Drug-induced Gastrointestinal Disease

‘Belfast Pathology 2017’
Wednesday, June 21st, 2017

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Iatrogenic gut injury is common:
- 5% of patients receiving drugs experience an adverse reaction
  - GI side-effects: diarrhoea, constipation, nausea & vomiting
  - Entire gut can be affected
  - Various patterns of injury (rarely specific)
    - Erosions / ulceration / necrosis / fibrosis & stenosis
    - Hyperplastic / reactive changes
    - Inflammatory infiltrate (lymphocytes/eosinophils)
    - Apoptosis / mitotic arrest / abnormal mitoses
    - Crystal deposition

Pattern of injury & mimics

1. Villous atrophy
2. Apoptotic / erosive
3. Abnormal mitoses
4. Ulcerative
5. Crystals

1. Villous atrophy: Mimics of Enteropathies (e.g. coeliac disease)

- Various drugs can elicit intraepithelial lymphocytosis with or without causing epithelial damage:
  - Olmesartan, angiotensin II receptor antagonist (Benicar®)
  - CTLA-4 monoclonal antibody (ipilimumab®) (melanoma, RCC, ovarian Ca)
69 year old female — Subtotal villous atrophy, ? Coeliac Disease

No improvement on GFD
Repeat biopsy: subtotal villous atrophy, ? Refractory Coeliac Disease Type 1

No improvement on GFD
Repeat biopsy, June 2012: subtotal villous atrophy, ? Refractory Coeliac Disease Type 1

IHC (CD8/CD3 ratio): normal pattern

Noted to be on Olmesartan medication

CD 8

CD 3

Off Olmesartan x 2/12: mild partial villous atrophy

Conclusion: Severe sprue-like enteropathy associated with Olmesartan

Olmesartan Medoxomil
22 patients with chronic diarrhoea (> 4 weeks) while taking olmesartan
- Cause of enteropathy not established after diagnostic evaluation - very ill patients
- Importantly - Clinical improvement after discontinuation

F/U duodenal biopsies:
- In 18 pts
- After a mean of 242 days (from date of stopping drug)
- Histological recovery in 17 pts
- Focal partial VA in 1 pt
- Clinical response observed in all patients

Angiotensin II receptor blockers (ARBs)
- 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)

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**Take home message**

Olmesartan (& other ARBs) causes symptoms & signs of coeliac disease

- In 2012, over 10 million prescriptions for 2 million patients (USA)

- In this era of poly-pharmacy, be vigilant of drug adverse effects

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**Clinical Details:**

Diarrhoea, weight loss, nausea and vomiting

**Macroscopy:** One pot labelled with patient details and 'D2, duodenum'.

Four pieces, 3 – 7mm. A/E. 3/1.

**Microscopy:**

Comment on orientation

Villous/crypt ratio – Normal (type 1) / Partial (type 2) / Total (type 3)

IELs – Normal / Increased (>25)

Presence of neutrophils, eosinophils, subepithelial collagen (> 10-20 micron)

**Comment:**

Correlation with clinical history, serology & medication history advised

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**2. Apoptotic & Erosive Pattern of Injury**

- Immunosuppressive or anti-neoplastic agents (predominantly):
  - Mycophenolate (cellcept®)
  - Anti-metabolites (methotrexate; capecitabine)
  - TNF-α antagonists (infliximab)

- IMMUNE CHECKPOINT INHIBITORS
  - CTLA-4 monoclonal antibody (ipilimumab®)
  - Anti-PD1 antibodies (pembrolizumab, nivolumab)

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**Mycophenolic Acid (MPA)**

- Mycophenolate mofetil (CellCept®)
- Mycophenolate sodium (Myfortic®)

- Immunosuppressive agents (transplant patients)

- Gastrointestinal injuries in ~45% of pts:
  - GVHD-like alterations throughout the GIT
  - Active oesophagitis with ulceration.
  - Chemical gastropathy; focal active gastritis
  - Crohn’s-like & coeliac-like damage in the duodenum
  - Cryptitis, crypt withering & distortion, & increased neuroendocrine cells in colon

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Iatrogenic injury vs. GVHD in BMT pts?

- Eosinophils more commonly associated with Mycophenolate
- Oesophageal mucosa involvement suggests GVHD

Mycophenolate-associated injury
- Active colitis with apoptosis
- Apoptotic microabscesses with eosinophils

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

Colon - apoptotic colitis

CTLA-4 monoclonal antibody (ipilimumab)
- A monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4
- Offers durable therapeutic responses in patients with metastatic malignant melanoma and renal cell carcinoma
- How does it work?
  - CTLA-4 is expressed on T cells & following antigenic stimulation, it inhibits T-cell signalling
  - mAb against CTLA-4 results in increased expansion of tumour-specific T cells & enhances tumour destruction

- Numerous immune-mediated toxicities, including enterocolitis, dermatitis, hypophysitis, uveitis, hepatitis & nephritis
- Major toxicity has been reported to be most frequently seen in the GIT (in 30% of patients receiving ipilimumab)
- 5% mortality rate in patients who develop fulminant colitis with colonic perforation

Colon - apoptotic colitis

APPROVED IMMUNE CHECKPOINT INHIBITORS

- Nivolumab (anti-PD1)
  - MSI-CRC, Metastatic lung carcinoma
- Pembrolizumab (anti-PD1)
  - MSI-CRC and all MSI cancers (FDA)
- Avelumab (anti-PD-L1)
  - Metastatic lung carcinoma
- Atezolizumab (anti-PDL1)
  - Metastatic melanoma & RCC
- Ipilimumb (anti-CTLA-4)
  - Metastatic melanoma & RCC

PRACTICE POINTS

- Median time to onset of GI side effect = 8 weeks
- Extent of colitis may predict response - therefore clinicians keen to manage colitis & not stop drug
- GI toxicity can be observed after cessation of treatment
- Can exacerbate known or unknown IBD or other autoimmune diseases
- Anti-PD1 & Anti-CTLA-4 may be combined & or given sequentially.
A 61 year old female

A Stage IV lung adenocarcinoma, PDL-1 positive.

A Bloody diarrhoea.

A Proctitis to 15cm

A Rectal biopsy
Tx: steroids +/- Infliximab
Anxious to stay on drug trial

Paper 1

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

Jonathan M. Chen, MD, PhD, Maryanne E. Pollock, MD, MS, Gregory V. Landis, MD, FACP, and Ricardo Masi, MD, FACP

Table 1: Clinical Features of Anti-PD-1 Colitis

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Anti-PD-1</th>
<th>Anti-PD-L1</th>
<th>Anti-T1</th>
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<tbody>
<tr>
<td>Patients with renal or hepatic insufficiency and cannot clear the drug [long ½ life] present with</td>
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<td>- cholera-like syndrome</td>
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<td>- bone marrow suppression</td>
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<td></td>
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<tr>
<td>- acute renal failure</td>
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</tbody>
</table>

3. Abnormal Mitosis & Mimics of Dysplasia

A Mitotic arrest & atypical mitotic figures

A Eosinophilic transformation +/- withering of glandular structures

A Nuclear pseudostratification

A Clue: Monster nuclei intermixed with normal nuclei

Colchicine Toxicity

Alkaloid that binds to tubulin with antimitotic ability (used in severe gout)

A Patients with renal or hepatic insufficiency and cannot clear the drug [long ½ life] present with |
| - ring mitoses |
| - Occurs 2-3 days after initiation or in toxicity |

Taxane Effect

[Taxol (paclitaxel); taxotere (docetaxel)]

A Histology similar to colchicine toxicity:

- ring mitoses
- Occurs 2-3 days after initiation or in toxicity

A diagnostic pitfall.

Various types of Colitis:

- Eosinophilic colitis
- Pseudomembranous colitis
- Ulcers (right colon)
  - NSAIDs & other drugs can present with an ulcerative & chronic patterns of mucosal injury
  - NSAIDs block COX 1 & 2 (cyclo-oxygenases)
  - Incidence of adverse effects reported in 70% with long-term Rx
  - Major pathology: ulceration & hemorrhage, more likely with high doses

NSAIDs & colonic damage - ‘A long story’

- Increasing due to use of enteric-coated or sustained (slow) release formulations (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)

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

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

NSAIDs-induced diaphragm disease—exsudative narrowing caused by concentric submucosal fibrosis, likely a result of ulceration of the top of muscular folds

Diaphragm Disease

Courtesy of S. Brown

4. Ulcerative & Chronic Ileitis / Microscopic Colitis

Pattern of Injury

- NSAIDs & other drugs can present with an ulcerative & chronic patterns of mucosal injury
- NSAIDs block COX 1 & 2 (cyclo-oxygenases)

Introduction

Case Summary

Conclusion

POSTER ISSP 2014
Right sided NSAIDs IBD-like

Differential diagnoses
- Solitary caecal ulceration
- Uleration secondary to a diverticulum
- Local ischaemia
- Steroid ulceration
- Solitary rectal ulcer syndrome

A sharply circumscribed on endoscopy with ischaemic-type histology

Differential diagnoses
- Solitary caecal ulceration
- Uleration secondary to a diverticulum
- Local ischaemia
- Steroid ulceration
- Solitary rectal ulcer syndrome

Recent study
- St. Vincent’s University Hospital, Dublin

Microscopic colitis

Collagenous Colitis
Lymphocytic colitis

NSAIDs, Olmesartan, others
NSAIDs, PPI, SSRIs, herbal remedies, ticlopidine, carbamazepine

222 patients with microscopic colitis
- patients taking a variety of medications at diagnosis thought to be associated with microscopic colitis, including:
  - NSAIDs (22%)
  - PPIs (19%)
  - aspirin (19%)
  - statins (15%)
  - SSRIs (selective serotonin receptor inhibitors) (10%)

Recent case: CRC patient with diarrhoea & focal active colitis

5-FU Colitis

Eosinophilic colitis
Ischaemic colitis

NSAIDs, Gold, L-Tryptophan, Carbamazepine, Methotrexate, Tacrolimus, Azathioprine, Rifampicin, Clozapine
NSAIDs, Digoxin, Cocaine, OCP/oestrogenic compounds

Microscopic colitis: clinical characteristics, treatment and outcomes in an Irish population


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NSAIDs, Digoxin, Cocaine, OCP/oestrogenic compounds
5. Drug Crystals

Various non-absorbable drugs can be associated with a wide spectrum of mucosal & mural alterations.

<table>
<thead>
<tr>
<th>Sodium Polystyrene Sulfate</th>
<th>Cholestyramine</th>
<th>Sevelamer</th>
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<tbody>
<tr>
<td>Shape</td>
<td>Angulated</td>
<td>Angulated</td>
</tr>
<tr>
<td>Appearance</td>
<td>Fish scale</td>
<td>Homogeneous</td>
</tr>
<tr>
<td>Colour</td>
<td>Purple</td>
<td>Red</td>
</tr>
<tr>
<td>Trade name(s)</td>
<td>Kayexalate</td>
<td>Questran</td>
</tr>
<tr>
<td></td>
<td>(hyperkalaemia)</td>
<td>(bile acid)</td>
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<td></td>
<td>Renage</td>
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<tr>
<td></td>
<td>(hyperphospataemia)</td>
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</tbody>
</table>

Appearance

Sodium Polystyrene Sulfate
- Fish scale
- Homogeneous
- Tree bark
- Purple
- Red
- Rusty/2 toned
- Fragments of tree bark

Recap - Pattern of injury & mimics

1. Villous atrophy
   - Coeliac disease
   - GVHD
2. Apoptotic / erosive
   - Neoplasia
3. Abnormal mitoses
   - IBD
4. Ulcerative
   - Vegetable matter
5. Crystals

CONCLUSION

Diagnosis of Drug-Induced Injury is Difficult

- Some compounds are associated with characteristic patterns of injury (many are not)
- Since the gut has a limited set of response patterns to injuries:
  - overlapping features with common primary GI diseases including coeliac disease & IBD is usual & to be expected
  - clinical correlation is always important when little or no clinical information is usually provided!
- Always consider drugs if you see an atypical "itis"

Histological pointers:
- "Apoptotic itis"
- "Withering crypts"
- "Ring mitoses"

Acknowledgement: Dr Aoife McCarthy & Dr Greg Lauwers