Eosinophils & Iatrogenic Pathology of the Intestines: what you need to know

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Classification of eosinophilic disorders of the small and large intestine

Aoife J. Mc Carthy and Kieran Sheahan
Virchows Archiv Annual Review 2018
History

• 2011
  – Abdominal pain
  – Gradual onset, severe

• CT imaging
  Small bowel dilatation consistent with obstruction
  – No specific cause identified
Histology

• **Small bowel resection**
  – Segment small bowel showing focal ulceration
  – Prominent eosinophils in muscularis propria and subserosa
  – No granulomas/lymphoid aggregates.

• **DX**
  – Crohn’s Disease (on balance of probabilities)

• **Treated with**
  – Budesonide
2017

- Nausea and vomiting
- Severe abdominal pain with recurrent hospital admissions
  - OGD
    - D2 – mildly increased IELs, Villi normal
    - Lower oesophagus: IEE 23/HPF – reflux v EOE
  - Colonoscopy
    - Acute inflammatory polyp at ICV. TI and colonic biopsies normal
  - MRI small bowel
    - Normal
- Review of resection
  - Degree and pattern of eosinophil infiltrate involving MP, and subserosa favoured EGID over Crohn’s Disease
- Eosinophils 0.2 check
- CRP 4
- IgE 275 (normal)
- RAST IgE
  - IgE milk 1.51 (0-0.35)
  - Class 2
OUTCOME

• TX
  – Well on an Exclusion diet
  – Montelukast (leukotriene receptor antagonist)
  – Sodium Cromoglycate (mast cell stabiliser)
  – No evidence of Crohn’s Disease
Allergy- Associated Colitis in adults

• Similar to disease process as in infants
  – Cow’s milk, human milk, soya
  – Exclusion diet for 2-3 years
• Allergy history
• Drug related – NSAIDS
• TI and colon>> rectum
• Clinical features are very non-specific
  – Epithelium, LP, submucosa
  – Lack of damage to epithelium
Eosinophils in GIT

• Histologically diagnosis of Eosinophilic gastointestinal disease (EGID) remains subjective
• Number differs by up to 40 times
  – Geographic regions
  – Seasons
• Small bowel

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of eosinophils/HPF</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal number of eosinophils in the small intestine</td>
<td>Up to 30 eosinophils/HPF</td>
<td>Lowichik et al.</td>
</tr>
<tr>
<td>Suggested minimum eosinophil count for a pathological diagnosis of eosinophilic gastroenteritis</td>
<td>&gt; 20 eosinophils/HPF</td>
<td>Uppal et al., Chen et al., Lee et al.</td>
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<tr>
<td></td>
<td>&gt; 30 eosinophils/HPF</td>
<td>Lowichik et al.</td>
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<tr>
<td></td>
<td>&gt; 50 eosinophils/HPF</td>
<td>Ingle et al.</td>
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*HPF high power field*
Eosinophils in Large Colon

- Up to 50 eosinophils/HPF seen in normal colon
- Higher prevalence in right colon
- Gradient from proximal to distal with second peak in rectosigmoid
- Inaccurate to apply threshold eosinophils to random colon biopsies
  - Right colon >50
  - Transverse colon >35
  - Left colon >25
Clinical Presentation (EGIDS)

• Mucosal
  – Nausea, vomiting, weight loss, diarrhoea
  – Protein-losing enteropathy, malabsorption, FTT

• Muscularis Mucosa
  – Intestinal obstruction, distention

• Subserosal
  – Ascites
Work Up

• Labs
  – Hypoalbuminaemia
  – Prolonged PT
  – Peripheral eosinophilia >500
  – IDA
  – IgE

• Stool for parasites
  – *Strongyloides* and *Toxocara* species

• Ascitic fluid sampling

• Endoscopy – mucosal
• Full Thickness R – submucosal

• Cross-sectional imaging

• Peripheral eosinophilia DDX
  – Adrenal insufficiency
  – HIV
  – Immune deficiency
  – Myeloproliferative neoplasms
Primary Eosinophilic Gastroenteritis

- 1/10,000-100,000
- Age: 20-50
- History of allergies
- +/- Serum Eosinophilia, raised IgE
- Primary
  - GI symptoms
  - GI eosinophil infiltrates
  - No other cause identified
- Stomach and proximal SB most common

- Mucosal disease 57%
  - Nausea/vomiting
  - Diarrhoea/Amaemia
- Muscularis Propria 30%
  - Intestinal obstruction
- Serosal/Subserosal 12.5%
  - Ascites
  - Intestinal obstruction
  - IgE mediated disease
Eosinophilic Colitis

- Typically causes diarrhoea
- Mucosal injury with preserved architecture
- Transmural +/- obstruction
- Endoscopically
  - Oedematous mucosa with loss of vascular pattern
  - Patchy erythema
  - Superficial ulceration
Secondary Causes of Mucosal Eosinophilia

• Coeliac Disease
• Eosinophilis in IBD
  – Typically lymphocytes + plasma cells
  – UC – quiescent v active
  – ? Predictor of response in UC
  – CD v UC colitis
• Parasitic infections
  – Helminthic
  – Eggs/larvae/worms may not be seen
  – Regional lymphadenopathy
  – Travel history
• Drug-induced
  – NSAIDS, clozapine, AZA, rifampicin, carbamazepine
  – OLT tacrolimus
  – Radiotherapy
• Hypereosinophilia Syndrome
• Serum eosinophilia > 1550 for 6/12
  – Males, 20-50 years
  – Peripheral organ embolic events
26 year old male: Microperforation of sigmoid colon in an incisional hernia – eosinophilic abscess in colonic wall

DX = PERFORATION OF SIGMOID COLON ASSOCIATED ENTEROBIUS VERMICULARIS
Secondary Causes

- Connective tissue
  - band-like colonic infiltrates
- Vasculitis
- Collagenous/lymphocytic colitis
- Neoplasia
- GVHD
- Appendicitis
- Cholecysitis
Coming to a Diagnosis

• No established criteria
  – Eosinophil quantification
  – Location of eosinophils
  – Extracellular eosinophils staining constituents – e.g. free granules/degranulation
  – Absence of pathological markers of other primary disorders
Treatment Options

• Dietary
  – Elemental diet
  – 6 food elimination diet (wheat, milk, soya, nuts, eggs, & seafood)

• Glucocorticosteroids
  – Prednisolone 20-40mg/day

• Sodium Chromoglycate
  – preventing the release of mast cell mediators

• Ketotifen
  – H1-antihistamine and mast cell stabilizer

• Montelukast

• Leukotriene receptor antagonist
Iatrogenic gut injury is common (700 DRUGS)

5% of patients receiving drugs experience an adverse reaction

Role of pathologist =
Recognize histological patterns
• Associated with
• Suggestive of
• Diagnostic of

Drug-induced injury

5% ADR
7% GIT
Never diagnose

? See in biopsy
5% mortality rate
Pattern of injury & Mimics

1. Villous atrophy • Coeliac disease

2. Apoptotic / erosive • Graft vs Host Disease

3. Ulcerative/colicitis • IBD
Pattern of injury & Mimics

1. Villous atrophy
2. Apoptotic / erosive
3. Ulcerative

- Coeliac disease
- GVHD
- IBD
Sept 2011: 69 year old female – unwell, weight loss, signs of malnutrition

Subtotal villous atrophy, ? Coeliac Disease

Courtesy of Professor Gene Connolly, Galway University Hospital
No improvement on a Gluten Free Diet

Repeat biopsy, June 2012: subtotal villous atrophy

Is this Refractory Coeliac Disease?

Noted to be on Olmesartan for hypertension
Off Olmesartan x 2 months: mild partial villous atrophy
Back on a Gluten-diet, Off Olmesartan x 7 months
MOST LIKELY OFFENDING AGENT

A. Aledronate
B. Simvastatin
C. Lanzoprazole
D. NSAIDS
E. Olmersartan
Diagnosis: Severe coeliac-like enteropathy associated with Olmesartan
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)
Chronic diarrhoea (> 4 weeks) while taking olmesartan

Cause of enteropathy not established after diagnostic evaluation – often very ill & all required admission

Clinical improvement after discontinuation

Also microscopic colitis & lymphocytic gastritis +/-collagen
Olmesartan causes symptoms & signs of coeliac disease

Limited number of literature citations on topic

• In 2012, approx. 10.6 million prescriptions for approx. 2 million patients

• In this era of polypharmacy, be vigilant of drug adverse effects (absolute incidence is RARE, < 1/1,000)
Pattern of injury & Mimics

1. Villous atrophy
2. Apoptotic / erosive
3. Ulcerative

- Coeliac disease
- GVHD
- IBD
PC & Background

- Severe diarrhoea (x 20/day)
- Tacrolimus 3mg BD
- Mycophenolate Mofetil 500mg BD
- Prednisolone 5mg OD
- Calcichew D3
- Ulcerative colitis
- Ileoanal pouch anastomosis
- Primary sclerosing cholangitis
- Orthotopic liver transplant
Pouch and pre pouch ileum on Admission
What would you do next?

Differential Diagnosis
- Pouchitis
- Crohn’s disease
- Viral enteropathy
- Drug-induced enteropathy

Investigations (all negative)
- Stool C&S, C. diff
- Full CMV workup
  - serum, stool, histology
  - CMV negative pre transplant
- HSV PCR
  - IgG positive pre transplant
- MR Enterography
Mycophenolate-associated injury to small intestine (enteropathy)
Iatrogenic injury Vs GVHD in BMT pts?

• Eosinophils more commonly associated w/ MPA
• Oesophageal mucosa involvement suggests GVHD

Mycophenolate-associated injury

Colon – hallmarks = crypt apoptoses, crypt withering, +/- eosinophilic abscess

Increased risk of CMV colitis; associated in 10% of pts
Outcome

- Mycophenolate Mofetil was discontinued
- Diarrhoea settled completely
- Discharged home
Mycophenolic Acid (MPA)

Mycophenolate mofetil (CellCept®)
Mycophenolate sodium (Myofortic®)

Used in Allograft rejection, GVHD, Autoimmune conditions

- GVHD-like alterations throughout the GIT
- Active oesophagitis with ulceration or erosion
- Chemical gastropathy; focal active gastritis
- Crohn’s-like damage in the duodenum
- Cryptitis, crypt withering & distortion, reparative changes & increased neuroendocrine cells
A retrospective review of OLT patients who had OGD and D2 biopsies over a 19 year period

152 D2 biopsies. 5% had coeliac type changes

Discontinuation or reduction of MPA was associated with improvement of symptoms within 1-3 weeks.

Be aware of CMV
Iatrogenic injury Vs GVHD in Bone Marrow Transplant patients

- Eosinophils more commonly associated w/ MPA
- Oesophageal mucosa involvement suggests GVHD

Mycophenolate-associated injury

Increased risk of CMV colitis; associated in 10% of patients
61 year old female
Stage IV lung adenocarcinoma

PDL-1 biomarker positive. Prescribed new oncological agent.

Bloody diarrhoea. Proctitis to 15cm

Pembrolizumab
45 year old female
Stage IV melanoma

Prescribed new oncological agent.

Diarrhoea.
CTLA-4 monoclonal antibody (ipilimumab)
small intestine
Ipilimumab (Anti-CTLA-4) Blocks CTLA-4
Restoring T Cell Activation

T cell

Antigen Presenting Cell

Signal 1

T Cell Receptor

HLA

B7.1/2

Antigen

Signal 2

CD28

CTLA-4

α CTLA-4

HEPATITIS, NEPHRITIS, HYPOPHYSITIS

20% GIT TOXICITY

COLITIS, ENTERITIS, ENTERIC NEUROPATHY

5 % MORTALITY

IMMUNE CHECKPOINT INHIBITORS
Ipilimumab (Anti-CTLA-4) Blocks CTLA-4 Restoring T Cell Activation

- 20% GIT TOXICITY
- HEPATITIS, NEPHRITIS, HYPOPHYSITIS
- 5% MORTALITY
- COLITIS, ENTERITIS

IMMUNE CHECKPOINT INHIBITORS
**PD-1 inhibitor gastroenterocolitis: case series and appraisal of ‘immunomodulatory gastroenterocolitis’**

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Michael M Feely 4 & Chanjuan Shi 2
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2 Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN.
3 Immunology and Pathogenesis Branch, Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA. and 4 Department of Pathology, Immunology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY.

**Figure 1.** Typical and atypical findings in patients with gastroenterocolitis secondary to a programmed cell death protein 1 (PD-1) inhibitor. A, Erythema and granularity of the colon were evident macroscopically in this patient taking a PD-1 inhibitor. B, This colonic biopsy shows lamina propria expansion, crypt distortion and crypt abscesses. C, Cryptitis and pronounced epithelial reactive change, including prominent nucleoli, are visible at higher power. There is a mild increase in crypt apoptosis above baseline, a feature seen in approximately half of colon biopsies. D, Changes resembling ischaemic colitis were seen in three specimens. E, Changes resembling collagenous colitis were seen in one specimen. F, Crypt rupture with responding histiocytes was a distinctive but uncommon feature, seen in five of the 34 biopsies available for review. In this colon biopsy, the histiocytes are arranged tightly, forming granulomas.
Enterocolitis due to immune checkpoint inhibitors: a systematic review

Emilie Soolarue,1,2 Patricia Lepage,3 Jean Frederic Colombel,4 Clelia Coutzac,5 David Faleck,4 Lysiane Marthey,1 Michael Collins,1,2 Nathalie Chaput,5,6 Caroline Robert,2,7 Franck Carbonnel1,2

Table 1  Risk factors of enterocolitis due to immune checkpoint inhibitors

<table>
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<tr>
<th>Risk factors</th>
<th>Combotherapy&gt;anti-CTLA-4&gt;anti-PD-1</th>
<th>References</th>
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<tbody>
<tr>
<td>Type of ICI</td>
<td>Dose-dependant toxicity with anti-CTLA-4</td>
<td>Ascierto et al11</td>
</tr>
<tr>
<td>Dose of ICI</td>
<td>Dose-dependant toxicity with anti-CTLA-4</td>
<td>Ascierto et al11</td>
</tr>
<tr>
<td>NSAIDs use</td>
<td>Suggested with anti-CTLA-4</td>
<td>Marthey et al25</td>
</tr>
<tr>
<td>Pre-existing IBD</td>
<td>About 30% risk of relapse with anti-CTLA-4; not reported with anti-PD-1</td>
<td>Johnson et al12, Kähler et al13, Menzies et al15</td>
</tr>
<tr>
<td>Microbiota</td>
<td>Baseline microbiota enriched in Firmicutes and poor in Bacteroidetes with anti-CTLA-4</td>
<td>Chaput et al84</td>
</tr>
<tr>
<td>Tumour histology</td>
<td>Increased risk in melanoma as compared with NSCLC and RCC with anti-PD-1</td>
<td>Khoja et al7, Wang et al8</td>
</tr>
</tbody>
</table>

CTLA-4, cytotoxic T-lymphocyte-associated protein-4; ICI, immune checkpoint inhibitor; NSAID, non-steroidal anti-inflammatory drug; NSCLC, non-small cell lung carcinoma; PD-1, programmed death-1; RCC, renal cell carcinoma.
Pattern of injury & Mimics

1. Villous atrophy
2. Apoptotic / erosive
3. Ulcerative/colitis

- Coeliac disease
- GVHD
- IBD
NSAIDS

- 70% GIT TOXICITY
- INCREASED RISK WITH HIGH DOSES
- ULCERATION & HAEMORRHAGE
- COX-1 & COX-2 inhibition

INCREASED RISK WITH HIGH DOSES
Prevalence of NSAID-induced enteropathy (small intestine) is underestimated

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

Increasing due to use of enteric coated or sustained (slow) release formulation (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)
Microscopic Colitis

Collagenous Colitis

NSAIDs, Olmesartan, others

Lymphocytic Colitis

NSAIDs, PPI, SSRI; herbal remedies, ticlopidine, carbamazepine
CONCLUSION

Diagnosis of Drug-Induced Injury is Difficult (could this be medication-induced injury?)

- Some compounds are associated with characteristic patterns of injury (many are not)

- Because the gut has a limited set of response patterns to injuries:
  - overlapping features with common primary GI diseases including coeliac disease & IBD are to be expected.
  - Other differential diagnoses include rare disorders like tropical sprue, CVID, autoimmune enteropathy.
  - clinical correlation is crucial

(when little or no clinical information is usually provided!)
Diagnosis of Drug-Induced Injury is Difficult

• CLINICIAN

• Knowledge
• Awareness

• PATHOLOGIST

• Always consider DRUGS in an atypical “itis”

• Specific pointers:
  - Apoptosis
  - Withering crypts
  - Marked nuclear pleomorphism / cytologic atypia
  - Obvious/numerous eosinophils
Acknowledgement: GI colleagues SVUH, Dr Aoife McCarthy (GI Pathology Fellow, Toronto) & Dr Greg Lauwers (Pathologist, Moffitt Cancer Centre, Tampa, Florida)

"I didn't experience any of the side effects listed in the enclosed literature. Should I be concerned?"