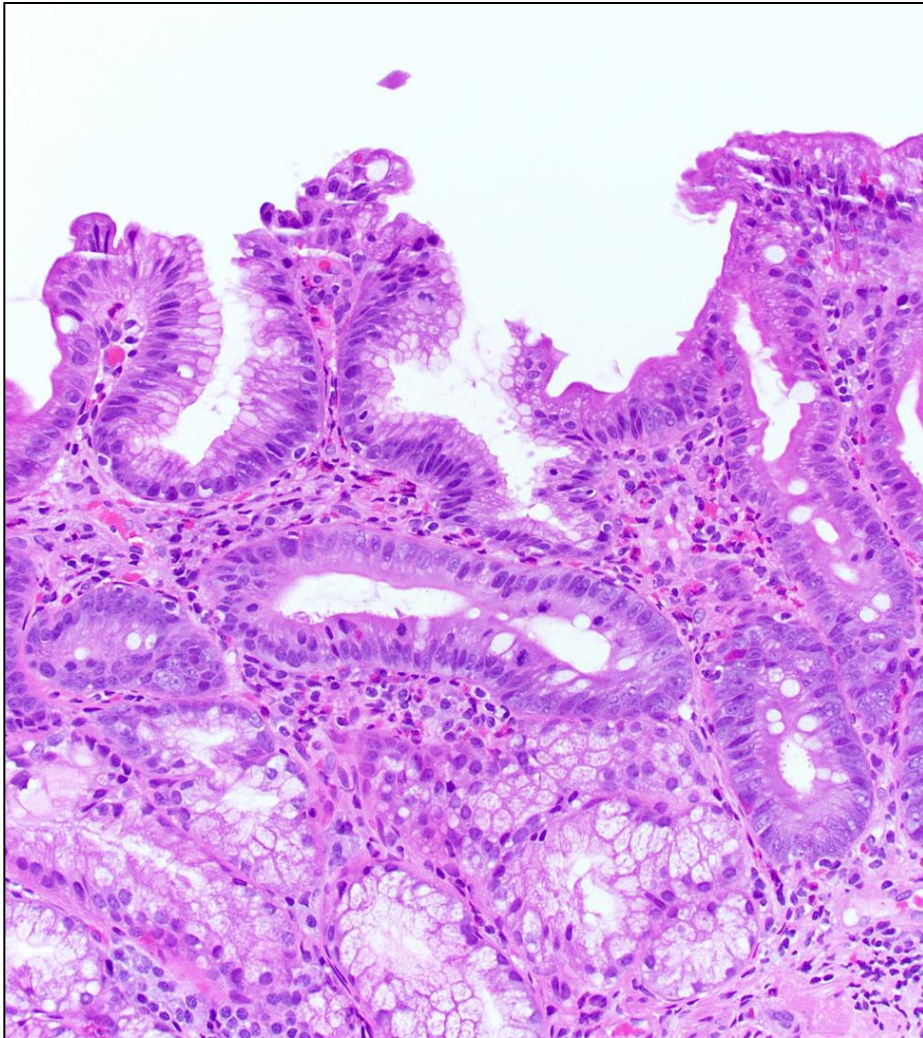
Pattern of injury & Mimics

1. Villous atrophy
 - Coeliac disease
2. Apoptotic / erosive
 - GVHD
3. Ulcerative/colitis
 - IBD

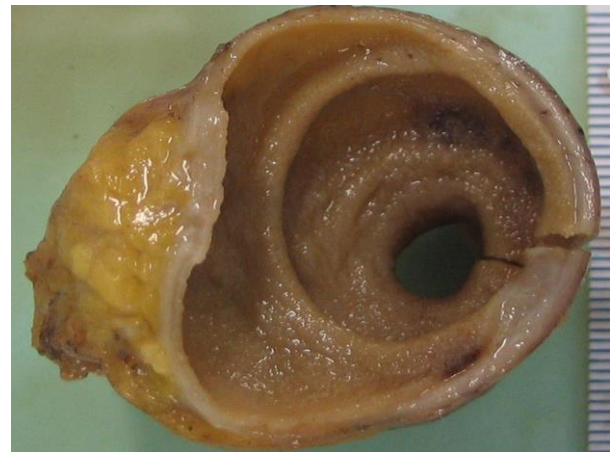




Prevalence of NSAID-induced enteropathy (small intestine) is underestimated

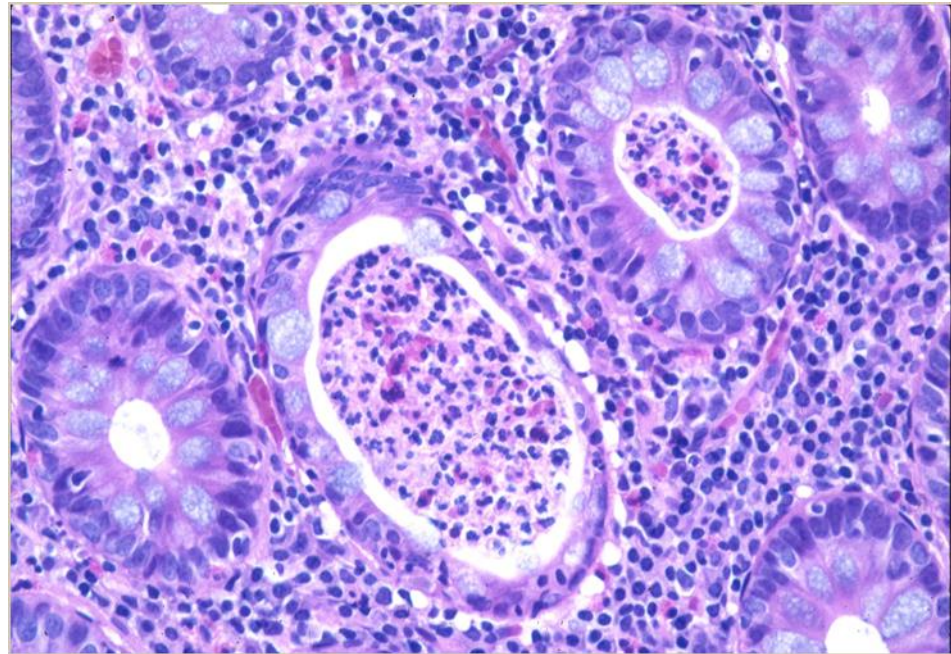


- > 50% of patients have mucosal damage in the small bowel (Video capsule endoscopy):
 - Mucosal erythema
 - Erosions, ulcers, perforation
 - Diaphragm disease & strictures



NSAIDs and colitis

Increasing due to use of enteric coated or sustained (slow) release formulation (higher concentrations in the proximal colon)

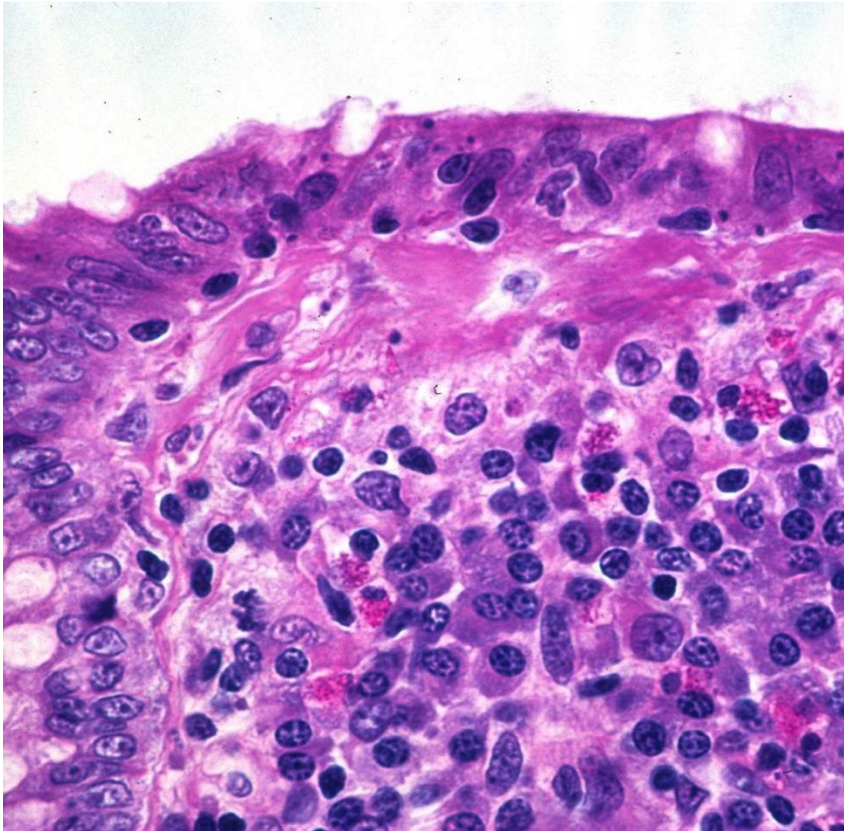


Various types of Colitis

- Focal active colitis & chronic colitis
- Collagenous colitis & lymphocytic colitis
- Pseudomembranous colitis (*Diclofenac*[®])
- Eosinophilic colitis (*Naproxen*[®])
- Ulcers (right colon)
- Diaphragm disease
- Exacerbation of pre-existing IBD or diverticular disease (or perforation)

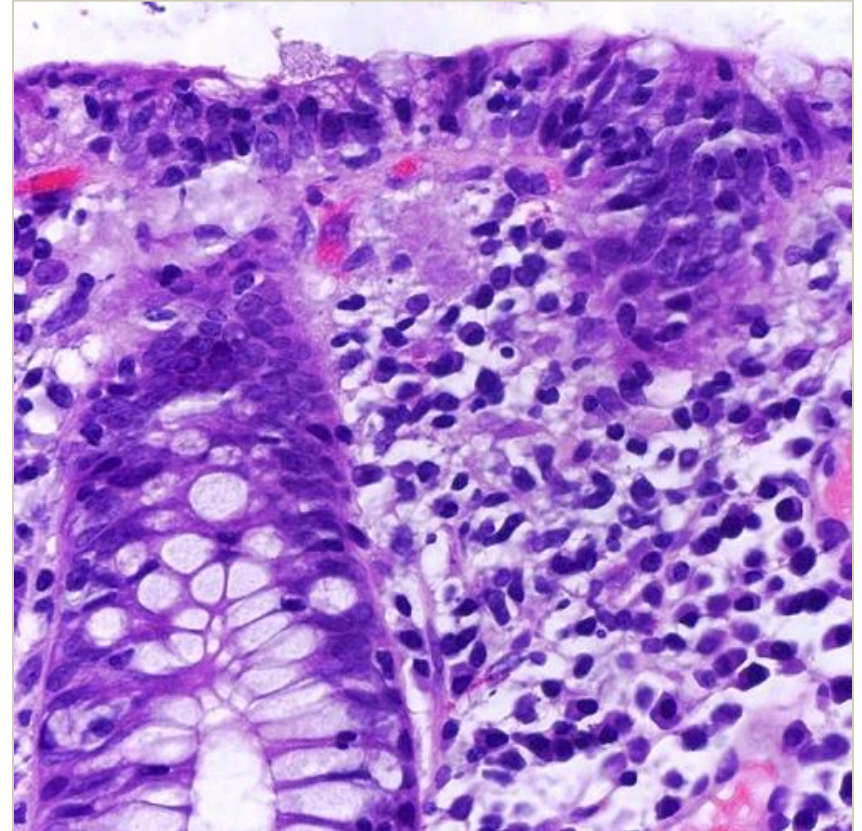
Microscopic Colitis

Collagenous Colitis



NSAIDs, Olmesartan, others

Lymphocytic colitis



NSAIDs, PPI, SSRI; herbal remedies, ticlopidine, carbamazepine

CONCLUSION

Diagnosis of Drug-Induced Injury is Difficult (could this be medication-induced injury ?)

- Some compounds are associated with characteristic patterns of injury (many are not)
- **Because the gut has a limited set of response patterns to injuries:**
- overlapping features with common primary GI diseases including coeliac disease & IBD are to be expected.
- Other differential diagnoses include rare disorders like tropical sprue, CVID, autoimmune enteropathy.
- clinical correlation is crucial

(when little or no clinical information is usually provided !)

Diagnosis of Drug-Induced Injury is Difficult

- **CLINICIAN**

- Knowledge
- Awareness



- **PATHOLOGIST**

- Always consider DRUGS in an atypical “*itis*”
- **Specific pointers:**
 - Apoptosis
 - Withering crypts
 - Marked nuclear pleomorphism / cytologic atypia
 - Obvious/numerous eosinophils



"I didn't experience any of the side effects listed in the enclosed literature. Should I be concerned?"

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