Envoi SPECIALIST PATHOLOGISTS *inside insights*

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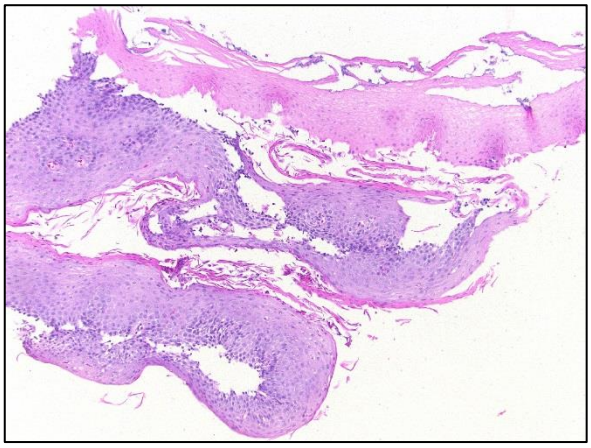
Drug induced injury of GIT

There are an increasing number of reaction patterns for drug-induced injury of the gastrointestinal tract, some with distinctive features allowing a specific drug (or drug class) to be suggested as likely causes. However, most patterns, whilst raising the possibility of drug-induced injury, have a number of other potential causative agents and require clinical correlation to allow a specific diagnosis.

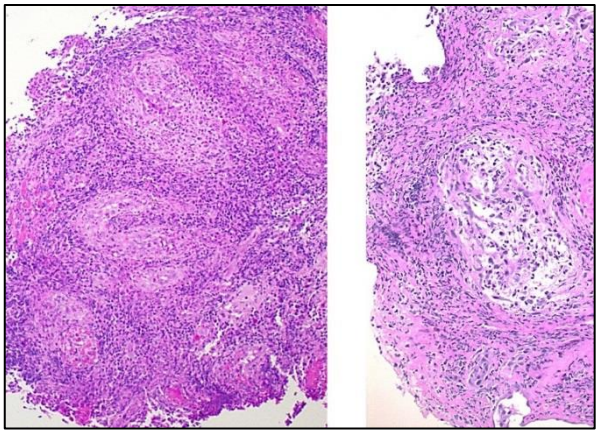
Oesophagus

Oesophagitis dissecans (alendronate)



- Clinical - causes include thermal, physical or chemical injury from agents such as hot beverages, caustic agents, alcohol and irritant foods, as well as medications such as the bisphosphonate alendronate (Fosamax).
- Endoscopy - white plaques in the oesophagus, sometimes with membranes.
- Histology - two-toned appearance of the squamous epithelium, with increased eosinophilia of the superficial part of the epithelial layer, sometimes with necrosis and a mid-epithelial clefting plane. Inflammation is generally sparse.

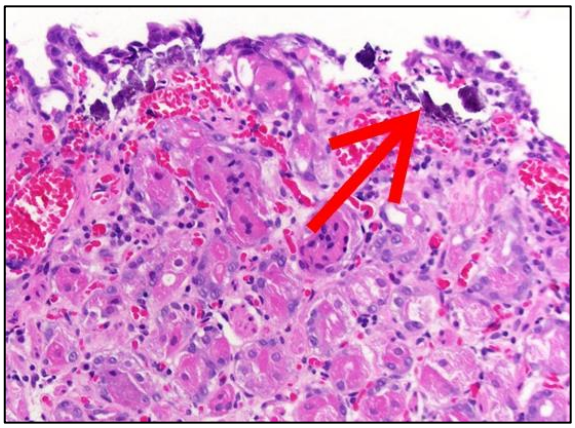
Doxycycline-induced oesophagitis/gastritis



- Endoscopy - ulceration of oesophagus and stomach.
- Histology - vascular inflammation, with a predominantly lymphocytic infiltration of larger vessels in the ulcer base. Vascular wall thickening, endothelial cell hyperplasia and a perivascular oedematous halo also seen.
- In the stomach, doxycycline causes a distinctive injury in small superficial capillaries

Stomach

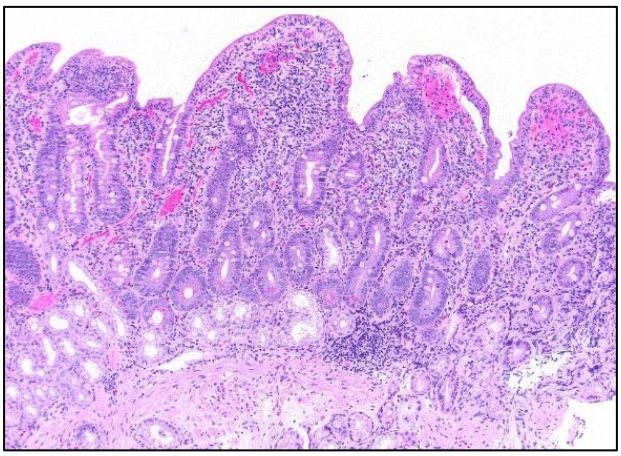
Osmoprep-associated gastropathy



- Endoscopy - erosions
- Histology - superficial acute mucosal erosion with minimal inflammation and deposition of large purplish granules reminiscent of calcium deposits. The staining profile of Perls' (-), von Kossa (+) and Alizarin red (-) is that of sodium phosphate and not iron or calcium.
- Ddx - gastric mucosal calcinosis, which occurs in the context of metastatic calcification (particularly in chronic renal failure and hypercalcaemia) or dystrophic calcification. Isotretinoin and sucralfate have also been implicated.

Small intestine

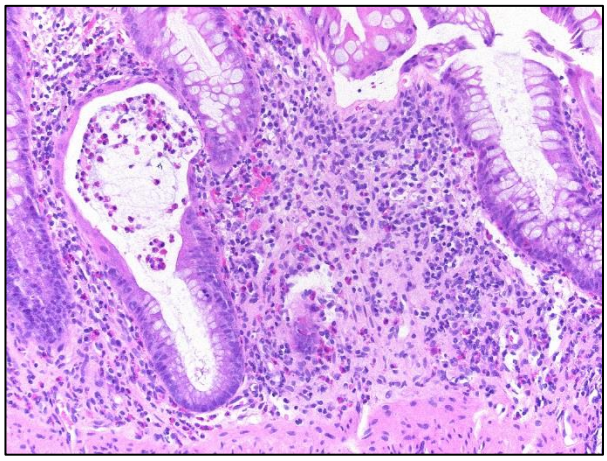
Sartan-induced enteropathy



- Clinical - Olmesartan has been recognised to cause a severe sprue-like injury with chronic diarrhea and significant weight loss that resolves with cessation of therapy. Case reports of other sartans causing a similar enteritis suggests a class effect (telmisartan, valsartan and irbesartan).
- Histology - resembles coeliac disease with severe villous atrophy and inflammation. Intraepithelial lymphocytes are significantly increased in only two thirds of cases. May also see eosinophils, eosinophilic cryptitis or collagenous enteritis. Collagenous gastritis, enteritis or colitis (including involvement at multiple sites) can be a clue.

Colon

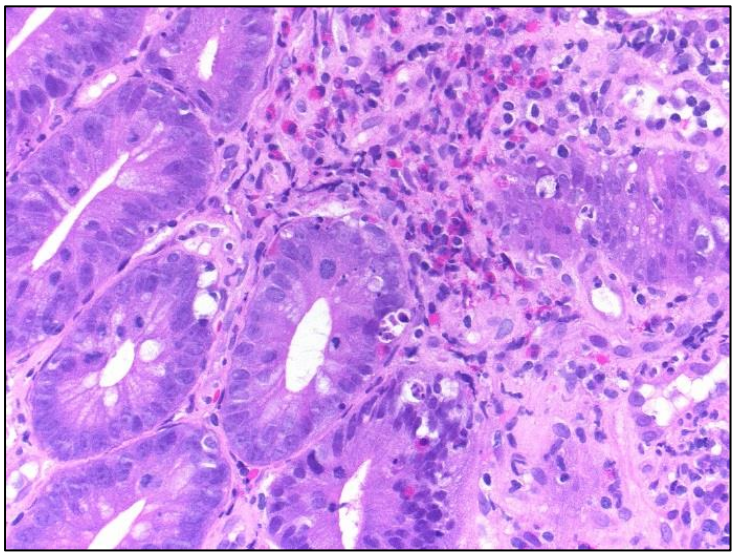
Mycophenolate colitis



- Clinical - Mycophenolate is a widely used immuno-suppressive that can produce both upper and lower gastrointestinal injury. As it is used in haematological stem cell transplantation, the distinction from its close mimic GVHD is important.

- Histology - several colonic injury patterns have been described including crypt apoptosis (GVHD-like), IBD-like, ischaemic colitis or focal active colitis. A mixed pattern of injury, usually incorporating apoptosis, crypt distortion and isolated crypt injury (individual crypts lined by attenuated eosinophilic epithelium) has been suggested as a diagnostic clue. In the small bowel, patchy villous atrophy can be seen.

Idelalisib-associated colitis and "immunomodulatory gastroenterocolitis"



- Clinical - Idelalisib is a small molecule inhibitor of PI3 kinase delta used in the treatment of B-cell haematological malignancies. Diarrhoea occurs in almost 50% of patients possibly because of immunomodulatory effects on regulatory lymphocytes and loss of tolerance to gut microbiota. Some patients develop enterocolitis and 10-20% have severe symptoms with a pancolitis, which may require cessation of therapy.

- Histology – typically there is a triad of intraepithelial lymphocytosis (sometimes mild), crypt apoptosis and neutrophilic cryptitis with crypt abscesses +/- eosinophils.

Similar changes have been described in the immune modulator ipilimumab, an anti-CTLA4 monoclonal antibody approved for immunotherapy for melanoma and potentially a number of other tumours. Other biological agents are

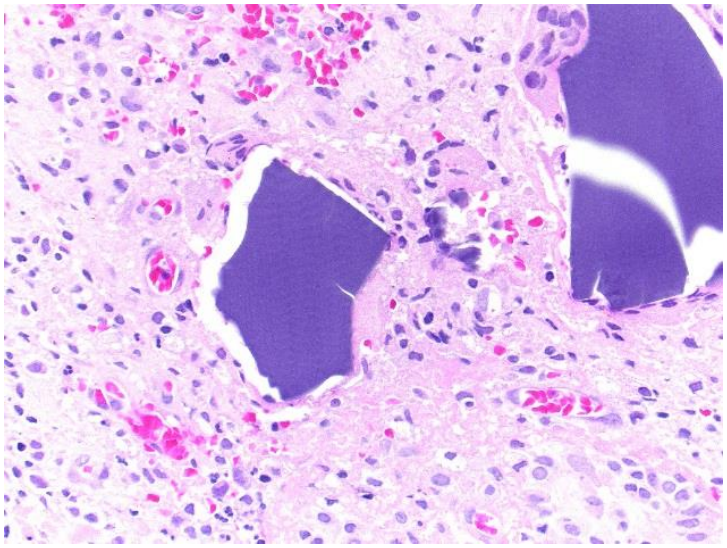
increasingly used in clinical practice for both inflammatory and neoplastic disorders and the GIT complications are being recognised. It has been suggested that the term "immunomodulatory gastroenterocolitis" may be appropriate for the disease pattern. Some of the agents are listed in Table 1.

Table 1. Biological agents causing GIT injury

Drug	Target	Action	GIT sites	Injury pattern(s)
Idelalisib	PI3 kinase δ	Lymphocyte apoptosis (& immunomodulation)	SI, Colon	IEL + apoptosis + cryptitis +/- eos
Ipilimumab **Tremelimumab**	Anti-CTLA4	Immune checkpoint inhibitor; Immunomodulatory	Stomach, SI, Colon	IEL + apoptosis + cryptitis +/- eos
Pembrolizumab **Nivolumab** **Atezolizumab**	Anti-PD-1 or Anti PD-L1	Immune checkpoint inhibitor; Immunomodulatory	Stomach, SI, Colon	Apoptosis + neuts + cryptitis +/- Eos +/- IEL
Etanercept **Infliximab** **Adalimumab**	Anti-TNF-α	Anti-inflammatory	SI, Colon	New onset or exacerbation of IBD; Crohn's; apoptotic enteropathy
Rituximab	Anti-CD20	Anti-B lymphocyte	Colon	Diffuse colitis - new onset of IBD
Bevacizumab	Anti-VEGF	Vascular inhibitor	Colon, Anastomoses	Ischaemia; Perforation
Sorafenib **Sunitinib**	VEGF tyrosine kinase inhibitor	Vascular inhibitor	Colon	Pneumatosis coli

Resin-induced colonic ulceration

- Clinical - non-absorbable resins such as potassium sequestrant sodium polystyrene sulphonate (Kayexalate) and the phosphate sequestrant sevelamer (Renagel) can cause colonic ulceration and even perforation requiring emergency colectomy. Sevelamer has been shown to cause GI ulceration and chronic crypt changes but necrosis appears to be rare. Bile acid sequestrants such as cholestyramine (Questran) and cholesevelam (Welchol) may be seen in biopsies in association with mild mucosal changes, but they are believed to be innocent bystanders and do not have any established role in causing significant mucosal injury.



- Histology - the various resins have differing morphological and staining features and are seen with mucosal ulceration.

Table 2. Non-absorbable resins seen in GI biopsies.

Resin	Binds	Colour – H&E	Colour – ZN	Internal structure
Kayexalate	Potassium	Purple	Black	Fish scales
Sevelamer	Phosphate	Yellow and pink	Magenta	Fish scales (curved)
Cholestyramine **Cholesevelam**	Bile acids	Orange-pink	Yellow	Homogenous