The Differential Diagnosis of Colitis in Endoscopic Biopsy Specimens

Joel K. Greenson, M.D.
Greenson, IBD and Dysplasia
Acute Infectious-type Colitis

Clinical Presentation
- Acute onset bloody diarrhea
- Similar symptoms are seen in acute onset UC
- Colon biopsies may be required to distinguish between ASLC and new onset UC
  - provided the patient’s symptoms last long enough to get past their “gate keeper” and see a gastroenterologist

Acute Infectious-type Colitis

Histopathology
- At peak activity ASLC shows cryptitis, crypt abscesses, edema, and surface damage with erosions.
- ASLC does not have crypt distortion or basal plasma cells
- UC often has both crypt distortion and basal plasma cells even at first onset
Markers of Chronic Injury

- Forked or branched crypts
- Crypts shaped like animals, continents, or Hebrew letters
- Paneth cells more distal than the right colon
- Basal plasma cells
Lamina propria may be hypercellular with increased lymphs, eos, polys, and a few plasma cells - Don't be fooled into calling this chronic colitis!

There may be an increase in intraepithelial lymphocytes such that the changes mimic lymphocytic colitis - Don't be fooled, as the clinical history is not right for this!
As ASLC resolves, there is mucus depletion with regenerative epithelial changes and a few residual foci of cryptitis or "focal active colitis"
Etiology of Focal Active Colitis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Adult #1*</th>
<th>Adult #2**</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>55%</td>
<td>48%</td>
<td>31%</td>
</tr>
<tr>
<td>Incidental</td>
<td>40%</td>
<td>29%</td>
<td>27.6%</td>
</tr>
<tr>
<td>Ischemia</td>
<td>5%</td>
<td>10%</td>
<td>0%</td>
</tr>
<tr>
<td>Crohn's</td>
<td>0%</td>
<td>13%</td>
<td>27.6%</td>
</tr>
<tr>
<td>Allergic</td>
<td>0%</td>
<td>0%</td>
<td>6.9%</td>
</tr>
<tr>
<td>UC</td>
<td>0%</td>
<td>0%</td>
<td>3.45%</td>
</tr>
<tr>
<td>Hirschprung's</td>
<td>0%</td>
<td>0%</td>
<td>3.45%</td>
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</tbody>
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Pseudomembranous Colitis

Differential Diagnosis

- **Clostridium difficile**
  - May look like ischemia, acute self limited colitis, or focal active colitis
- **E. coli O157:H7**
  - Probably through an ischemic process
  - Thrombi often seen in biopsies
  - Often right sided
- **Ischemia**
  - Segmental distribution
Ischemia vs C. difficile
Histologic and Clinical predictors

- **Ischemia**
  - **Strong:** Hyalinized lamina propria, Atrophic or withered crypts, localized process on endoscopy.
  - **Weak:** Mass or polyp seen on endoscopy, lamina propria hemorrhage, full-thickness mucosal necrosis, diffuse membranes in biopsy.

- **Clostridium difficile**
  - **Strong:** Pseudomembranes seen on endoscopy.
"A mild increase in the number of inflammatory cells on colonic or rectal biopsy was observed without crypt abscesses, pus on a rectal mucosal smear, abnormal sigmoidoscopic appearance, or abnormal barium enema."


**Microscopic Colitis**
**Original Definition**

**Microscopic Colitis:**
**What it means today**

- Chronic watery diarrhea with normal or near normal endoscopic findings:
  - Collagenous Colitis
  - Lymphocytic Colitis
  - Chronic non-distorting colitis with/without neutrophils
  - Apoptotic Colopathy?

**Collagenous Colitis**
**Clinical Features**

- Chronic watery diarrhea
  - Months to years
- Female to male ratio = 8:1
- Middle aged or older
- Normal endoscopic appearance

**Collagenous Colitis**
**Histopathology**

- Irregular subepithelial collagen layer
  - Traps capillaries
  - Seen easily with trichrome stain
- Surface epithelial damage with increased intra-epithelial lymphocytes
- Superficial plasmacytosis of lamina propria
  - May have increased eosinophils and paneth cell metaplasia
- No crypt distortion and few polys
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Thickness of Collagen in Collagenous Colitis by Site

Collagenous Colitis
Diagnostic Pitfalls
- Tangential section - crypt sheath
- Thickened basement membrane
- Crush artifact
- Enema effect
- Radiation colitis
- Diffuse fibrosis of lamina propria
Lymphocytic Colitis
Clinical Features

- Chronic watery diarrhea
  - Months to years
- Middle aged patients
- Female to male ratio 3:1
- Normal endoscopic findings

Lymphocytic Colitis
Histopathology

- Surface epithelial damage with increased intra-epithelial lymphocytes
- Superficial plasmacytosis of lamina propria
- No crypt distortion and few polyps
  - may have rare foci of cryptitis, but not a major feature.
- May have somewhat patchy distribution
Lymphocytic Colitis/Colonic Lymphocytosis

- Celiac Disease
  - 15% of LC patients have Celiac disease.
  - 5-31% of Celiac patients have LC/CL and up to 67% of refractory sprue patients have LC
- Brainerd diarrhea
  - Outbreaks of chronic watery diarrhea of presumed infectious etiology
  - Colon Bx shows increased IELs without surface damage
- Resolving Infectious Colitis

LC and CC
Associations/Etiology

- Drugs
  - NSAIDs, Ranitidine, Carbamazepine, Cyclo 3 Fort
- Bile Acids?
  - Post cholecystectomy cases treated with cholestyramine
- Luminal antigen of some sort:
  - CC goes away if colon is diverted and recurs when hooked back up.

Other Microscopic Colitides

- Increased chronic inflammation of the lamina propria without distortion, IELs or collagen.
  - Chronic watery diarrhea with normal endoscopy
- Same as above with some cryptitis
  - Bo-Linn et al, J Clin Invest 75:1559-1569, 1984
- Same as above with apoptosis
**Diversion Colitis**

- Occurs in a diverted segment of colon
  - Usually Hartmann's pouch
- Caused by lack of short chain fatty acids in fecal stream
  - Colonocyte malnutrition
- Symptoms: None, bloody or mucus discharge, pain
- Resolves if bowel hooked back up or with fatty acid enemas

**It's the Surgeon's Fault!**
Diversion Colitis
Pathology

- Cryptitis, Crypt abscesses, polyps in lamina propria.
- Aphthous lesions
- May have plasmacytosis and some crypt distortion (due to large lymphoid follicles)

Life in the Fecal Stream

Happy colonocytes bathed in short chain fatty acids

Life without the Fecal Stream

Help, We're starving, please restore the fecal stream!
**Restoration of the Fecal Stream**
(Life is good)

Colonocytes are happy again!

**Diversion Colitis**
Differential Diagnosis

- Crohn’s Disease
  - Common problem in Crohn’s patients with a diverted segment: Is it Crohn’s or diversion?
- Ulcerative Colitis
- Infectious Colitis
- Pouchitis: Remember a Hartmann’s Pouch is diverted segment of colon - not a real pouch!
- History is paramount

U.C. CRN’SE
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- Cryptitis
- Normal

- FOCAL
- PATCHY
- DIFFUSE
Variants of Ulcerative Colitis
(Things I used to call Crohn’s Disease)

- Patchy Distribution
  - Left sided UC with peri-appendiceal disease
    (The cecal red patch)
  - After therapy there is often uneven healing
- Rectal Sparing
  - Steroid enemas
  - Burnout in long-standing disease
  - Rare cases can present with a normal rectum

Ulcerative Colitis
Extra-Colonic Disease?

- Gastritis
  - Focally enhanced gastritis (FEG) thought to be typical
    of Crohn’s.
  - 2 recent studies found 12% and 50% of UC patients
    had FEG compared to 43% and 35% of CD patients.
- Duodenitis
  - Over the last 5 years many case reports have found
    diffuse duodenitis in patients with resection proven UC
  - Several of these patients also had gastritis
  - Pts tolerated endorectal pull-through procedures

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Ulcerative Colitis
Histology in the new millennium

- Patchy distribution is often seen once the patient is on medical therapy.
- Rectal sparing can be seen in longstanding disease, in patients using steroid enemas, and rarely in de novo UC.
- Skip lesions (cecal patch) can be seen in UC.
- Focal gastritis and diffuse duodenitis can be seen in UC.