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IATROGENIC PATHOLOGY OF THE GASTROINTESTINAL TRACT

Cord Langner, MD
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Agenda

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- When should a drug-induced injury be suspected?
- Examples of drug induced injury at different sites along the gastrointestinal tract
  - Oesophagus
  - Stomach
  - Small and large bowel
- Take home messages

Pathological effects of drugs on the gastrointestinal tract: a review

Jeremy R. Parfitt MD, David K. Driman MBChB, FRCPC*

Table 1 Morphological classification of drug-induced pathology of the GI tract

Esophagus	
Erosions and ulcers	KCl, alendronate, doxycycline, quinidine, iron, Kayexalate, Taxol
Strictures	KCl, alendronate
Stomach	
Parietal cell hypertrophy and hyperplasia	PPIs
Fundic gland cysts and polyps	PPIs
Erosions and ulcers	NSAIDs, KCl, alendronate, iron, Kayexalate, HAIC, SIR, colchicine
Reactive gastropathy	NSAIDs
Epithelial atypia mimicking dysplasia	HAIC, SIR, colchicine, Taxol
Apoptosis	PPIs, colchicine
Small intestine	
Erosions and ulcers	NSAIDs, KCl, iron, Kayexalate, colchicine
Strictures	KCl
Diaphragms	NSAIDs
Large intestine	
Erosions and ulcers	NSAIDs, KCl
Strictures	KCl, pancreatic enzyme replacement
Microscopic colitis	PPIs, ticlopidine, ranitidine, simvastatin, flutamide, carbamazepine, paroxetine, sertraline, penicillin V, Cyclo 3 Fort, NSAIDs
Pseudomembranous colitis	Antibiotics, PPIs
Neutropenic enterocolitis	Cytosine arabinoside, cisplatin, vincristine, adriamycin, 5-FU, mercaptopurine
Malakoplakia	Corticosteroids
Sigmoid diverticular perforation	Corticosteroids
Ischemic colitis	Digitalis, diuretics, BCP, ergotamine, cocaine, Kayexalate, glutaraldehyde, sumatriptan, α-interferon, dopamine, methysergide, and NSAIDs
Focal active colitis	NaPO4, NSAIDs
Epithelial atypia mimicking dysplasia	IV cyclosporin
Apoptosis	NSAIDs, NaPO4, melanosis, 5-FU

Abbreviations: BCP, birth control pill; NaPO4, sodium phosphate bowel preparation.

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- Entire gut may be affected by a drug-induced injury
- Some drugs predominantly affect the upper GI tract (e.g. PPI, iron pill, olmesartan)
- Some drugs predominantly affect the lower GI tract (e.g. MMF, immune checkpoint inhibitors)

Parfitt & Driman. Hum Pathol 2007

Iatrogenic pathology of the intestines

Aoife J McCarthy,[1] Gregory Y Lauwers[2] & Kieran Sheahan[1]
[1]*Department of Histopathology, St Vincent's University Hospital, Elm Park, Dublin 4, Ireland, and* [2]*Department of Pathology, Massachusetts General Hospital, Boston, MA, USA*

Table 1. Patterns of injury and drugs most commonly associated with them

Pattern of injury	Drug
Focal active colitis	Ipilimumab, NSAIDs, sodium phosphate
Chronic colitis	Mycophenolate, ipilimumab, TNF-inhibitors, NSAIDs, rituximab
Apoptosis excess	Ipilimumab, mycophenolate, antimetabolites, TNF-inhibitors, colchicine, taxane, NSAIDs, sodium phosphate enema
Dilated damaged crypts and apoptosis	Mycophenolate, sodium phosphate enema, 5-FU
Small intestinal villous atrophy (coeliac disease-like)	Olmesartan, mycophenolate, ipilimumab, colchicine, azathioprine, NSAIDs
Microscopic colitis	Olmesartan, ipilimumab, NSAIDs, lansoprazole, ranitidine, ticlopidine, simvastatin, paroxetine, carbamazepine, penicillin, flutamide, cyclo3 fort, sertraline
Increased mitoses	Colchicine, taxane
Erosions/ulcers	NSAIDs, KCl, kayexalate
Diaphragms/stenosis	NSAIDs
Ischaemic colitis	NSAIDs, kayexalate, cocaine, diuretics, sumatriptan, dopamine, methysergide, amphetamines, oestrogens, ergotamine, alostron, digitalis, pseudoephedrine, vasopressin, interferon
Pseudomembranous colitis	Antibiotics, proton pump inhibitors
Crystal deposition	Kayexalate, kalimate, sevelamer, cholestyramine, bisphosphonates
Strictures	KCL, pancreatic enzymes
Pseudomelanosis coli	Laxatives
Sigmoid diverticular perforation	Corticosteroids
Hypereosinophilia	NSAIDs, oestrogen-progesterone drugs, plavix
Malakoplakia	Corticosteroids
Epithelial atypia	i.v. cyclosporin

NSAIDs: Non-steroidal anti-inflammatory drugs; TNF inhibitors: tumour necrosis factor alpha inhibitors; 5-FU: fluorouracil; KCL: potassium chloride; i.v.: intravenous.

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- Drug-induced injury may mimic virtually any gastrointestinal disease
  - Chronic active colitis (DD IBD, diverticular colitis
  - Small bowel intraepithelial lymphocytosis and villous atrophy (DD celiac disease)
  - Large bowel intraepithelial lymphocytosis (DD microscopic colitis)
  - Ischaemia (DD vascular obstruction)
  - Apoptotic excess (DD GvHD, autoimmune enteropathy)

McCarthy et al. Histopathology 2015

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Diaphragms/stenosis	NSAIDs
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NSAIDs: Non-steroidal anti-inflammatory drugs; TNF inhibitors: tumour necrosis factor alpha inhibitors; 5-FU: fluorouracil; KCL: potassium chloride; i.v.: intravenous.

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One specific drug may cause different patterns of injury (within the same organ and/or at different sites of involvement)

McCarthy et al. Histopathology 2015

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Malakoplakia	
Epithelial atypia	

NSAIDs: Non-steroidal anti-inflam
KCL: potassium chloride; i.v.: intravenous.

One specific drug may affect different organs and may cause different patterns of injury (at different sites)

Consider a drug-induced injury in every case of (unclear) inflammatory (non-neoplastic) lesion within the gastrointestinal tract!

McCarthy et al. Histopathology 2015

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Pill oesophagitis

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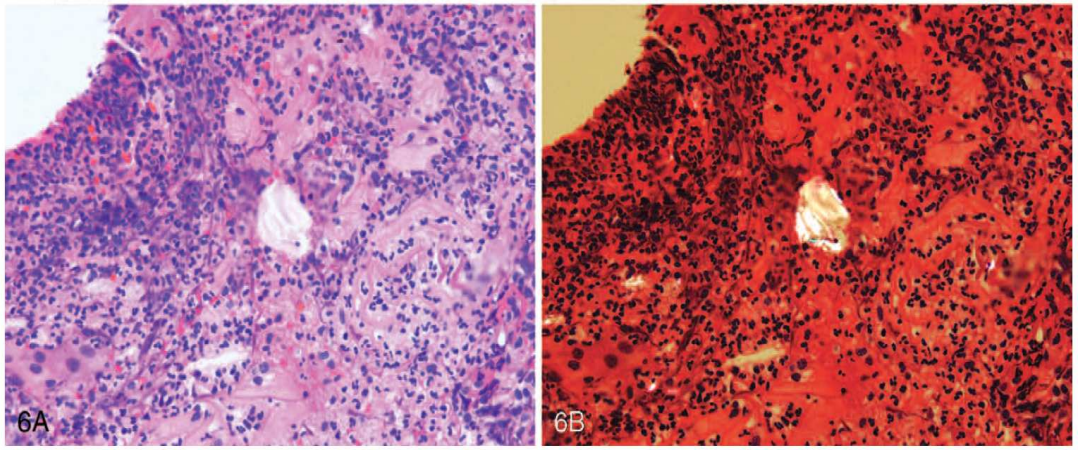
Table 3. Drugs or Chemicals Associated With Esophageal Injury

- Alprenol chloride
- Antibiotics
  - Chloramphenicol
  - Clindamycin
  - Cloxacillin
  - Doxycycline
  - Erythromycin
  - Lincomycin
  - Minocycline
  - Penicillin
  - Sulfa drugs
  - Tetracycline
  - Tinidazole
- Anti-inflammatory agents
  - Acetaminophen
  - Acetylsalicylic acid
  - Ibuprofen
  - Indomethacin
  - Mefaminic acid
  - Naproxen
  - Piroxicam
  - Sulindac
  - Tolmetin
- Ascorbic acid
- Barbiturates
- Benadryl
- Bisphosphonates
- Carbachol
- Chemotherapeutic agents
  - Actinomycin D
  - Adriamycin
  - Cytosine arabinoside
  - 5-Fluorouracil
  - Estramustine phosphate
- Chloral hydrate
- Clinitest tablets
- Co-trimoxazole
- Cromolyn sodium
- Digoxin, digitoxin
- Emepronium bromide
- Ferrous salts
- Pantogar
- Pantozyme
- Phenylbutazone
- Phenobarbital
- Phenoxymethyl penicillin
- Piroxicam
- Potassium chloride
- Prednisone and prednisolone
- Quinidine
- Sclerosants for varices
- Sodium amytal
- Theophylline
- Vasopressin
- Zidovudine



- Pills can become impacted in the distal esophagus or at the level of the midoesophagus by the aortic arch
- Most commonly implicated are antibiotics (especially of the tetracycline family), nonsteroidal anti-inflammatories, bisphosphonates, slow-release potassium medications, and iron supplements
- Biopsies show acute inflammation and ulceration in a nonspecific pattern (often resulting in stricturing); if pill fragments are identified in the exsudate, this can aid in making a specific diagnosis

Noffsinger. Arch Pathol Lab Med 2009
Grin & Streutker. Arch Pathol Lab Med 2015

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Iron-induced mucosal injury to the upper gastrointestinal tract

A Haig & D K Driman
Department of Pathology, London Health Sciences Centre and University of Western Ontario, London, Ontario, Canada

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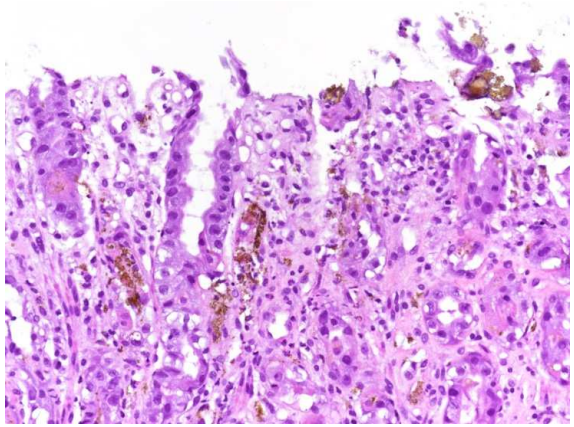

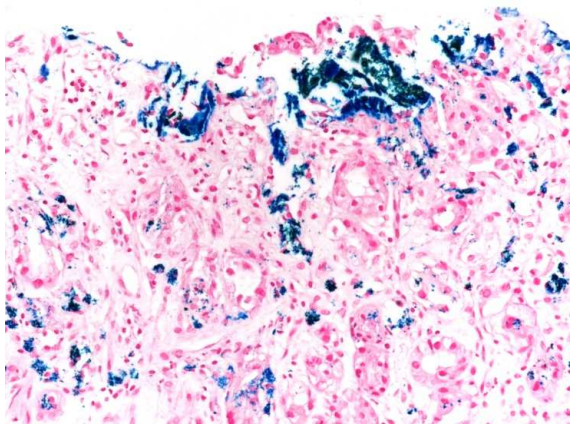

Table 2. Clinical and pathological details: Erosive iron injury (group 2)

Biopsy location	Age, years	Sex	Oral iron	Clinical symptoms and indication for endoscopy
Oesophagus	79	F	Yes	Melaena
Oesophagus	78	M	Yes	Dysphagia
Oesophagus	60	M	Yes	Coffee ground emesis
Oesophagus	82	M	Yes	Melaena
Oesophagus	89	F	Yes	Coffee ground emesis
Gastric	55	M	Unknown	Dysphagia
Gastric	75	F	Yes	Anaemia
Gastric	82	F	Yes	Duodenal obstruction
Gastric	70	M	Yes	Melaena
Gastric	87	M	Yes	Dyspepsia

- **Iron pill injury** is typically erosive, but may also lead to iron deposits in not eroded mucosa

Haig & Driman. Histopathology 2006

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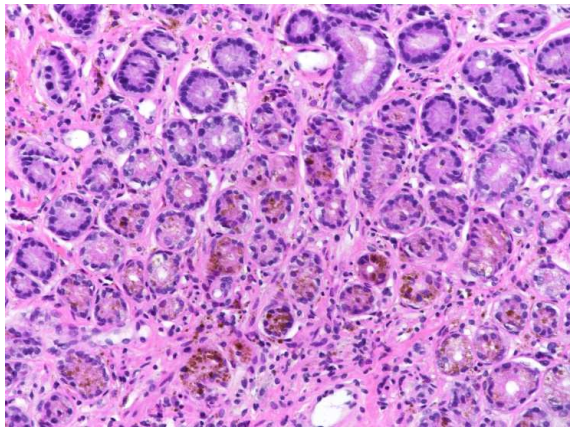

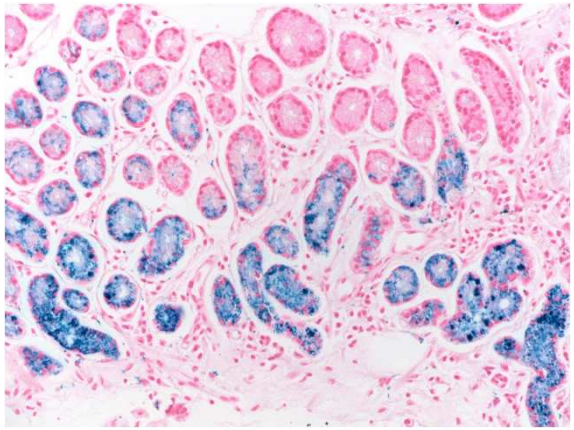

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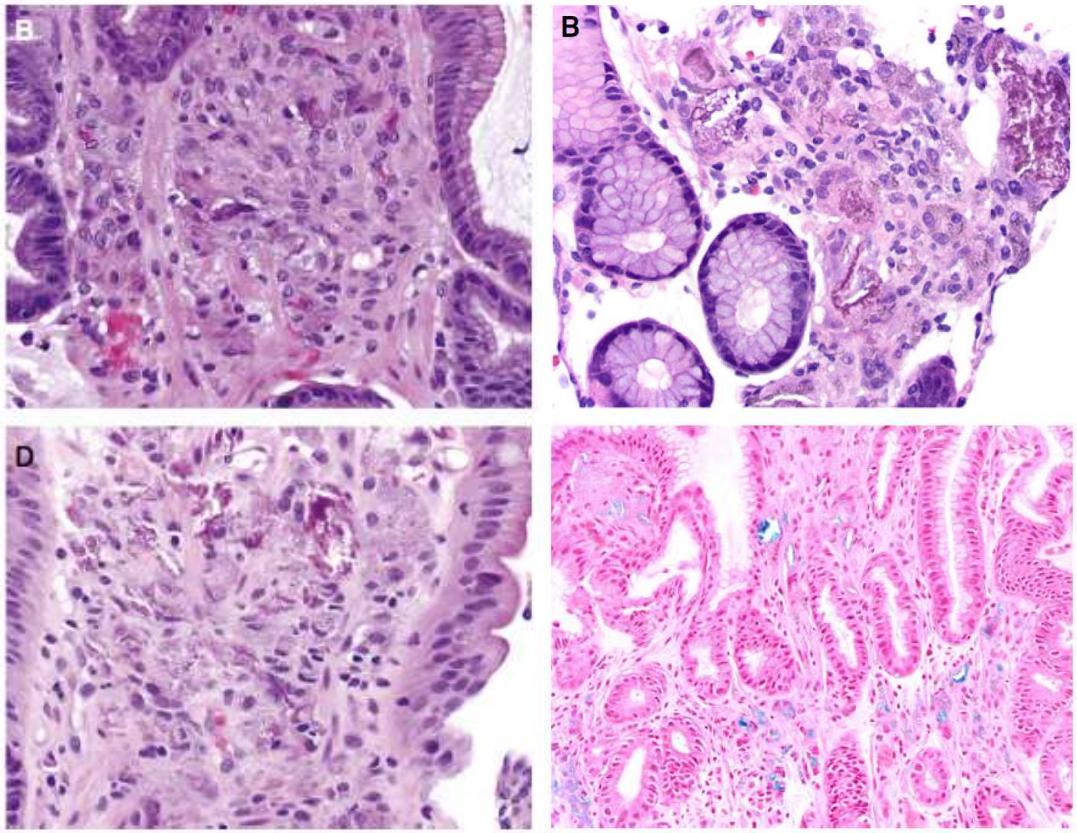
Gastric	87	M	Yes	Dyspepsia

- **Iron pill injury** is typically erosive, but may also lead to iron deposits in not eroded mucosa
- **Iron overload** due to hemochromatosis and/or repeated blood transfusions is usually non-erosive (affecting stroma and/or epithelium/glands)

Haig & Driman. Histopathology 2006

Lanthanum deposition from oral lanthanum carbonate in the upper gastrointestinal tract

Raza S Hoda,[1] Soma Sanyal,[2] Jerrold L Abraham,[2] Jamie M Everett,[1,*] Gregory L Hundemer,[3] Eric Yee,[4,†] Gregory Y Lauwers,[1,‡] Nina Tolkoff-Rubin[3] & Joseph Misdraji[1]
[1]*Department of Pathology, Massachusetts General Hospital, Boston, MA,* [2]*Department of Pathology, SUNY Upstate Medical University, Syracuse, NY,* [3]*Department of Medicine, Nephrology Service, Massachusetts General Hospital, and* [4]*Department of Pathology, Beth Israel Beth Israel Deaconess Medical Center, Boston, MA, USA*



- Lanthanum carbonate is an oral phosphate binder used to treat hyperphosphatemia in patients with end stage renal disease
- The medication can deposit throughout the gastrointestinal tract mucosa, most commonly in the stomach but also in the small intestine and colon
- Lanthanum may become embedded in the mucosa following digestion by gastric acid; deposition may be detected years after cessation of therapy
- Aggregates of light brown to purple material in the mucosa, engulfed by epithelioid histiocytes (may be faintly positive on iron stain, von Kossa negative)

Hoda et al. Histopathology 2017

Vascular Injury Characterizes Doxycycline-induced Upper Gastrointestinal Tract Mucosal Injury

Angela R. Shih, MD, Gregory Y. Lauwers, MD,* Anthony Mattia, MD,†*
*Esperance A.K. Schaefer, MD,‡ and Joseph Misdraji, MD**

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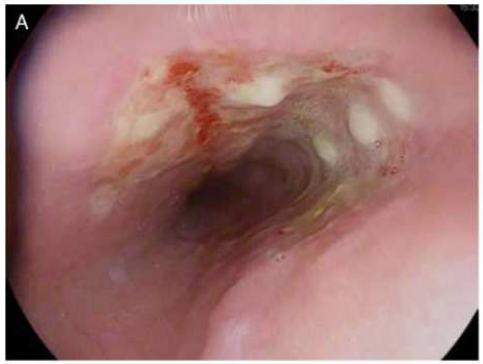
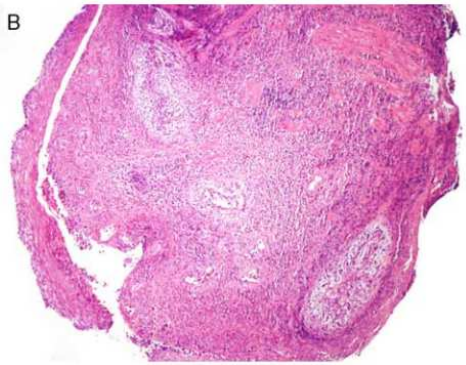
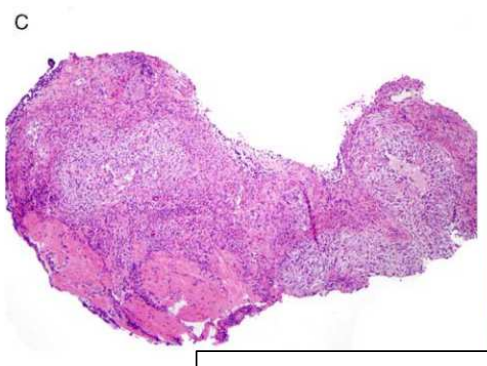
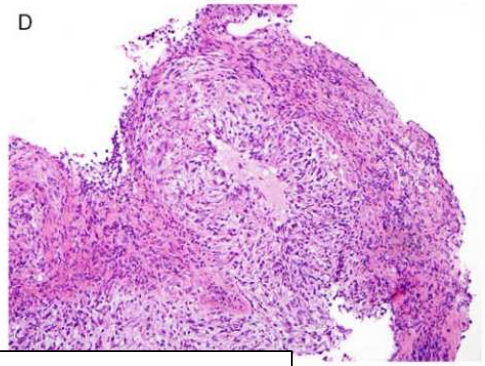
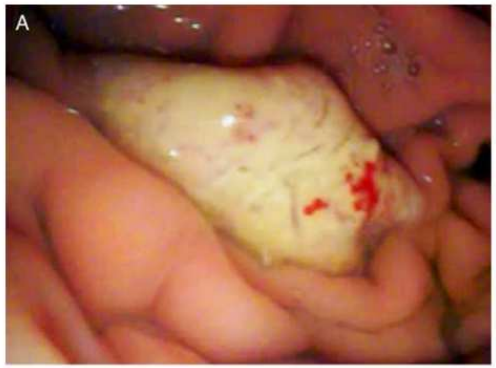


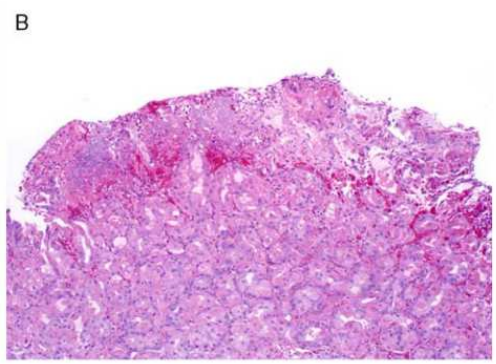


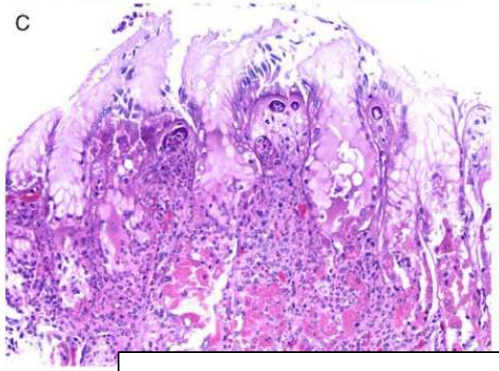


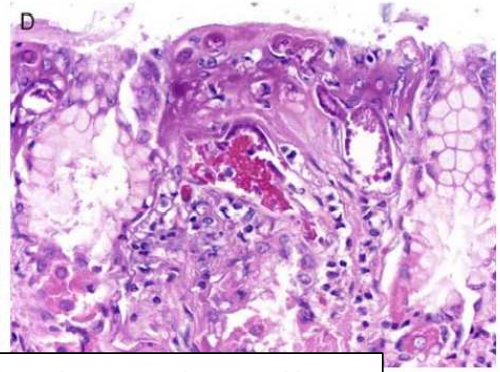


Oesophageal ulceration with vasculitis-like changes









Gastric erosion with fibrinoid capillary necrosis and endoluminal thrombosis

Shih et al. Am J Surg Pathol 2017

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NSAID damage in the (small and large) bowel

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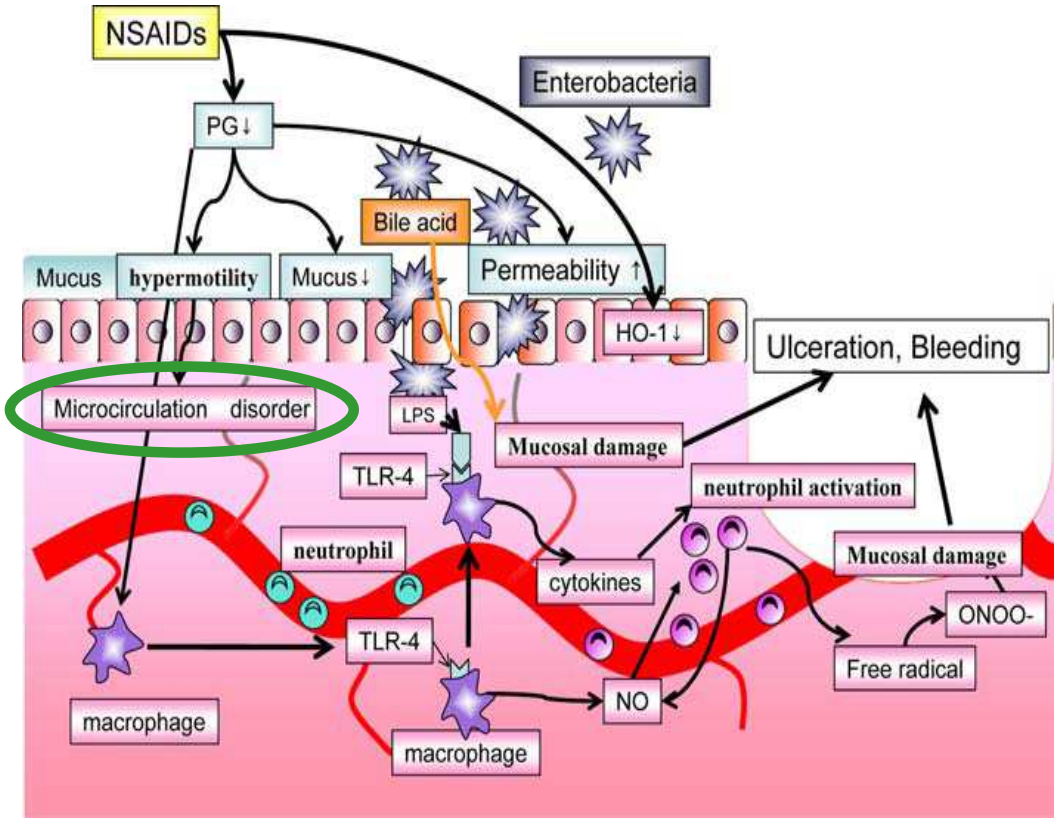

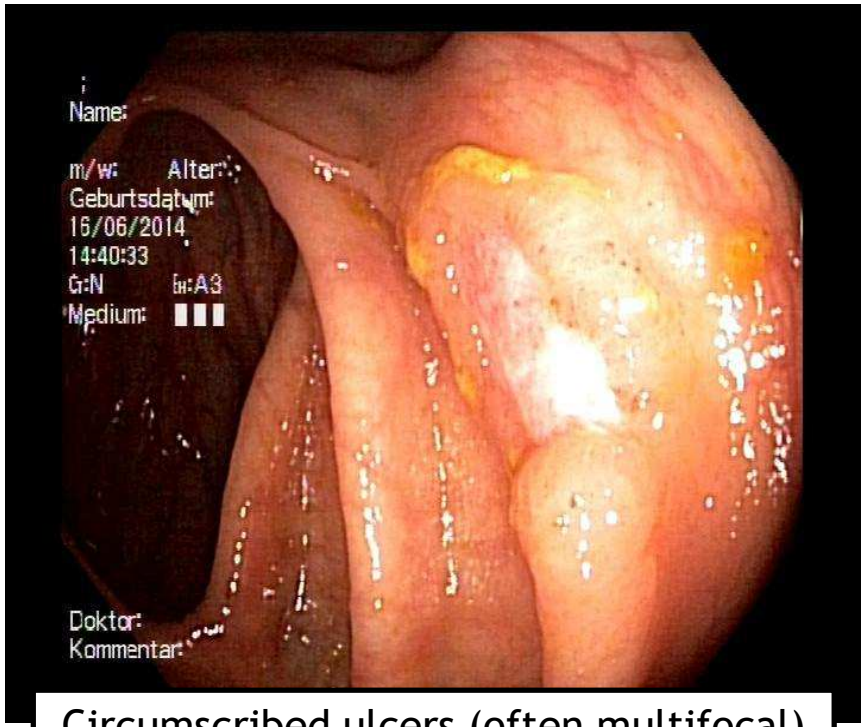

Circumscribed ulcers (often multifocal)
right colon (and ileum) > left colon

Higuchi et al. J Gastroenterol 2009

NSAID damage in the (small and large) bowel

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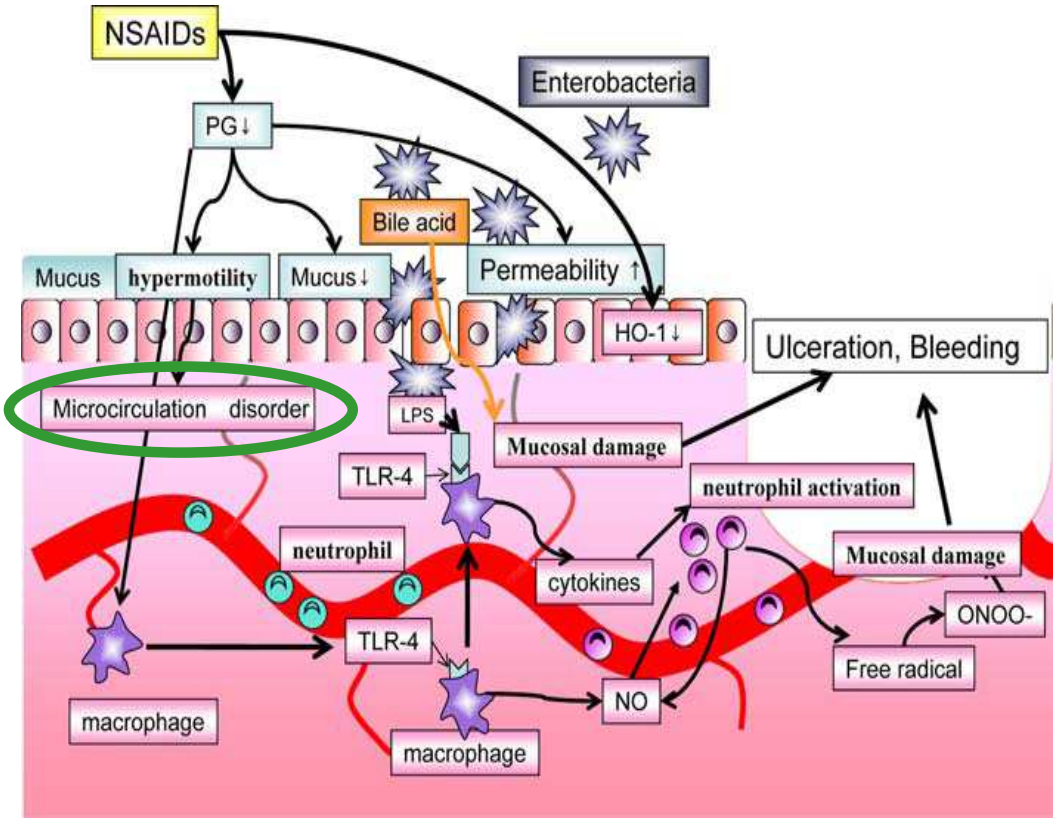

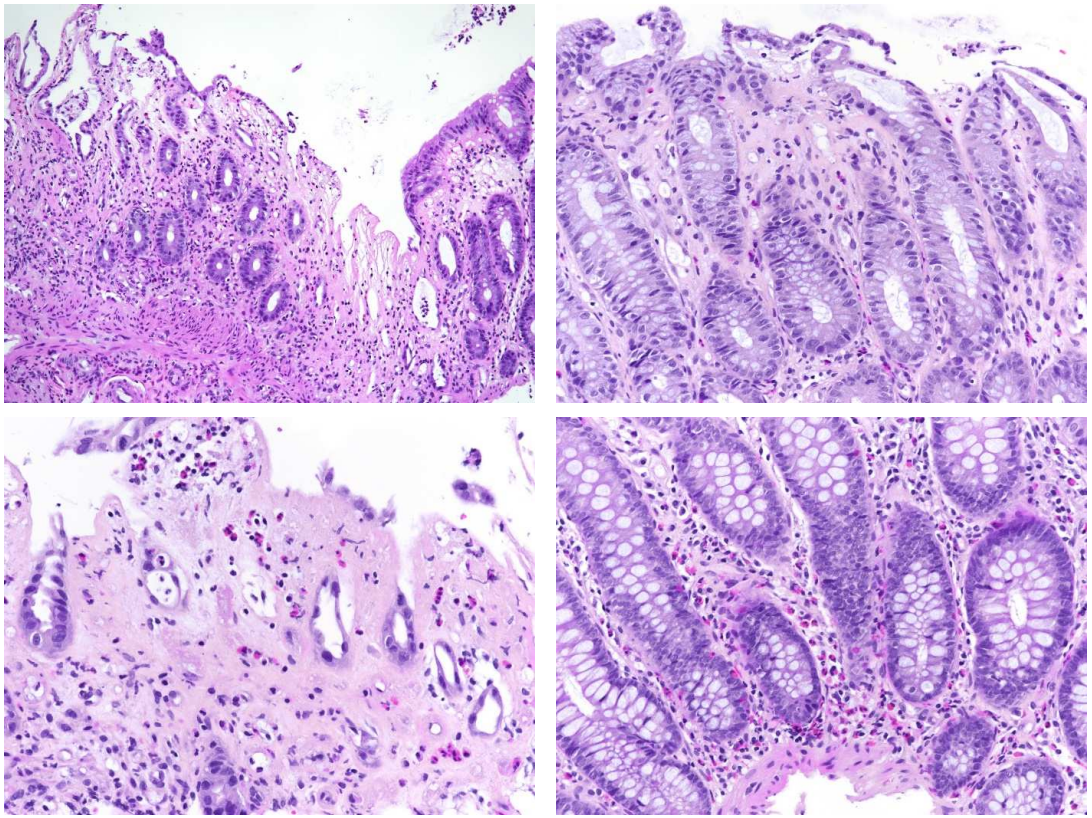

Higuchi et al. J Gastroenterol 2009

Differentiation from ischaemic colitis

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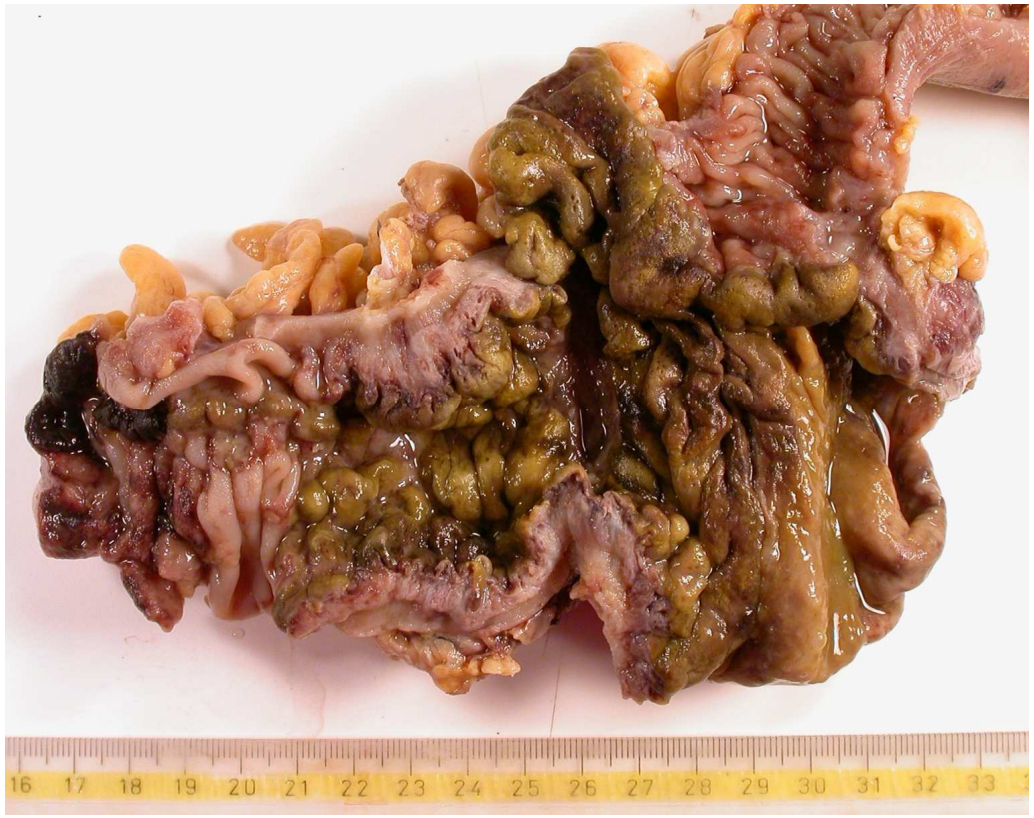

- Typically (but necessarily) older individuals affected (depending on the aetiology)
- Colon is the most common **site within the gastrointestinal tract:** right colon 8%, transverse colon 15%, splenic flexure (23%, watershed area), descending colon 27%, sigmoid colon 23%, rectum 4%
- Endoscopy: **geographical distribution** (redness, ulcers and/or pseudomembranes)

ORIGINAL ARTICLE

MAYO CLINIC

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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

Abstract

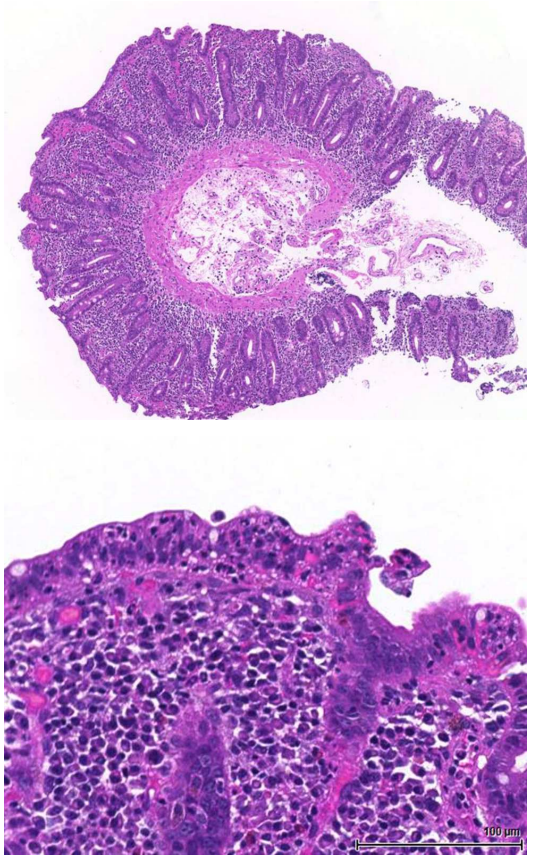
Objective: To report the response to discontinuation of olmesartan, an angiotensin II receptor antagonist commonly prescribed for treatment of hypertension, in patients with unexplained severe spruelike enteropathy.

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. Celiac 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, 47-81 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, 18 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 15 patients, and marked subepithelial collagen deposition (collagenous sprue) 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 demonstrated in all cases. Histologic recovery or improvement of the duodenum after discontinuation of olmesartan was confirmed in all 18 patients who underwent follow-up biopsies.

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

 ■ Mayo Clin Proc. 2012;87(8):732-738



Rubio-Tapia et al. Mayo Clin Proc 2012

Association of sprue-like enteropathy and angiotensin receptor-1 antagonists (ARB)

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- Main **histological features**
  - Villous atrophy of varying extent in 98%
  - Intraepithelial lymphocytosis in 65%
  - Increased cell content within lamina propria
- A total of 73 case reports have been described so far that show evidence of **ARB-associated enteropathy** with villous atrophy and full recovery 3–12 months after discontinuation of the sartan in question
  - Olmesartan (n=59), Telmisartan (n=4), Valsartan (n=3), Losartan (n=2), Candesartan (n=1), and Eprosartan (n=1)

Ianiro et al. Aliment Pharmacol Ther 2014
Wenzel & Datz. Wien Klin Wochenschr 2019

Gastrointestinal Disorder Associated with Olmesartan Mimics Autoimmune Enteropathy

Sophie Scialom[1,2☯], Georgia Malamut[1,2,3☯*], Bertrand Meresse[1,3], Nicolas Guegan[1,3], Nicole Brousse[1,4], Virginie Verkarre[1,4], Coralie Derrieux[1,5], Elizabeth Macintyre[1,5], Philippe Seksik[6], Guillaume Savoye[7], Guillaume Cadiot[8], Lucine Vuitton[9], Lysiane Marthey[10], Franck Carbonnel[10], Nadine Cerf-Bensussan[1,3], Christophe Cellier[1,2,3]

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Table 1. Clinical and immune characteristics.

Case	Sex	Age (y)	Autoimmunediseases	BMI	DQ2/8	Anti AIE 75 kDa	anti-E	tTG	IGA	ANA	Duod	Lymphocytosis		
												Duod	Sto	Col
Olme-sartan														
1	F	74	Goujerot Sjogren	17	+	+	*nd*	+	-	+	TVA	30%	-	-
2	F	72	-	23	*nd*	+	*nd*	-	-	*nd*	STVA	40%	-	-
3	F	69	Uveitis Cholangitis	17	+	-	-	-	*nd*	+	STVA	40%	-	-
4	M	79	-	20	+	-	-	-	*nd*	+	TVA	30%	-	-
5	M	60	-	21	-	-	-	-	*nd*	-	TVA	100%	+	-
6	F	65	Cholangitis	20	-	-	*nd*	-	-	+	TVA	30%	-	-
7	M	77	-	24	+	*nd*	-*	-	-	*nd*	STVA	30%	-	-
Mean		**71**		**20**	**67%**	**33%**	**0%**	**14%**	**0%**	**80%**		**43%**	**14%**	**0**
AIE														
8	F	17	Auto I Pancreatitis anti-	16	+	+	*nd*	-	-	+	TVA	40%	-	-
9	F	23										90%	+	+
10	F	19									A	57%	-	+
11	F	41									A	65%	-	-
Mean		**25**										**63%**	**25%**	**50%**

Olmesartan induced enteropathy usually resolves after olmesartan interruption but in some patients immunosuppressive drugs may be necessary to achieve remission (these patients may show intestinal damage mimicking autoimmune enteropathy with increased apoptosis)

Scialom et al. Plos One 2015

Sevelamer Crystals in the Gastrointestinal Tract (GIT)

A New Entity Associated With Mucosal Injury

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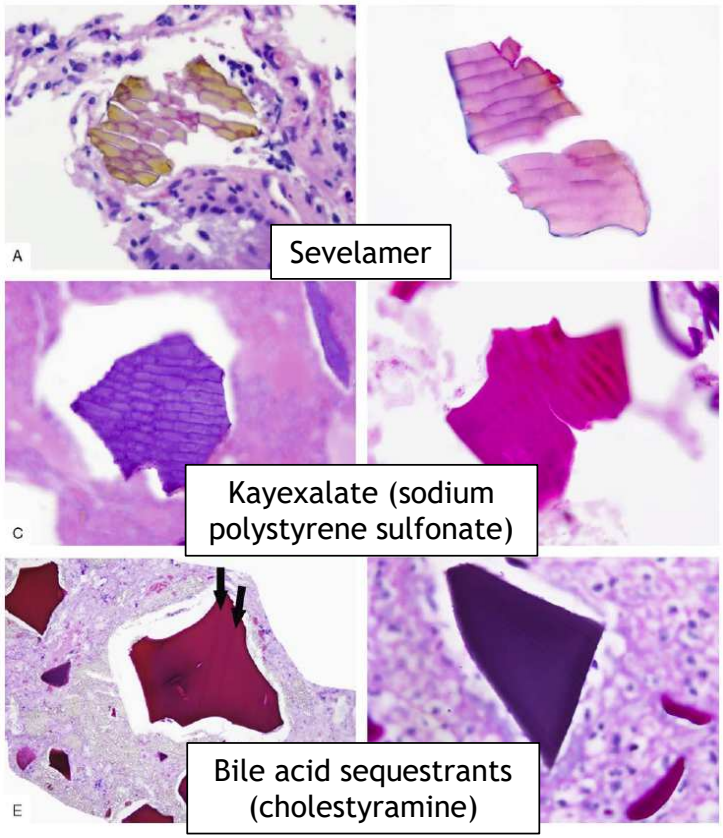


TABLE 2. Sevelamer Crystals Were Commonly Associated With Background Mucosal Injury

Patient	Biopsy/Resection Location	Associated Mucosal Findings
1	Small bowel resection	Ischemia, necrosis, amyloidosis
2	Colon Bx	Inflammatory polyp with acute inflammation
3	Colon Bx	Acute colitis
	Colon Bx	Inflammatory polyp with acute inflammation
	Colon Bx	Crypt distortion, Paneth cell metaplasia
	Colon Bx	Crypt distortion, Paneth cell metaplasia
	Colon Bx	Crypt distortion, Paneth cell metaplasia
	Colon Bx	Crypt distortion, Paneth cell metaplasia
	Colon Bx	Cryptitis, crypt distortion, Paneth cell metaplasia
	Colon Bx	Hyperplastic polyp vs. serrated epithelial change
4	Duodenal Bx	None
	Esophagus Bx	Extensive ulceration
5	Colon Bx	Mucosal prolapse
6	Colon Bx	Fragments of tubular adenoma
7	Esophagus Bx	Extensive ulceration

*All patients were on sevelamer carbonate (Renvela) except for patient 7 who was on sevelamer hydrochloride (Renagel).
Bx indicates biopsy; UNK, unknown.

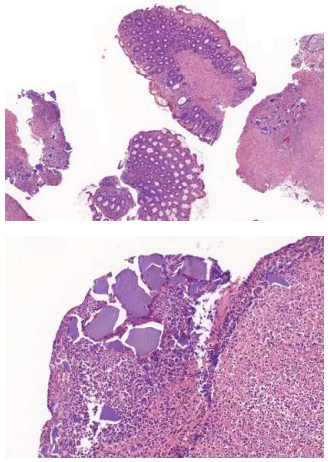


Table 1 Resin summary

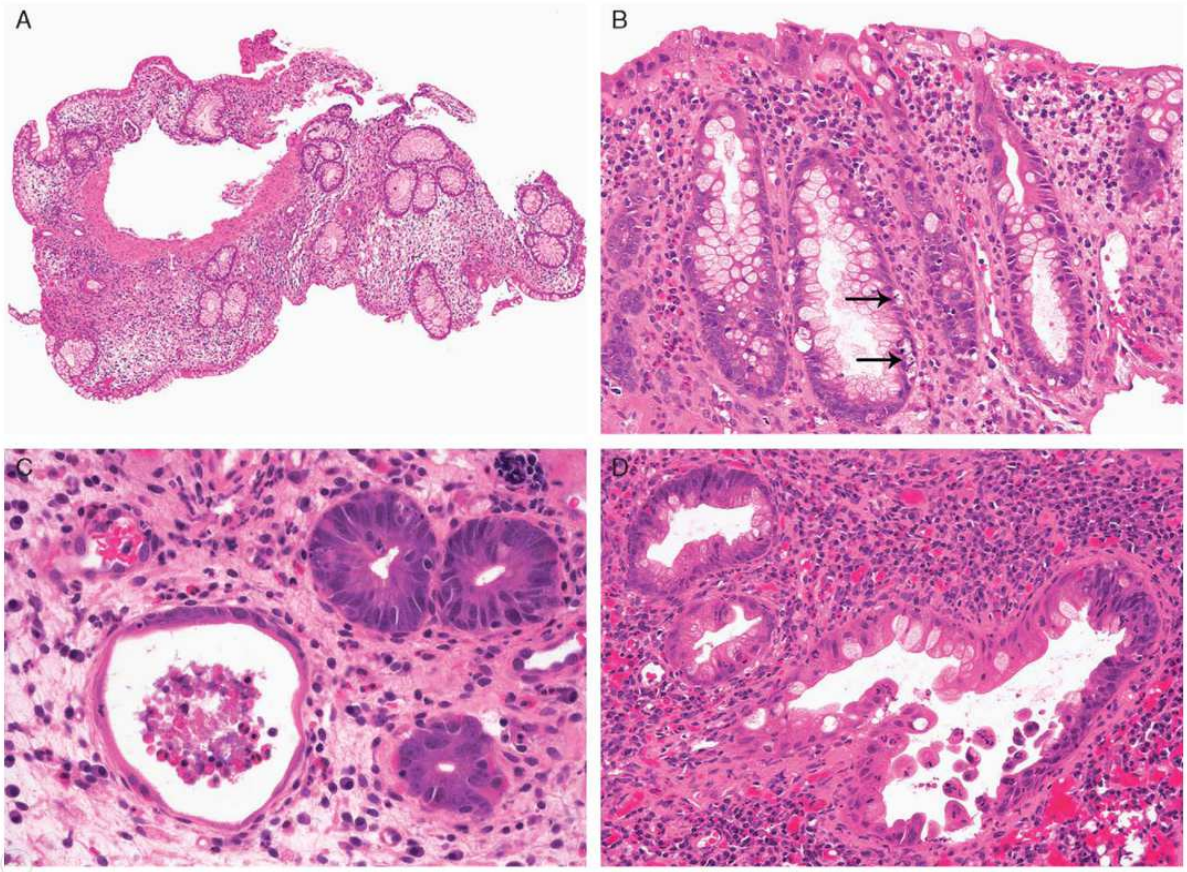
Brand name	Generic name	Route	Indications	Binding target	Causes mucosal injury
Kayexalate	Sodium Polystyrene Sulfonate	PO, Enema	Hyperkalemia (usually chronic kidney disease)	Potassium	Yes
Renvela, Renagel	Sevelamer	PO	Hyperphosphatemia (usually chronic kidney disease)	Phosphate	Possibly
Welchol	Colesevelam	PO	Diarrhoea, hypercholesterolaemia, dyslipidemia, diabetes mellitus	Bile acids	No
Colestid	Colestipol	PO	Diarrhoea, hypercholesterolaemia, dyslipidemia, and pruritus	Bile acids	No
LoCholest	Cholestyramine	PO	Same as above	Bile acids	No
Prevalite	Cholestyramine	PO	Same as above	Bile acids	No
Questran	Cholestyramine	PO	Same as above	Bile acids	No

Swanson et al. Am J Surg Pathol 2013
Voltaggio et al. J Clin Pathol 2014

Mycophenolate Mofetil-related Gastrointestinal Mucosal Injury: Variable Injury Patterns, Including Graft-versus-Host Disease-like Changes

Jeremy R. Parfitt, MD, Saumya Jayakumar, MD,† and David K. Driman, MBChB, FRCPC**

Medical University of Graz



- MMF inhibits purine (guanosine) synthesis for DNA synthesis via the *de novo* pathway
- T cells depend on *de novo* guanine nucleotide synthesis to rapidly proliferate in response to antigenic challenge

TABLE 1. Pathologic Features of MMF in Colonic Biopsies

	MMF Patients (n = 16)	Non-MMF Patients (n = 14)	
Morphologic Feature	**n (%)**	**n (%)**	***P***
Crypt architectural disarray	12 (75)	2 (14)	0.001
Erosions/ulcers	4 (25)	2 (14)	> 0.05
Lamina propria edema	9 (56)	2 (14)	0.017
Increased lamina propria inflammation	13 (81)	3 (21)	0.001
Cryptitis	6 (37)	3 (21)	> 0.05
Dilated damaged crypts	7 (44)	1 (7)	0.024
Crypt loss	4 (25)	2 (14)	> 0.05
Increased crypt epithelial apoptosis	9 (56)	2 (14)	0.017
GVHD-like changes	9 (56)	2 (14)	0.017
IBD-like changes	2 (13)	0 (0)	> 0.05

GVHD indicates graft-versus-host disease; IBD, inflammatory bowel disease; MMF, mycophenolate mofetil

Parfitt et al. Am J Surg Pathol 2008

28-year-old female with history of kidney transplantation (under corticosteroids and MMF)

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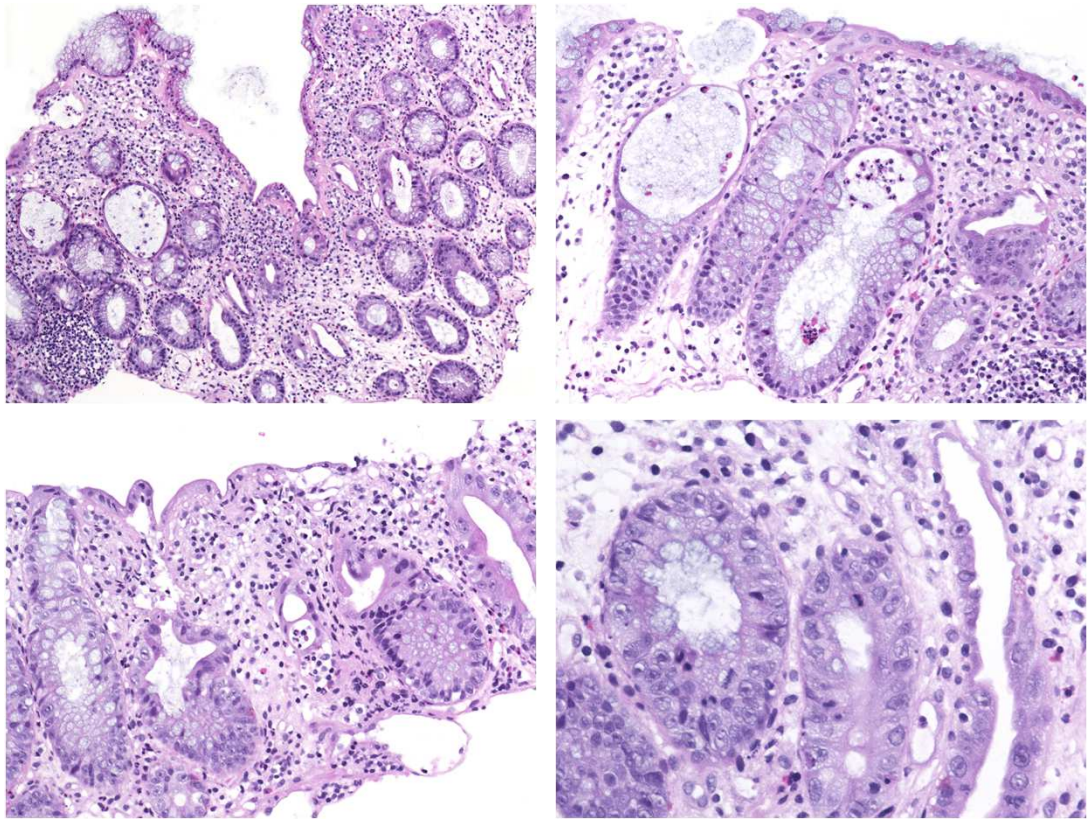
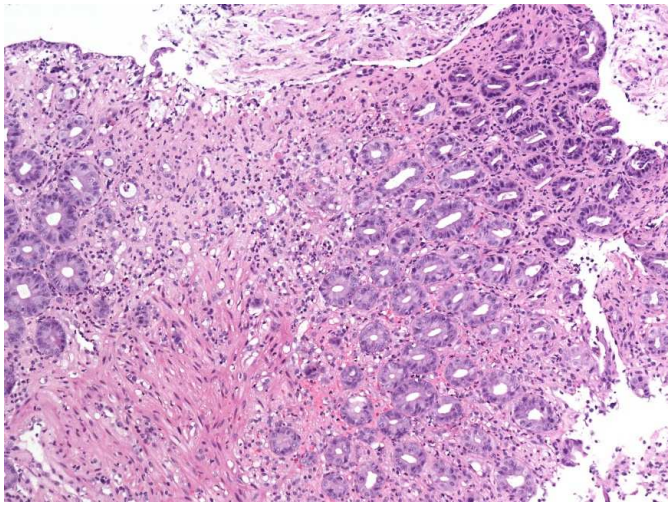
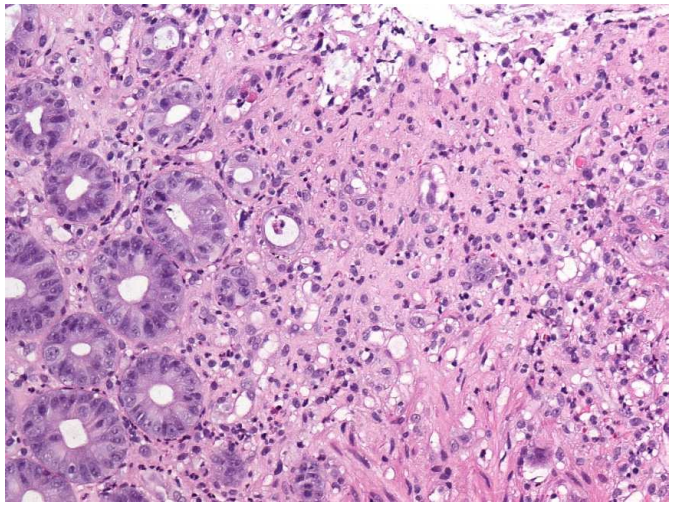
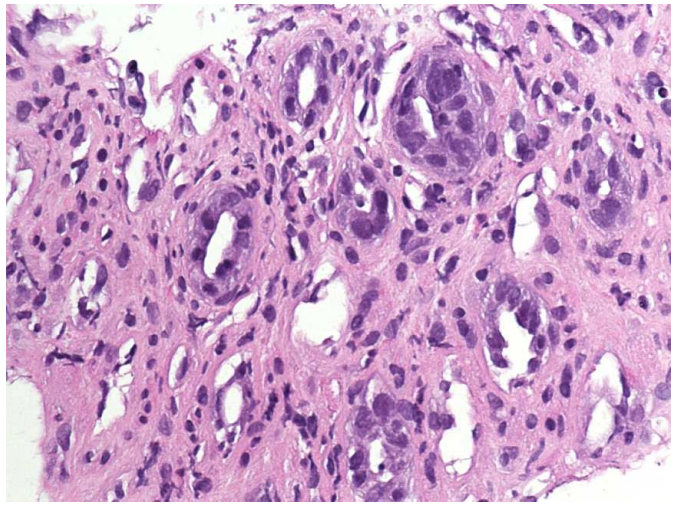


- Crypt withering with dilatation and epithelial degeneration (e.g. flattening, eosinophilia, nuclear atypia) → **ischemic-like**
- Apoptotic bodies → **GvHD-like**
- Active inflammation and crypt distortion → **IBD/Crohn-like**

DD ischaemic colitis

- Crypts appear withered or atrophic, may have marked regenerative atypia
- Lamina propria appears hyalinised or smudgy; stains blue on trichrome stain
- Little if any inflammation, possibly mucosal hemorrhage and/or presence of hemosiderin-laden macrophages

Greenson. Diagnostic Gastrointestinal Pathology 2010

DD graft versus host disease (GvHD)

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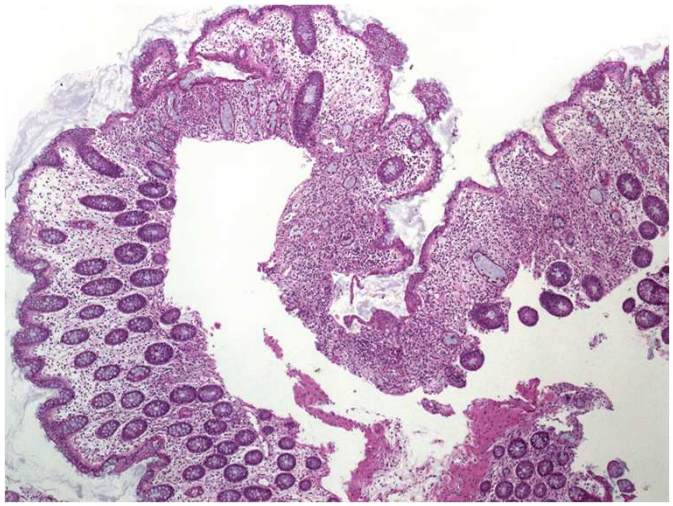
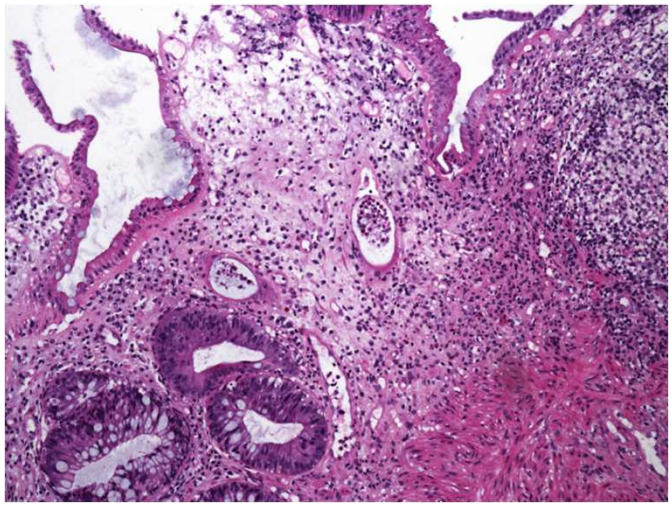
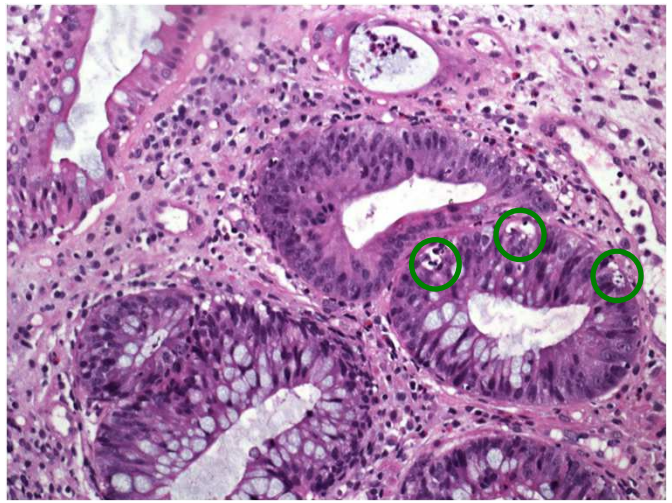

- Apoptosis is hallmark of GvHD, can totally denude the mucosa
- May have some eosinophils in damaged crypts (“apoptotic debris”)
- May end up with marked crypt distortion
- Usually has paucity of lamina propria inflammation

Greenson. Diagnostic Gastrointestinal Pathology 2010

Drug-induced injury in oncological patients

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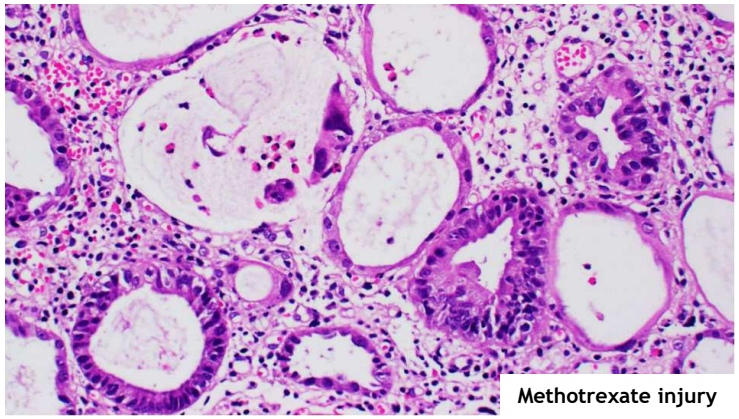
- Antimetabolite chemotherapy induced colitis (5-FU, MTX)
  - Crypt epithelial cells (small bowel > large bowel) demonstrate loss of nuclear polarity, pyknosis, and apoptosis → dilated crypts with nuclear debris, stromal hemorrhage
  - Cave nuclear atypia ("monster nuclei") mimicking dysplasia (degenerative cytoplasmic changes with eosinophilia/vacuolization, retained N/C ratio → do not stain Ki67/p53)



Methotrexate injury

Courtesy of Prof. Bence Kövari, Lee Moffitt Cancer Center, Tampa, USA

Drug-induced injury in oncological patients

Medical University of Graz

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  - Crypt epithelial cells (small bowel > large bowel) demonstrate loss of nuclear polarity, pyknosis, and apoptosis → dilated crypts with nuclear debris, stromal hemorrhage
  - Cave nuclear atypia ("monster nuclei") mimicking dysplasia (degenerative cytoplasmic changes with eosinophilia/vacuolization, retained N/C ratio → do not stain Ki67/p53)
- Cellular effects associated with microtubule polymerization inhibitors
- Selective internal radiation therapy (SIRT) affecting the upper GIT
- The ever growing world of immune checkpoint inhibitors and more recent drug developments
- Neutropenic enterocolitis

Gastrointestinal Tract Epithelial Changes Associated With Taxanes: Marker of Drug Toxicity Versus Effect

Jason A. Daniels, MD, Michael K. Gibson, MD,† Li Xu, MS,† Shaoli Sun, MD,‡ Marcia Irene Canto, MD, MHS,§ Elisabeth Heath, MD,† Jean Wang, MD,§ Malcolm Brock, MD,‖ and Elizabeth Montgomery, MD**

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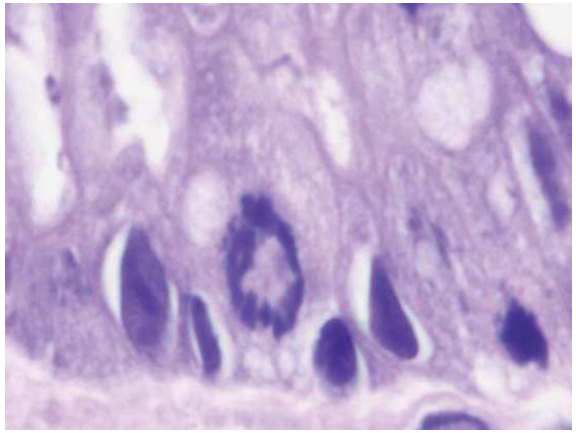

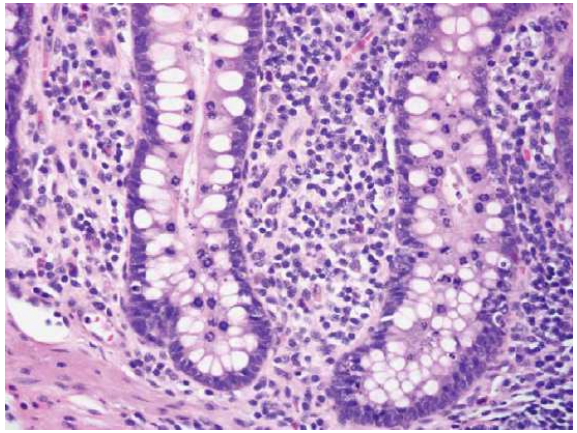

TABLE 1. Grading and Interval Between Taxane Administration

Grade	Total Samples	Median After Taxane (d)	Range After Taxane (d)
0	191	27	4-966
1	21	35	8-287
2	4	42.5	12-405
3	5	1	1-3

- Taxanes bind to microtubules, thereby promoting polymerization and inhibiting depolymerization
- Electron microscopy has shown this central core of polymerized microtubules surrounded by dispersed chromatin, resulting in a "ring" structure during metaphase (in the proliferative compartment of the respective epithelium)
- **Pitfall:** epithelial changes associated with taxanes can mimic high-grade dysplasia (HGD) → do not perform Ki67/p53 immunostaining

Ott & Langner. Histopathology 2007
Daniels et al. Am J Surg Pathol 2008

Gastrointestinal injury associated with the intake of immune checkpoint inhibitors (ICI)

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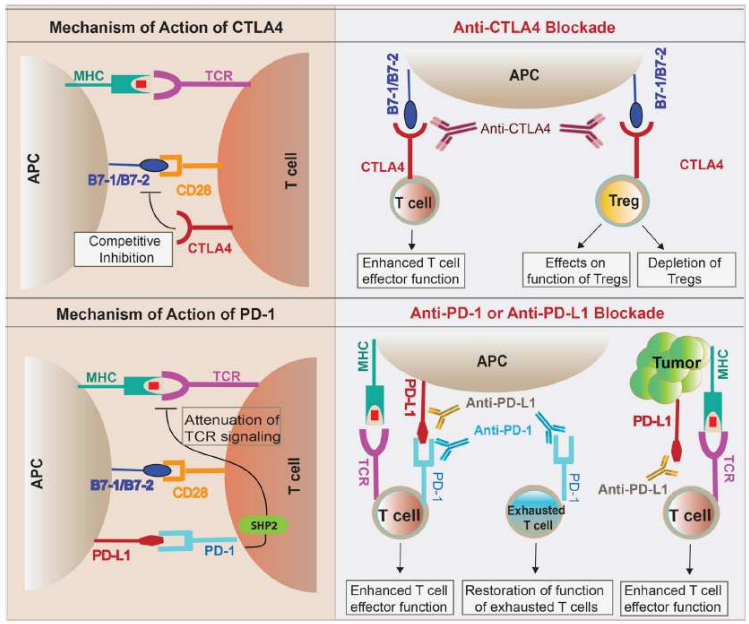
Ipilimumab



Nivolumab
Pembrolizumab

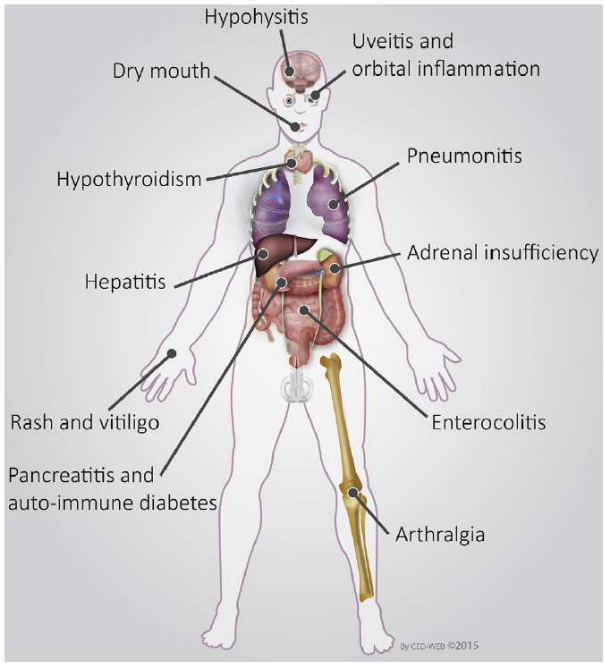
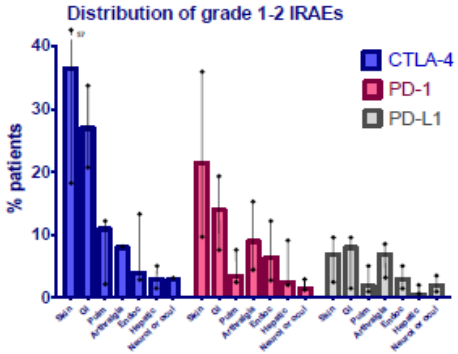
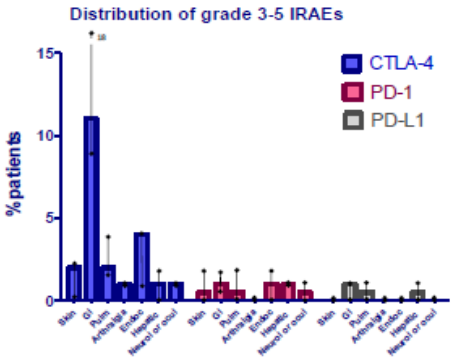


Fig. 3. The clinical spectrum of IRAEs. IRAEs: immune-related adverse events.





Michot et al. Eur J Cancer 2016
Khan & Gerber. Semin Cancer Biol 2020

Histopathologic Features of Colitis Due to Immunotherapy With Anti-PD-1 Antibodies

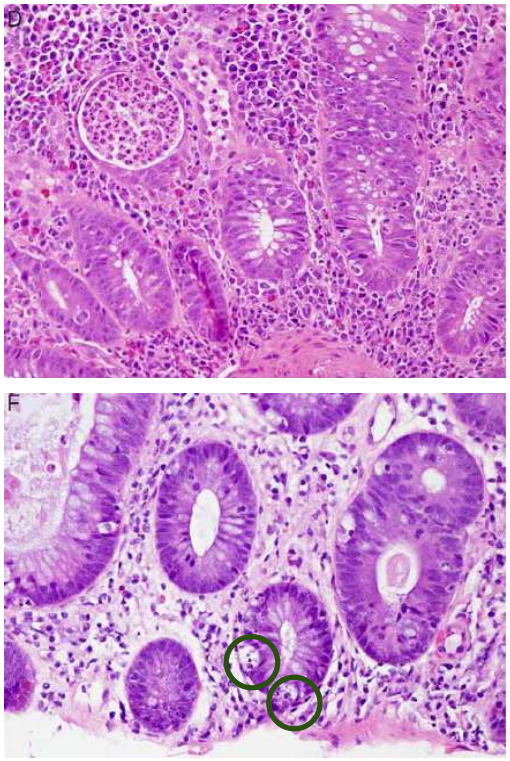
Jonathan H. Chen, MD, PhD, Maryam K. Pezhouh, MD, MSc,† Gregory Y. Lauwers, MD,‡ and Ricard Masia, MD, PhD**

Medical University of Graz

TABLE 2. Histopathologic Features of Anti-PD-1 Colitis

Patient	1	2	3	4	5
Pattern	Active Colitis With Apoptosis				
Colon sites involved	Right, left	Distal transverse	Right, left	Transverse, sigmoid	Rectum
Colon sites uninvolved				Rectum	
Extent of involvement	Diffuse	Patchy	Diffuse	Diffuse	Diffuse
Neutrophilic cryptitis	Y	Y	Y	Y	Y
Neutrophilic microabscesses	Y	Y	Y	Y	Y
Expansion of lamina propria	N	N	N	N	N
Basal lymphoplasmacytosis	N	N	N	N	N
Architectural changes	N	N	N	N	N
Paneth cell metaplasia	N	N	N	N	N
Increased crypt epithelial apoptosis	Y	Y	Y	Y	Y
Crypt atrophy/dropout	Y	Y	Y	Y	Y
Increased intraepithelial lymphocytes	N	N	N	N	N
Surface epithelial injury	N	N	Y	N	N
Thickened subepithelial collagen table	N	N	N	N	N

NA indicates not available; N, no; Y, yes.



Depending on duration of symptoms and timing of biopsy: chronic active colitis (with apoptosis)

Chen et al. Am J Surg Pathol 2017

50-year-old male with malignant melanoma under combined therapy with Ipilimumab/Nivolumab

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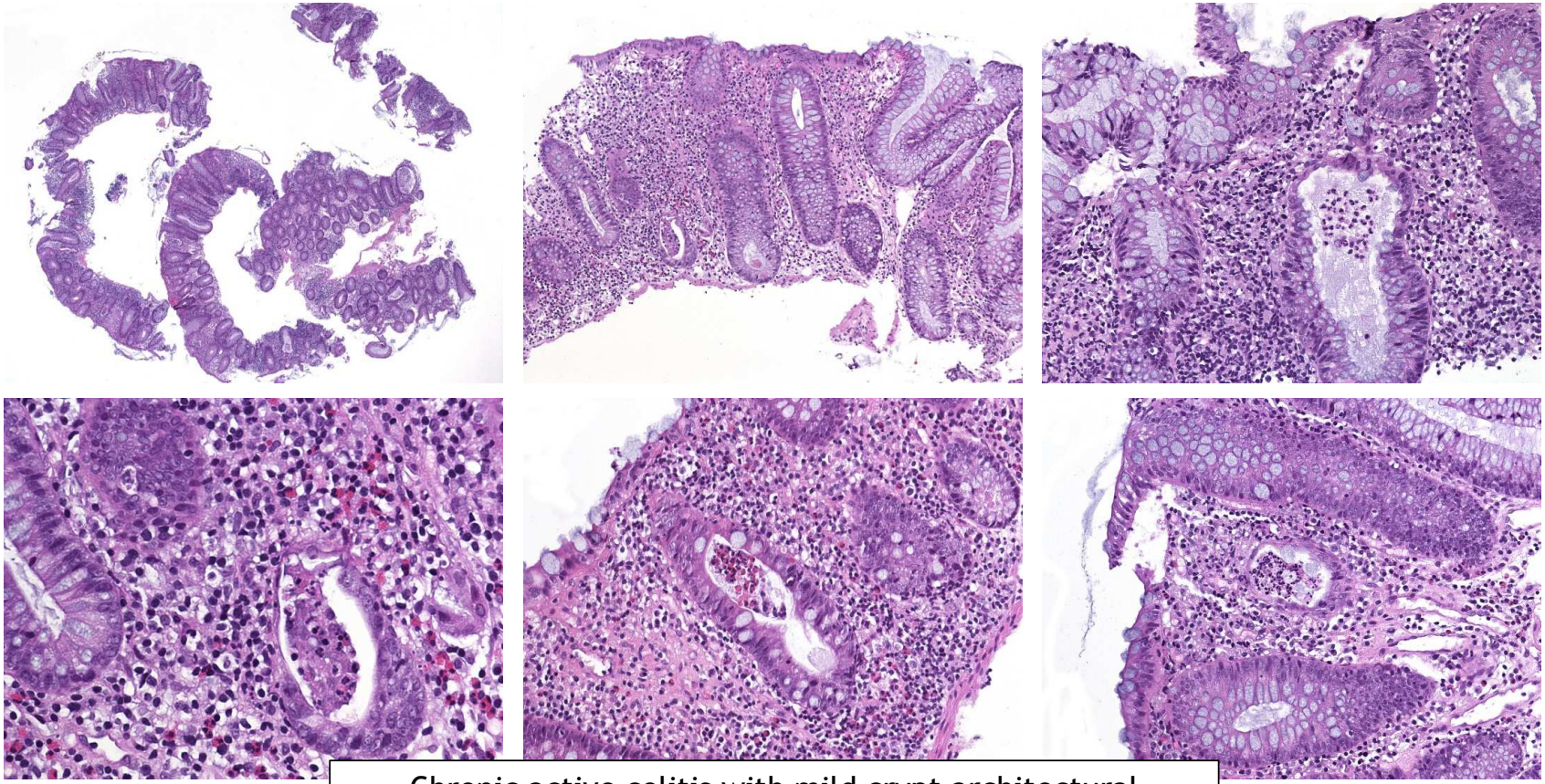


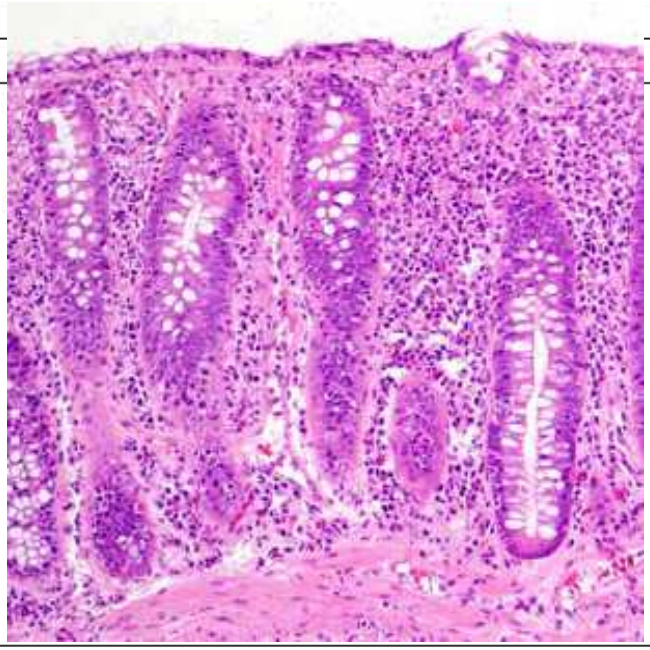
Chronic active colitis with mild crypt architectural distortion and basal plasmacytosis

Histopathologic Features of Colitis Due to Immunotherapy With Anti-PD-1 Antibodies

Jonathan H. Chen, MD, PhD, Maryam K. Pezhouh, MD, MSc,† Gregory Y. Lauwers, MD,‡ and Ricard Masia, MD, PhD**

Medical University of Graz

TABLE 2. Histopathologic Features of Anti-PD-1 Colitis

Patient		6	7	8	
Pattern		**Lymphocytic Colitis**			**Total**
Colon sites involved		Right, left	NA	Sigmoid	
Colon sites uninvolved					
Extent of involvement		Diffuse	Diffuse	Patchy	6/8 diffuse (75%)
Neutrophilic cryptitis		Y	N	N	6/8 (75%)
Neutrophilic microabscesses		N	N	N	5/8 (63%)
Expansion of lamina propria		Mild, superficial	Mild, superficial	Mild, superficial	3/8 (38%)
Basal lymphoplasmacytosis		N	N	N	0/8 (0%)
Architectural changes		N	N	N	0/8 (0%)
Paneth cell metaplasia		N	N	N	0/8 (0%)
Increased crypt epithelial apoptosis		Y	Y	N	7/8 (88%)
Crypt atrophy/dropout		N	N	N	5/8 (63%)
Increased intraepithelial lymphocytes		Y	Y	Y	3/8 (38%)
Surface epithelial injury		Y	Y	Y	4/8 (50%)
Thickened subepithelial collagen table		N	N	N	0/8 (0%)

NA indicates not available; N, no; Y, yes.

Chen et al. Am J Surg Pathol 2017

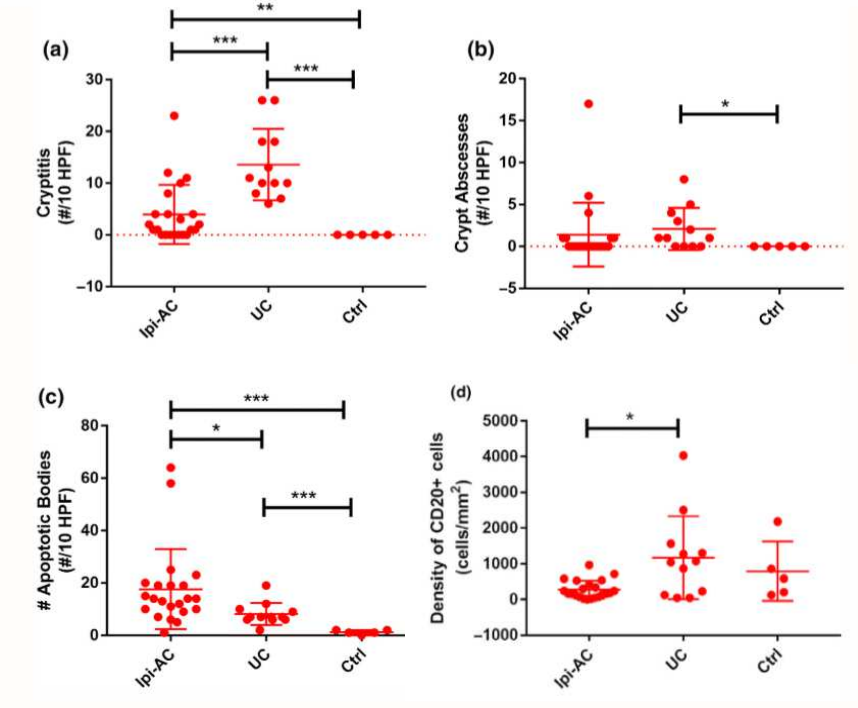
Histopathological and immunophenotypic features of ipilimumab-associated colitis compared to ulcerative colitis

B. L. Adler[1,#], M. K. Pezhouh[2,#], A. Kim[3], L. Luan[2], Q. Zhu[2], F. Gani[4], M. Yarchoan[5], J. Chen[6], L. Voltaggio[2], A. Parian[3], M. Lazarev[3], G. Y. Lauwers[6], T. M. Pawlik[7], E. A. Montgomery[2], E. Jaffee[5,8], D. T. Le[5], J. M. Taube[2,8] & R. A. Anders[2,8]

From the Departments of [1]Rheumatology; [2]Pathology; [3]Gastroenterology; [4]Surgery; [5]Medical Oncology, Johns Hopkins University School of Medicine, Baltimore, MD; [6]Department of Pathology, H. Lee Moffitt Cancer and Research Institute, Tampa, FL; [7]Department of Surgery, Ohio State University Wexner Medical Center, Columbus, OH; and [8]The Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins, Baltimore, MD, USA

Table 1 *Demographic, clinical characteristics, endoscopic findings and histopathologic findings of ipilimumab-associated colitis (Ipi-AC, n = 22), ulcerative colitis (UC, n = 12) and normal controls (Ctrl, n = 5)*

	Ipi-AC (n = 22)	UC (n = 12)	Ctrl (n = 5)
Age (years)	62 ± 11.7	42 ± 17.8*	49 ± 16.6#
Sex (% female)	7 (32%)	8 (67%)	3 (60%)
Most common clinical symptom	Watery diarrhoea (n = 21, 95%)	Haematochezia (n = 9, 75%)	Watery diarrhoea (100%)
Most common endoscopic findings	Oedematous and erythematous mucosa (n = 8, 36%)	Erythematous, friable and ulcerated mucosa (n = 9, 75%)	Normal (n = 5, 100%)
Sites biopsied [*N* (%)]			
Left colon	22 (100%)	12 (100%)	5 (100%)
Right colon	11 (50%)	7 (58%)	2 (40%)
Ileum	6 (27%)	3 (25%)	3 (60%)
Presence of mucosal ulceration [*N* (%)]	10 (45%)	7 (58%)	0 (0%)#
Cryptitis			
Presence [*N* (%)]	16 (73%)	10 (83%)	0 (0%)##
Quantitative (#/10 HPF)	3.6 ± 5.3	11.6 ± 6.3***	0 ± 0##
Crypt abscesses			
Presence [*N* (%)]	7 (32%)	8 (67%)*	0 (0%)
Quantitative (#/10 HPF)	1.8 ± 3.8	1.8 ± 2.4	0 ± 0
Presence of basal plasmacytosis [*N* (%)]	3 (14%)	11 (92%)***	0 (0%)
Crypt distortion [*N* (%)]			
Presence (any)	5 (23%)	9 (75%)**	0 (0%)
Mild	4 (18%)	3 (25%)	0 (0%)
Moderate	1 (5%)	4 (33%)	0 (0%)
Severe	0 (0%)	2 (17%)	0 (0%)
Apoptotic Bodies (per 10 HPF)	16.6 ± 15.6	7.3 ± 4.7*	0.8 ± 0.4###



In conclusion, Ipi-AC has many overlapping features with ulcerative colitis but is a distinct pathologic entity with notable clinical and histopathological differences

Adler et al. J Intern Med 2018

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

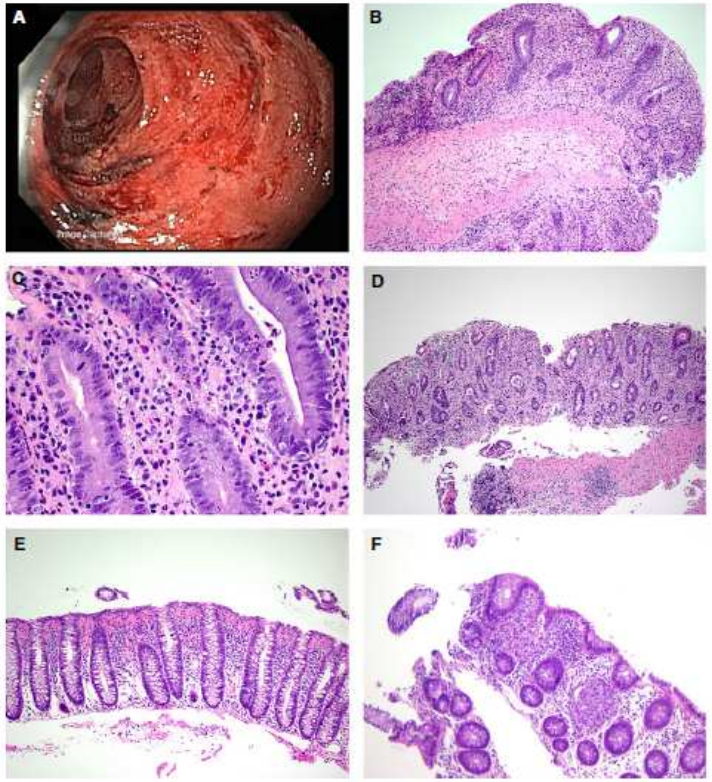
Raul S Gonzalez,[1] Safia N Salaria,[2] Caitlin D Bohannon,[3] Aaron R Huber,[1] Michael M Feely[4] & Chanjuan Shi[2]

Medical University of Graz

Table 2. Histopathological findings in biopsies of programmed cell death protein 1 (PD-1) inhibitor gastroenterocolitis*

	Stomach ($n = 6$)	Duodenum ($n = 6$)	Terminal ileum ($n = 5$)	Colon ($n = 17$)
Erosion/ulceration	2 (33%)	2 (33%)	2 (40%)	7 (41%)
Ischaemic appearance	0 (0%)	0 (0%)	0 (0%)	3 (18%)
Crypt/gland distortion	0 (0%)	0 (0%)	1 (20%)	**9 (53%)**
Crypt/gland dropout	1 (17%)	0 (0%)	1 (20%)	6 (35%)
Crypt/gland rupture with histiocytes/granulomas	0 (0%)	1 (17%)	1 (20%)	3 (18%)
Epithelial reactive change	**3 (50%)**	2 (33%)	0 (0%)	4 (24%)
Gastric metaplasia	NA	1 (17%)	0 (0%)	0 (0%)
Lamina propria expansion	**4 (67%)**	**5 (83%)**	**3 (60%)**	**13 (76%)**
Lamina propria neutrophils	2 (33%)	1 (17%)	2 (40%)	6 (35%)
Lamina propria edema	0 (0%)	0 (0%)	0 (0%)	4 (24%)
Increased eosinophils	1 (17%)	**5 (83%)**	2 (40%)	2 (12%)
Villous blunting	N/A	**4 (67%)**	**3 (60%)**	N/A
Increased apoptosis	1 (17%)	1 (17%)	**3 (60%)**	8 (47%)
Increased intraepithelial lymphocytes	0 (0%)	2 (33%)	0 (0%)	0 (0%)
Intraepithelial neutrophils	**4 (67%)**	**4 (67%)**	**3 (60%)**	**12 (71%)**
Neutrophilic crypt/gland abscesses	**3 (50%)**	1 (17%)	2 (40%)	8 (47%)
Eosinophilic crypt/gland abscesses	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Goblet cell decrease	NA	**3 (50%)**	0 (0%)	3 (18%)
Paneth cell decrease	NA	1 (17%)	0 (0%)	1/6 (17%)†

NA, Not applicable. Findings seen in at least half of specimens from a particular organ are shown in bold type.
*Specimens from patient taking PD-L1 inhibitor were excluded from table (see text for details).
**11 colon specimens were taken from regions that normally lack Paneth cells or that were not identified by colon subsite.



Gonzalez et al. Histopathology 2017

Apoptotic colopathy: a pragmatic approach to diagnosis

Dipti M Karamchandani,[1] Runjan Chetty[2]

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Table 1 Comparison between the common causes of apoptotic colopathy

Causes	Histological features	Clinical history	Other pearls
GI-GVHD*	1. Apoptosis with 'exploding crypt cells' 2. Apoptotic microabscesses and hypereosinophilic crypts 3. Neutrophilic cryptitis and crypt abscess 4. Neuroendocrine cell clusters 5. Occasional scattered eosinophils (typically <15/10 HPF*) 6. Frequent crypt distortion 7. Endothelial cell injury (lamina propria pericapillary haemorrhage)	H/O* HSCT* (typically after 21 days post-transplant)	1. Presence of skin and/or liver GVHD should increase the clinical suspicion. 2. Diagnosis before day 21 to be made with caution, as conditioning regimens can show similar histological features. 3. Dual pathology may exist and CMV* immunostain is recommended in HSCT with apoptosis.
Mycophenolate mofetil (MMF/ CellCept)-induced colitis	1. Apoptosis 2. Mixed lamina propria infiltrate typically with >15 eosinophils/10 HPF 3. Normal or mild crypt architectural distortion 4. Isolated crypt damage (degenerated crypts) 5. Typically, absent apoptotic microabscess and absent neuroendocrine cell clusters	H/O MMF drug use (solid organ transplant, HSCT, autoimmune / inflammatory diseases)	1. Apoptotic bodies in site other than colon favour GVHD over MMF injury. 2. Normal biopsies from sites away from focal lesions (such as focal ulcers seen in MMF colitis) should raise the question of MMF colitis rather than GVHD.
CPI* therapy	1. Apoptosis 2. Neutrophilic abscess/cryptitis 3. Atrophic crypts and apoptotic microabscess 4. Variable increase in intraepithelial lymphocytes	H/O advanced carcinoma with CPI therapy	Suspicion for CPI therapy-induced colitis should remain high for several months after therapy.
CMV	1. Apoptosis 2. Crypt atrophy and dropout 3. Variable inflammatory response (ranging from minimal/mild to severe with mucosal ulcers) 4. Viral inclusions (intranuclear and/or intracytoplasmic) seen in endothelial cells, but also in glandular epithelial cells or stromal cells	H/O immunosuppression, however can affect immunocompetent people also	It is worthwhile to perform CMV immunostain in apoptotic colopathy as CMV can present as a sole or dual pathology.
CVID	1. Apoptosis (not present in all cases) 2. Paucity of plasma cells 3. Intraepithelial lymphocytosis typically more pronounced in the deep mucosa 4. Presence of lymphoid aggregates 5. Variable foci of architectural distortion	1. Lack of history of transplantation or drugs 2. History of recurrent infections may be present	

Karamchandani & Chetty, J Clin Pathol 2018

Neutropenic Enterocolitis

New Insights Into a Deadly Entity

Taha Sachak, MD, Michael A. Arnold, MD, PhD,*† Bita V. Naini, MD,‡ Rondell P. Graham, MBBS,§ Sejal S. Shah, MD,§ Michael Cruise, MD, PhD,‖ Jason Y. Park, MD, PhD,¶# Lindsey Clark, MD,** Laura Lamps, MD,** Wendy L. Frankel, MD,* Nicole Theodoropoulos, MD,* and Christina A. Arnold, MD**

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Clinical Features

Chemotherapy within the last month (100%)

Gastrointestinal symptoms (100%)

Neutropenia (100%)

Positive imaging, most commonly thickened caecum or right colon (97%)

Positive microbial studies (87%)

Fever (60%)

Sepsis (50%)

TABLE 2. Gross and Microscopic Findings in Patients With Histologically Confirmed NE

Gross distribution pattern	
Focal	3/12
Patchy	7/12
Diffuse	1/12
Gross regional involvement	
Small bowel	2/17
Appendix	0/17
Cecum	16/17
Right colon	14/17
Transverse colon	5/17
Left colon	2/17
Rectum	0/17
Necrosis	18/20
Invasive microorganisms	17/20
Ulcer	15/19
Hemorrhage	15/20
Edema	15/20
Depletion of inflammatory cells	15/20
Abnormal terminal ileum	5/16
Pneumatosis	3/20
Perforation	3/20
Pseudomembranes	3/17
Stricture	2/12
Abscess	2/20

Sachak et al. Am J Surg Pathol 2015

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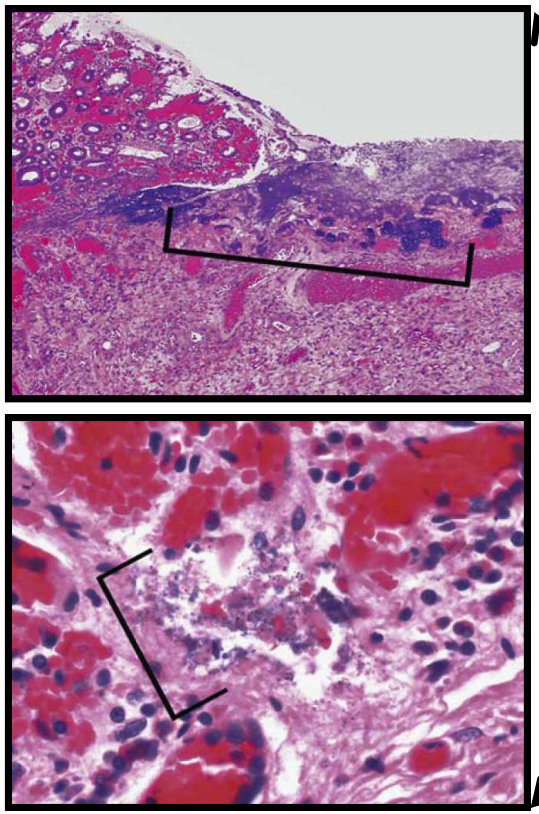

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Sachak et al. Am J Surg Pathol 2015

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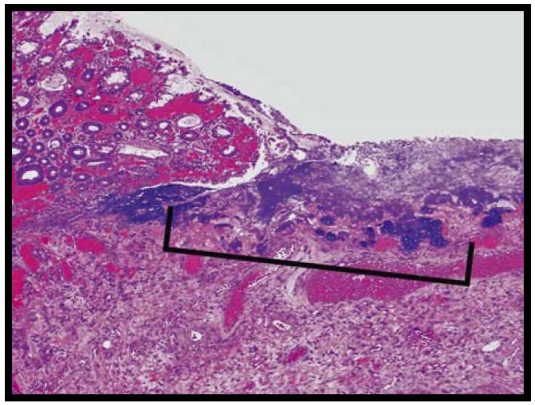


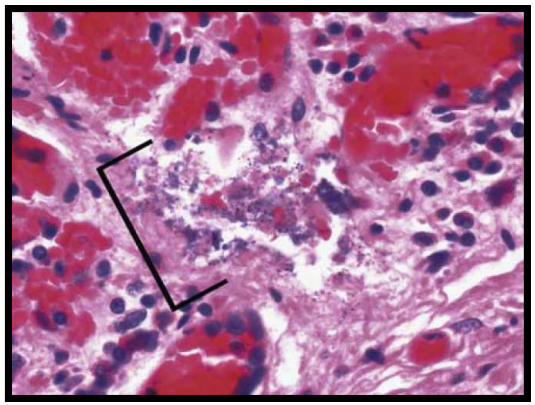


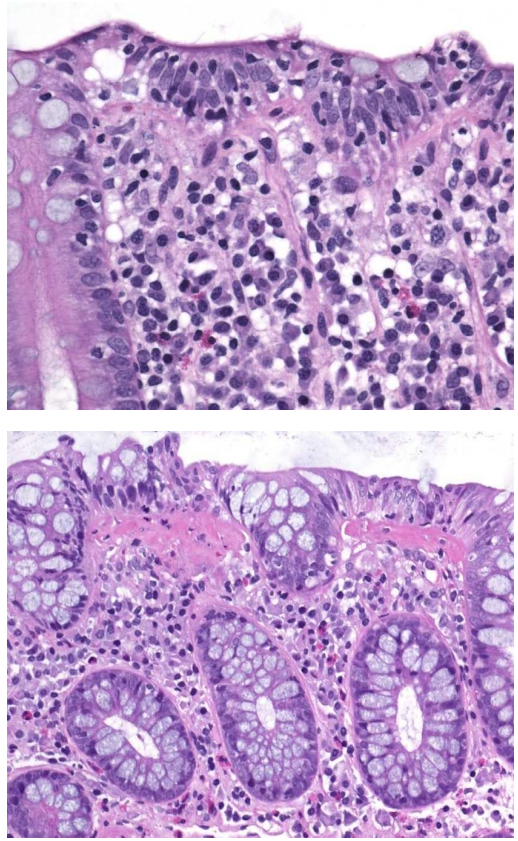
TABLE 4. Clinical Outcomes in Patients With Histologically Confirmed NE With Surgery Versus Supportive Care Only

	Surgery, n (%)	Supportive Care Only, n (%)
Dead	11/15 (73)	4/4 (100)
Dead of NE	4/11 (36)	3/4 (75)
Dead of other Disease	7/11 (64)	1/4 (25)
Median time to death of NE (d)	2.5	0
Median time to death of non-NE Death (d)	1095	245
Median follow-up if alive (d)	360	NA

Sachak et al. Am J Surg Pathol 2015

Microscopic colitis

- No or little crypt architectural distortion
- Diffuse (“transmucosal”) mononuclear inflammation in the lamina propria (lymphocytes and plasma cells)
- **Lymphocytic colitis:** increased surface intraepithelial lymphocytes (>20 per 100 epithelial cells)
- **Collagenous colitis:** thickening (>10 µm) of the subepithelial collagen band (most prominent in right colon, rectosigmoid may be normal)
- Surface epithelial injury (vacuolization, flattening, mucin depletion, detachment)



Langner et al. Histopathology 2015

Increased Risk of Microscopic Colitis With Use of Proton Pump Inhibitors and Non-Steroidal Anti-Inflammatory Drugs

Gwen M.C. Masclee, MD, MSc[1,2], Preciosa M. Coloma, MD, MSc, PhD[1], Ernst J. Kuipers, MD, PhD[2] and Miriam C.J.M. Sturkenboom, PharmD, PhD[1,3]

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Table 3B. Risk of microscopic colitis, cases compared with colonoscopy controls

	Within 1 year before the index date[a]				Within 2 years before the index date excluding the 1 year before index date[b]			
	OR-matched (95% CI)	*P*-value	OR-adj[c] (95% CI)	*P*-value	OR-matched (95% CI)	*P*-value	OR-adj[c] (95% CI)	*P*-value
Use of NSAIDs								
Never use (>12 mo)	1 (REF)		1 (REF)		1 (REF)		1 (REF)	
Past use (3–12 mo)	6.7 (2.1–20.7)	0.001	12.4 (1.7–93.1)	0.014	4.0 (1.4–11.2)	0.009	1.7 (0.3–9.2)	0.552
Current use (<3 mo)	3.4 (1.4–7.9)	0.005	0.8 (0.2–2.7)	0.718	12.0 (3.7–38.6)	<0.001	5.6 (1.2–27.0)	0.031
Use of PPIs								
Never use (>12 mo)	1 (REF)		1 (REF)		1 (REF)		1 (REF)	
Past use (3–12 mo)	19.7 (6.3–61.5)	<0.001	16.8 (4.2–66.7)	<0.001	4.3 (1.1–16.6)	0.036	0.6 (0.1–6.7)	0.645
Current use (<3 mo)	9.8 (4.7–20.3)	<0.001	4.4 (1.6–12.1)	0.005	41.1 (9.5–178.9)	<0.001	10.6 (1.8–64.2)	0.010

Masclee et al. Am J Gastroenterol 2015

High risk of drug-induced microscopic colitis with concomitant use of NSAIDs and proton pump inhibitors

B. P. M. Verhaegh[*,†], F. de Vries[‡,§], A. A. M. Masclee[*,†], A. Keshavarzian[‡,¶], A. de Boer[‡], P. C. Souverein[‡], M. J. Pierik[*] & D. M. A. E. Jonkers[*,†]

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Table 1 | Baseline characteristics of cases and controls

	Cases		Controls		Crude OR (95% CI)
	n = 1211	%	*n* = 6041	%	
Female	886	73.2	4423	73.2	1.00
Mean age at diagnosis (s.d.)	63.3	14.1	63.2	14.1	1.00
No drug use (6 months before index date)	429	35.4	3408	56.4	0.38 (0.33–0.44)**
Drug use (6 months before index date)					
NSAIDs	250	20.6	679	11.2	2.09 (1.78–2.46)**
PPIs	506	41.8	1054	17.5	3.79 (3.29–4.37)**
SSRIs	186	15.4	451	7.5	2.27 (1.88–2.72)**
Statins	327	27.0	1431	23.7	1.23 (1.06–1.43)*
H2RAs	56	4.6	119	2.0	2.40 (1.73–3.31)**
Presence of (before index date)					
Auto-immune related arthritis	37	3.1	135	2.2	1.37 (0.95–2.00)
Coeliac disease	37	3.1	15	0.2	9.00 (4.79–16.92)*
Irritable bowel syndrome	255	21.1	458	7.6	3.36 (2.83–3.99)**
Smoking status					
Never	400	33.0	2392	39.5	0.74 (0.64–0.84)**
Current	259	21.4	962	15.9	1.47 (1.26–1.73)**
Former	547	45.2	2541	42.1	1.15 (1.01–1.31)*
Unknown	5	0.4	146	2.4	0.16 (0.07–0.40)**

OR, odds ratio; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drug; PPIs, proton pump inhibitor; SSRIs, selective serotonin reuptake inhibitor; H2RAs, histamine-2 receptor antagonist.

*$P < 0.05$, **$P < 0.01$.

Verhaegh et al. Aliment Pharmacol Ther 2016

Take home messages

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- Drug induced injury may be seen in all parts of the gastrointestinal tract and may show a variety of morphological patterns
- Many of these are unspecific (e.g. necrosis, ulceration), while others are suspicious (e.g. increased epithelial apoptosis)
- Few are diagnostic (crystal deposition, selective internal radiation therapy (SIRT) using Yttrium-90 microspheres)
- Clinical information is often lacking, but clinicopathological interaction is crucial for accurate diagnosis
- Pathologists need to recognize patterns that are suggestive of drug induced injury, consider the respective drug, and should actively search for appropriate clinical information
- Clinicians should know about the pathologist's diagnostic dilemma and provide information on drug use in all patients with GI inflammation

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Thank you very much for your kind attention!

Cord Langner MD

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