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)
Esophagitis:

Drugs

FeSO4 tablet
Iron pill gastritis with severe reactive epithelial changes
Iron pill gastritis with severe reactive epithelial changes, reticulin stain.
Iron pit gastritis - the iron becomes oxidized to purple, brown, and black over time!

The flip side - gastric siderosis - undamaged surface subtle brown in deep glands

Gastric siderosis
Gastric siderosis, associated with hemochromatosis or iron overload from multiple transfusions, “bottom heavy” iron stain

Medications/Drugs:

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

Gastric kayexalate bezoar with phlegmonous gastritis.

Gastric kayexalate bezoar with phlegmonous gastritis.

Gastric kayexalate bezoar with phlegmonous gastritis.

Gastric kayexalate bezoar with phlegmonous gastritis.
Kayexalate-associated ischemic colitis

Kayexalate crystal
cholestyramine (Questran, Questran Light, Cholybar) – bile acid sequestrant

Occasionally large bile sequestrant crystals can be cracked

Cholestyramine v Kayexalate
More 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 remains 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 newer 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.

References:
Lanthanum carbonate - trade name Fosrenol - in stomach

Esophagitis: Drugs
Pathology:
Rarely see the actual drug
  • Except iron and kayexalate
Erosions or ulcers
Esophagitis: Drugs - Fosamax (alendronate sodium) for osteoporosis – other bisphosphonates have similar side effects.

Bisphosphonates (consumer reports says stick to alendronate)

Pill and candida
Polarizable pill “filler” lodged in damaged squamous epithelium with striking reactive changes.

Esophagitis dissecans/sloughing esophagitis.

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

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Doxycycline – associated injury

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Doxycycline – associated injury
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 - Duodenum

- Expanded proliferative compartment.
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
Taxol effect, appendix

Taxane effect in gallbladder mimicking dysplasia
Taxane Effect

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

Yttrium-associated gastric injury

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.*
Yttrium-associated Gastric injury
Drug eluting microspheres resulting in an infarcted gallbladder.

Drug eluting microspheres.
Iatrogenic Findings in Small Bowel Biopsies

Yttrium-associated injury
Olmestaran (other “sartans”) -associated injury
Graft versus host disease
Mycophenolate-associated injury
T-lymphocyte antigen -4 (CTLA-4)/Ipilimumab-Associated Injury (Yervoy)
PD1 Blockade-associated injury
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
Olmesartan-associated enteropathy

Olmesartan-associated gastropathy – gastric body - parietal cells have disappeared

Olmesartan-associated gastropathy – gastric body - apoptosis, marked reparative changes, prominent eosinophilia
Olmesartan gastropathy – negative gastrin stain supports gastric body location.

Olmesartan gastropathy – chromogranin stain shown no enterochromaffin-like (ECL) cell hyperplasia.

**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.

**Normal duodenal mucosa**

**Duodenum – Mycophenolate-associated injury**
Mycophenolate effect; duodenum - apoptotic injury

Chronic mycophenolate-associated injury - colon - crypt loss but not much chronic inflammation
Chronic mycophenolate-associated injury, prominent eosinophils

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
One 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 pembrolizuman et al

AND they do!!!!!
Two mechanisms for PD-L1 up-regulation in tumors

**Innate Resistance**
- Constitutive tumor signaling induces PD-L1 on tumor cells

**Adaptive Resistance**
- PD-L1 expression reflects immune reaction

Blockade of PD-1 or PD-L1 "releases the brakes" on the immune system

Nivolumab in previously untreated melanoma without BRAF mutation

….and Guess What
Since anti-PD1 drugs essentially make us autoimmune, there are GI biopsy findings
There will be more and more of these

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

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


Medications discussed at USCAP 2016 in Abstract Form

621. Doxycycline
622. Ipilimumab
668. Brincidofovir (an antiviral)
683. Lanthanum
699. Yttrium
703. Ipilimumab
735. Lanthanum and hemodialysis-associated amyloid
807. Ipilimumab

Everyone was bored of this by 2017

683. Crospovidone (pill filler)
701. Anti TNF drugs
781. Olmesartan
803. Crospovidone
<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Code</th>
<th>Examples</th>
</tr>
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<tbody>
<tr>
<td>Human antibodies</td>
<td>-limu-</td>
<td>Ada-limu-mab, Ipi-limu-mab</td>
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<tr>
<td>Murine antibodies</td>
<td>-limo-</td>
<td>Afe-limo-mab</td>
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<td>Chimeric antibodies</td>
<td>-lixi-</td>
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<tr>
<td>Humanized</td>
<td>-lizu-</td>
<td>Pembro-lizu-mab</td>
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<tr>
<td>Chimeric and humanized</td>
<td>-lixiu-</td>
<td>Ote-lixiu-mab</td>
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<tr>
<td>Interleukin</td>
<td>-kinu-</td>
<td>Cana-kinu-mab</td>
</tr>
<tr>
<td>Inflammatory lesion</td>
<td>-leso-</td>
<td>Su-leso-mab</td>
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OMG – person taking both ipilimumab and nivolumab

- be sure to exclude cytomegalovirus and sally forth
Person taking both ipilimumab and nivolumab, crypt apoptosis

Bone marrow transplant patient – rule out graft versus host disease

Residual endocrine nests

What is this???
Cytomegalovirus immunolabeling

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

Normal lymphoid aggregate
Macrophages are normally present in the superficial lamina propria. They aggregate in the superficial lamina propria where they form a rind just under the epithelium, where they phagocytose cellular debris from normal apoptosis of surface epithelial cells.

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

Artifacts due to oral phosphosoda bowel preparation

Aphthoid lesions
Focal neutrophilic cryptitis (focal active colitis)
Apoptotic bodies in crypt bases

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

Glutaraldehyde-associated chemical colopathy with iatrogenic perforation - Image courtesy of Dr. Noam Harpaz
Air insufflation artifact:
Due to insufflation of gas into the bowel lumen during endoscopy—tracks into mucosa/submucosa, particularly in area of lymphoid aggregates.

Ileum, note black material
Titanium from toothpaste
What happened to the crypt epithelium?
Is this ischemic bowel?
Ischemic colon

Colonic mucosa with Paneth cells versus endocrine cells. Note the cytoplasmic granules oriented luminally as opposed to those of enterochromaffin cells (Kulchitsky cells), which are oriented basally.
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).
NSAIDs-induced ulcer at top of small bowel mucosal fold

NSAIDs-induced diaphragm disease—circumferential narrowing caused by concentric submucosal fibrosis, most likely a result of ulceration the top of mucosal folds.
Diaphragm disease – nasty half digested pills

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.