Inflammatory Bowel Disease: Frequent Diagnostic Pitfalls
James Michael Mitchell, MD

Problems encountered
- Distribution or locality of disease not demonstrated by bx sample(s)
- Limited biopsy sample
- Assessing and diagnosing disease/activity
- All biopsy samples submitted in one container
- "Random colon"
- Limits assessment of chronicity
- Granulomata

- Treatment effect
- Other medication effect
- Question being asked cannot be answered
- Pathologist cannot differentiate between CD and UC on biopsy

Histopathologic mimicry

Problems encountered
- Pathologist blinded or does not understand reason(s) for biopsies
- Lack of clinical information
  - Signs and symptoms
    - Abdominal pain, diarrhea
  - Temporality of disease
  - Laboratory findings (microbiology, serology)
  - Endoscopy findings
    - Spatial distribution
  - Imaging
  - Pathologist cannot answer question if there is not one
  - Pathologist is unaware of criteria to make diagnosis

  Endoscopist lacks clinical information to answer question

Normal histology
1. Classify colitis
   - Acute
   - Chronic
   - Active
   - Inactive

2. Grade activity
   - Mild
   - Moderate
   - Severe

3. Clinico-pathologic correlation

Pattern-based approach to colitis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Acute Colitis</th>
<th>Chronic Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crypt architecture</td>
<td>Usually superficial, almost normal crypts</td>
<td>Often abnormal</td>
</tr>
<tr>
<td>Expansion of lamina propria</td>
<td>Usually absent</td>
<td>Present, when crypts are injured</td>
</tr>
<tr>
<td>Lymphatic aggregates</td>
<td>Usually absent</td>
<td>Present, when crypts are injured</td>
</tr>
<tr>
<td>Nasal polymorphs</td>
<td>Usually absent</td>
<td>Present, when crypts are injured</td>
</tr>
<tr>
<td>Acute inflammation</td>
<td>Usually absent</td>
<td>Present, superficial and deep</td>
</tr>
<tr>
<td>Cryptitis and abscesses</td>
<td>Present, superficial and deep</td>
<td>Present, superficial and deep</td>
</tr>
<tr>
<td>Pyogenic or lymphoid cell massa</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Lamina propria fibrosis</td>
<td>Absent</td>
<td>May be present</td>
</tr>
</tbody>
</table>

Microscopic features of acute vs. chronic colitis

Acute colitis

- Generally preserved crypt architecture
- Acute cryptitis and abscesses
- Chronic inflammatory infiltrate

Focal active colitis (FAC)

- Acute cryptitis limited to one or few crypts
- Associated with epithelial injury
- +/- increased chronic inflammatory infiltrate

Previously thought to have strong correlation with CD (Greenson, et al.)

Acute self-limited colitis
- NSAIDs, sodium phosphate
- Irritable bowel syndrome
- Crohn’s disease
- Ischemic colitis

Pitfall: lymphoid aggregates

Table:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Adults (%)</th>
<th>Adults (%)</th>
<th>Adults (%)</th>
<th>Children (%)</th>
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<tbody>
<tr>
<td>Incidental</td>
<td>40</td>
<td>29</td>
<td>8</td>
<td>26.6</td>
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<tr>
<td>Ischemia</td>
<td>6</td>
<td>10</td>
<td>9</td>
<td>8</td>
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<td>Crohn’s disease</td>
<td>0</td>
<td>83</td>
<td>11</td>
<td>27.6</td>
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<td>Hemorrhagic colitis</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>1.4%</td>
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<tr>
<td>Drugs</td>
<td>29</td>
<td>0</td>
<td>24</td>
<td>8</td>
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<tr>
<td>Irreversible bowel syndrome</td>
<td>14</td>
<td>0</td>
<td>32</td>
<td>8</td>
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<tr>
<td>Allergic</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>6.9</td>
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<tr>
<td>Overactive disease</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>3.4%</td>
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</tbody>
</table>

Presenting symptoms
- Sudden-onset diarrhea
- Abdominal tenderness
- Fever

<table>
<thead>
<tr>
<th>163 adult patients</th>
<th>(F&gt;M)</th>
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<tbody>
<tr>
<td>40</td>
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<tr>
<td>6</td>
<td>10</td>
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<tr>
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<table>
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<th>31 pediatric patients</th>
<th>(F&gt;M)</th>
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</table>
**Chronic colitis**
- Crypt architectural distortion
- Basally located lymphoid aggregates
- Basal plasmacytosis
- Chronic inflammatory infiltrate
- Paneth cell metaplasia/hyperplasia
- Lamina propria fibrosis

**Granulomata**

**Microscopic features of untreated IBD**

**Histologic Mimics of IBD**

- **Infectious agents**
  - Infectious colitis: Salmonella, E. coli, Yersinia, C. jejuni, Shigella, E. histolytica, Tuberculosis
  - STD-associated proctitis: Syphilis, N. gonorrhea, C. trachomatis (LGV)
- Drug-induced colitis
  - NSAIDs
  - Mycophenolate
  - Biologics: Infliximab, Rituximab, Bevacizumab
- Systemic conditions involving the GI tract
  - Vasculitis: Behçet’s disease, Henoch Schönlein purpura
  - Chronic granulomatous disease
  - Hermansky-Pudlak syndrome
  - Common variable immunodeficiency syndrome
  - Systemic mastocytosis
  - Langerhans cell histiocytosis
  - Idiopathic hypereosinophilic syndrome
- Diverticular colitis
- Crohn-like colitis
- Ulcerative colitis-like

**Pitfall: colorectal fissure in IBD (CD vs UC)**

**Pitfall: discontinuous disease in UC**

Rectal biopsy prior to therapy with chronic active colitis

Rectal biopsy after 6 months of mesalamine therapy with complete resolution of disease
Infectious mimics of IBD

- Acute self-limited colitis
  - Shigella
  - Campylobacter
  - Non-typhoid Salmonella
  - Aeromonas
- Ischemic colitis w/ or w/o pseudomembranes
  - Shigella
  - STEC
- Granulomatous inflammation
  - Yersinia
- Lymphohistiocytic inflammation
- Architectural distortion
  - S. typhi
  - Shigella
  - Aeromonas (occasionally)

Histologic pattern of injury – bacterial pathogens

**Salmonella infection**
- Acute self-limited colitis
- Minimal crypt architecture distortion

**Yersinia infection**
- Neutrophil-rich granuloma
- Generally preserved crypt architecture

**Shigella infection**
- Acute self-limited colitis
- Minimal crypt architectural distortion
- Reactive epithelial features
- Acute crypt abscess
- Mucin granuloma

Isolated ulcers of the TI (Yersinia infection)

Biopsy: Virtually indistinguishable from CC

Erosions/ulcerations
- Chronic lymphocytic inflammation in lamina propria
- Villous architectural abnormalities
- Pseudopyloric gland metaplasia
**Entamoeba histolytica colitis**

- Trophozoites
- Round to oval
- 25-40 nm
- Luminal

**Mycobacterial infection**

- IC > IS
- Preferentially affects TI and cecum

**C. difficile-induced pseudomembranous colitis**

- Pseudomembranes in chronic active UC
- Ulceration
- Crypt architectural distortion
- Acute cryptitis
- Crypt abscesses
- Basal lymphoplasmacytosis

**Concomitant CMV infection**

**STI-associated proctitis**

- Intense lymphohistiocytic infiltrate with prominent plasma cells
- Lymphoid aggregates
- Mild to moderate acute inflammation
- Minimal basal plasmacytosis
- Minimal crypt distortion
- Rare granulomata
- Paneth cell metaplasia
Treponema pallidum infection

Lymphogranuloma venereum infection

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Histologic Mimics of IBD

Biopsy: Virtually indistinguishable from CC
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  - Pseudopyloric gland metaplasia

Isolated ulcers of the terminal ileum (NSAIDs)

Mycophenolate injury
- Scattered epithelial apoptotic bodies
- Increased plasma cells and eosinophils in lamina propria

Non-steroidal anti-inflammatoris
- Variable mucosal injury
- Subepithelial fibrosis

Ipilimumab colitis
- Robust lymphoplasmacytic infiltrate extending in submucosa
- Crypt abscesses
- Epithelial cell apoptosis
• Infectious agents
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Histologic Mimics of IBD

Behçet’s disease

Common variable immunodeficiency

Henoch-Schönlein purpura

Systemic mastocytosis

- Diffuse, severe colitis
  - Numerous inflammatory polyps and erosions
  - Crypt architectural distortion
  - Basal lymphoplasmacytosis
  - Leukocytoclastic vasculitis in lamina propria
  - PAUCITY of neutrophils in lamina propria and crypts

- GI involvement: ~75% of pts
  - Endoscopy: Normal or non-specific changes (G or D ulcers)
  - Expansion of lamina propria by chronic inflammatory infiltrate with eosinophilia
  - +/- crypt architectural distortion
  - Clusters/aggregates of CD117+/tryptase mast cells

- Majority with normal crypt architecture
  - No significant chronic inflammatory infiltrate in lamina propria
  - Prominent crypt cell apoptosis

- Marked crypt architectural distortion
  - Paucity of plasma cells
  - Concomitant pathology

- Common variable immunodeficiency

- Expansion of lamina propria by chronic inflammatory infiltrate with eosinophilia

- Clusters/aggregates of CD117+/tryptase mast cells
Bimodal: Childhood & middle age
  GI involvement: Rare
Pediatric: Disseminated disease
Adults: Systemic or localized (CR)
  Vague granulomatous infiltrate expanding lamina propria and associated eosinophilia
  Ill-defined collections of LC with abundant eosinophilic cytoplasm
  Eccentrically located nuclei with grooves and irregular contours

Langerhans cell histiocytosis

Diverticular disease-associated colitis

• Usually childhood
  • Peripheral eosinophilia
  • Systemic s/s of hypersensitivity
    • Eczema, asthma, atopy etc.
  • GI s/s: diarrhea & abd pain
  • May affect entire GI tract

Eosinophilic gastroenteritis

Diverticular disease-associated colitis

• Infectious agents
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Histologic Mimics of IBD
Superficial lymphoplasmacytosis
Intraepithelial lymphocytes
Increased subepithelial collagen layer
Epithelial separation/lifting
Basal lymphoplasmacytosis
\(+/-\) crypt architecture distortion

Collagenous colitis

Surface erosion
Regenerative changes
Crypt architecture distortion
Fibromuscularization of lamina propria

Mucosal prolapse syndrome (SRUS)

Right-sided biopsy

Superficial lymphoplasmacytosis
Intraepithelial lymphocytes
Increased subepithelial collagen layer
Basal lymphoplasmacytosis
Crypt architecture distortion

Collagenous colitis in IBD

Inflamed lamina propria
Elongated hyperplastic crypts
“Cap” of granulation tissue with ulcer debris

Inflammatory “cap” polyp

Crypt architecture distortion
Mucosal atrophy
Pseudopyloric gland metaplasia

Chronic radiation injury

Lymphoid follicular hyperplasia with conspicuous germinal centers
Erosions/ulcerations
Crypt architectural distortion
Mucin granulomata (occasionally)

Diversion colitis