Biopsy Artifacts and Iatrogenic Injury To The Gastrointestinal Tract

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The plan
We’ll start in the upper tract and work our way down with a bit of rapid transit time or regurgitation here and there
No disclosures

Medications/Drugs: Mucosal Injury – Upper Tract
- Iron
- Fosamax (alendronate sodium for osteoporosis)
- Potassium chloride
- Aspirin/NSAIDs
- Kayexalate
- Renvela (renagel)

(Not this kind of medication-associated injury – remember to remove wrapper)

Esophagitis: Drugs

FeSO4 tablet
Iron Medication Injury

In our patient population, mucosal iron (ferrous sulfate) is found in about 1% of patients undergoing upper tract endoscopic biopsies.

Iron can cause corrosive injury in the esophagus or can potentiate injury in a pre-existing ulcer or erosion.

Medications/Drugs:

- Kayexalate
  - Ischemic injury
  - Seen in Esophagus, stomach, colon

Gastric kayexalate bezoar with phlegmonous gastritis

Kayexalate-associated ischemic colitis

Cholestyramine (Questran, Questran Light, Cholybar) – Bile acid sequestrant

Cholestyramine v Kayexalate
Occasionally large bile sequestrant crystals can be cracked

**WELCHOL**
(colestevam hydrochloride) – this one tends to crack but it is red like cholestyramine

**Recently recognized medication - Renvela®**
Generic name is **Sevelamer**
Used to lower high blood phosphorus (phosphate) levels in patients who are on dialysis due to severe kidney disease
Manufacturer has reported GI side effects but they are not well studied
Same patient population as those with kayexalate-associated injury

**Renvela, cont**
In our experience was seen associated with mucosa injury throughout the GI tract, but experience is limited

Crystals were associated with mucosal injury in 14/15 cases (but this may be coincidence)

Renvela® - Sevelamer looks like kayexalate but "two-toned" and not purple and the scales are more curved than rectangular
Renvela v Kayexalate

A new one (or an old one newly recognized)

Lanthanum carbonate – trade name Fosrenol
Prescription medication used in people with end stage renal disease (ESRD) to reduce phosphatemia.
Prevents absorption of phosphate
Chewable tablet form.
Common side effects of lanthanum carbonate - nausea, vomiting, and diarrhea.


Esophagitis: Drugs
Pathology:
Rarely see the actual drug
• Except iron and kayexalate
Erosions or ulcers
Bisphosphonates (consumer reports says stick to alendronate)

Polarizable pill "filler" lodged in damaged squamous epithelium with striking reactive changes

Squamous mucosa and strips of detached surface epithelial cells

Detached layer of necrotic superficial epithelium

No fungus
The intact squamous mucosa has a sharply delineated superficial layer of squamous cells with eosinophilic cytoplasm and pyknotic nuclei (mummified layer).

**Esophagitis dissecans (not “dessicans”)**

Also called “sloughing esophagitis”
Associated with infirmity, polypharmacy, alcohol abuse, but poorly understood
?hot beverages or other external injury in compromised host (alcoholic, elderly)
Generally self-limiting

**Medications that result in odd mitotic arrest patterns.**

**Colchicine Toxicity**

Usually in patients with renal or hepatic disease who cannot clear the medication [it has a long half life]
Findings best seen in duodenum
Only see mitotic arrest in normal mucosa in toxic patients but it is seen in neoplasms in patients with therapeutic drug levels
Regardless of site, the mitotic arrest pattern is seen in the proliferative compartment of the sample (esophagus, basal layer; stomach, between base of pits and surface; colon, base of crypts; gallbladder, between base and surface)
**Colchicine Toxicity**

Alkaloid with antimitotic ability used to treat a variety of medical conditions (classically gout but a host of autoimmune disorders). Toxicity can result in multiorgan failure and death.

Patient with metastatic cancer; esophagus biopsy searching for primary source.
Taxol effect in gallbladder mimicking dysplasia.
Taxane effect in gallbladder mimicking dysplasia

Has essentially the same histologic features as colchicine toxicity (ring mitoses and apoptosis in proliferative compartment)

Seen in the first 2-3 days after administration of the agent or in toxicity

You have to call the clinical colleague and correlate

The two main ones are taxol (paclitaxel) and taxotere (docetaxel)


Moving down the digestive tract

Damaged duodenum
Diagnosis - ISCHEMIC ENTERITIS/RADIATION ENTERITIS ASSOCIATED WITH YTTRIUM MICROSPHERES/ SIRS (SELECTIVE INTERNAL RADIATION SPHERES)

Yttrium spheres

Y⁹⁰, a pure β emitter, is produced by neutron bombardment of yttrium-89 in a reactor. Y⁹⁰ has a physical half-life of 64.2 hours (2.67 days) and decays to stable zirconium 90. The average/maximal penetration range of 2.5 mm and 11 mm, respectively, in tissue.

In therapeutic use, in which the isotope decays to infinity, 94% of the radiation is delivered in 11 days.

Y⁹⁰ is the active moiety in a number of targeted radioimmunotherapies used in the treatment of a variety of solid organ and hematological malignancies.

Injected through the hepatic artery but sometimes there is a little stray injection.
Iatrogenic Findings in Small Bowel Biopsies

- Yttrium-associated injury
- Olmesartan-associated injury
- Graft versus host disease
- Mycophenolate-associated injury
- T-lymphocyte antigen-4 (CTLA-4)/Ipilimumab-Associated Injury (Yervoy)
- Kayexalate-associated injury (rare)
- Colchicine-associated injury
- NSAID-associated injury

Olmesartan

One of several angiotensin II receptor antagonists used for management of hypertension since 2002
Trade name is Benicar in the US (other names in Europe, Australia, etc)
Patients present with chronic diarrhea and enteropathy on biopsy; resolves after stopping the drug

Graft versus host disease (GVHD)

Secretory diarrhea, abdominal pain, and, at times, hemorrhage in patients with bone marrow transplants or related interventions. Syndrome of upper GI GVHD, presents clinically as anorexia, dyspepsia, food intolerance, nausea, and vomiting. Original grading criteria were published by Snover grade 1 = increased crypt apoptosis; grade 2 = apoptosis with crypt abscess; grade 3 = individual crypt necrosis grade 4 = total denudation of areas of mucosa. chronic graft versus host disease results in non-specific features of lamina propria fibrosis and mucosal atrophy.

Mycophenolic Acid (MPA)

Fermentation Product of Penicillium brevicompactum fungi, isolated 1898

2 Preparations: mycophenolate mofetil (CellCept), mycophenolate sodium (Myfortic)

Both have same efficacy in preventing rejection in solid organ transplants

Mycophenolate-Associated Injury

Mycophenolate inhibits purine (guanosine) synthesis for DNA synthesis in the de novo pathway

B&T lymphocytes depend almost completely on this pathway so the medication inhibits cytotoxic T lymphocytes

Enterocytes are less dependent on this pathway but still damaged

Side Effects of MPA and Documented GI Injuries

Side Effects: GI (Diarrhea, N/V, gastritis, and ulcer) Hematologic (anemia and opportunistic infections)

Documented GI Injuries by MPA

1. Papadimitriou (2001 & 2005): Colonic injury pattern similar to GVHD with increased apoptosis in the crypts, crypt distortion, reparative changes, increased neuroendocrine cells.
Duodenum – Mycophenolate-associated injury

Mycophenolate effect; duodenum – apoptotic injury

Chronic mycophenolate-associated colitis

What if the patient is taking mycophenolate and has also had a bone marrow transplant?

Clues: more eosinophils and less striking apoptosis associated with mycophenolate*

Mycophenolate less likely to damage squamous mucosa (skin and esophagus) since these sites are less dependent on the de novo pathway, so squamous involvement a clue to graft versus host disease

T-lymphocyte antigen -4 (CTLA-4)/Ipilimumab-Associated Injury

Or any of the monoclonal antibody preparations
TRADE NAME - YERVOY

Ipilimumab-Associated Injury

Monoclonal antibodies against cytotoxic T lymphocytes are given in tumor immunization protocols
Given to patients on protocols for melanomas and some carcinomas

Ipilimumab-Associated Injury

Produces a somewhat nonspecific pattern of injury – lymphoplasmacytic expansion of lamina propria, intraepithelial lymphocytosis and apoptosis.
Small bowel has villous blunting (looks like celiac disease)
Colon biopsies may have cryptitis

So – now there is something completely different that has every oncologist drooling and thrilled
PD1/PDL1 blockade!!!!!!
Programmed Death 1 (PD-1) Pathway

Negative feedback pathway repressing Th1 cytotoxic immune responses
It is intended to protect from autoimmune immune responses

PD1 Blockade

Because of the issues of harnessing the immune system, we would expect that tumors with a dense inflammatory cell component (often this is the case for melanoma) would have a great response to pembrolizumab et al

AND they do!!!!!
...and Guess What

Since anti-PD1 drugs essentially make us autoimmune, there are GI biopsy findings:

Guess what – looks like graft versus host disease in the intestines!!!!!

2 reports of injury associated with idelalisib (given for chronic lymphocytic leukemia/B cell lesions Zydelig, - phosphoinositide 3-kinase inhibitor)

There will be more and more of these
<table>
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<tr>
<th>Medications discussed at USCAP 2016 in Abstract Form</th>
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<tbody>
<tr>
<td>621. Doxycycline</td>
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<td>668. Brincidofovir (an antiviral)</td>
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<td>699. Yttrium</td>
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<td>735. Lanthanum and hemodialysis-associated amyloid</td>
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Decoding the Names
Interleukin – human (“kinu”) – 
Briakinumab
Canakinumab
Fezakinumab
Fletikumab
Guselkumab
Secukinumab
Sirukumab
Tralokinumab
Ustekinumab

Decoding the Names
Interleukin – humanized (“kizu” or “kinzu”) – 
Anrukinzumab
Clazakizumab
Enokizumab
Gevokizumab
Ixekizumab
Lebrikizumab
Olokizumab
Perakizumab
Tildrakizumab

Decoding the Names
Inflammatory “lesions” (“les”) Mouse (“leso”) – 
Besilesomab
Fanolesomab
Lemalesomab
Sulesomab

Working into the colon

If you see muscularis propria on a mucosal biopsy, let someone know!

Normal right colon
More cellular, fewer goblet cells, few Paneth cells possible

Normal left colon
Less cellular, more goblet cells, no Paneth cells
More Kappa than Lambda is normal in the Colon

Kappa  Lambda

Macrophages are normally present in the superficial lamina propria.

Intraepithelial lymphocytosis is normal over lymphoid aggregates.
Intraepithelial lymphocytosis is normal over lymphoid aggregates.

What stuff in biopsies that is not strictly normal can we ignore?

- **Artifacts**
  - Artifacts due to hypertonic enemas
    - Flattened surface epithelium, focal surface tufting with PMNs, edema in the lamina propria, clumpy superficial hemorrhage regenerating crypts
  - Artifacts due to oral phosphosoda bowel preparation
    - Aphthoid lesions
    - Focal neutrophilic cryptitis (focal active colitis)
    - Apoptotic bodies in crypt bases

- **Trivial abnormalities**

Endoscopic aphthoid lesions due to phosphosoda are lymphoid aggregates on biopsy.

Focal neutrophilic cryptitis due to oral phosphosoda bowel preparation.
Basal crypt apoptosis due to oral phosphosoda bowel preparation

Air insufflation artifact:
Due to insufflation of gas into the bowel lumen during endoscopy—tracks into mucosa/submucosa, particularly in areas of lymphoid aggregates.

Ileum, note black material
Titanium from toothpaste
Titanium from toothpaste
What happened to the crypt epithelium?

Is this ischemic bowel?

Ischemic colon
Colon Biopsies

Be proud to diagnose normal
Be ready to think outside the box
Have fun!

Colonic mucosa with Paneth cells versus endocrine cells. Note the cytoplasmic granules oriented luminally as opposed to those of enterochromafin cells (Kulchitsky cells), which are oriented basally.

Signet cell change in a hemorrhoidectomy specimen. Sloughed epithelium in damaged mucosa may acquire a signet ring appearance. Note the cells are contained within the basement membrane.

Signet cell change. In doubtful cases, an e-cadherin stain can be performed and will demonstrate intact membranous labeling, in contrast to many true signet cell carcinomas, which lose their labeling.

Remember that “signet cell change” is very different from the in situ signet ring cell cancers in patients with CDH1 (the gene encoding for e-cadherin) germine mutations.
**NSAIDs-induced intestinal injuries**

**Most common:**
Ulcers anywhere in colon, but more common in right colon—sharply circumscribed with ischemic-type histology

Diaphragm disease—circumferential narrowing caused by concentric submucosal fibrosis, most likely a result of ulceration the top of mucosal folds (classically in small bowel).
Diaphragm disease – nasty half digested pills

Diaphragm disease

NSAIDs-induced colonic injuries

Other:
Collagenous colitis (and associated with ulcers in CC)
Pseudomembranous colitis
Eosinophilic colitis
Reactivation of IBD
Increased risk of perforation of colonic diseases--diverticulosis

Summary

Several drugs are associated with characteristic patterns of injury
Unfortunately the GI tract has a limited set of responses to various injuries so clinical correlation is always important
Some diseases have overlapping features with iatrogenic injuries
When in doubt, we always blame NSAIDs
A fooler

Courtesy of Dr. Dora Lam-Himlin, Mayo clinic Scottsdale

Case

Adult patient with mild diarrhea, intact immune system, underwent upper endoscopy and biopsies
Case, cont
Reported as mycetoma
Nocturnal brain flash followed by emergency trip to grocery store
The plot thickens…….
It's Baby Bella

Not mycetoma