DIAGNOSIS OF NON-IBD COLITIS IN COLORECTAL BIOPSY

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Outline

- Acute infectious (self-limited) colitis
- Focal active colitis
- Pseudomembranous colitis
- Ischemic colitis
- Collagenous colitis and lymphocytic colitis
- Diversion colitis
- Diverticular disease associated (segmental) colitis
- Iatrogenic colitis (radiation, NSAIDs induced, mycophenolate induced)

Normal Cecum and Rectum

Cerilli & Greenson
Evaluation of Colon Biopsy
- Evaluation is best performed at a low magnification (to recognize pattern of injury and compare changes among different fragments of biopsy)
- Clinical and endoscopic data combined with histopathology is essential

Acute Infectious (Self-Limited) Colitis
- Transient acute inflammatory disorder of the colon
- Food borne
- Common bacterial pathogens: Campylobacter jejuni (poultry), Shigella, Salmonella
- Enterohemorrhagic E.coli produces an ischemic colitis appearance
- In the majority of cases the exact pathogen is not identified

Acute Infectious Colitis
- Acute onset of bloody diarrhea
- Patients recover in 10-14 days without residual inflammation or recurrent symptoms
- The majority of cases are never biopsied
- If symptoms persist, colorectal biopsies are used to rule out new onset ulcerative colitis
Endoscopic Findings

- Acute full-blown infectious colitis-diffuse mucosal friability
- Early stage/resolving/treated-non-specific erythema

Acute Infectious Colitis versus Ulcerative Colitis

Cerilli & Greenson
**Resolving Acute Infectious (Self-Limited) Colitis**
- Few persistent foci of cryptitis (focal active colitis)
- Small granulomas, usually secondary to crypt rupture
- Patchy lamina propria inflammation with increased lymphocytes, neutrophils, eosinophils, and only few plasma cells
- Modest increase in intraepithelial lymphocytes

**Focal Active Colitis**
- Colonic injury characterized by the presence of focal neutrophilic infiltrates within the colonic epithelium (and/or lamina propria) in the absence of any other significant microscopic abnormality.
  - Single crypt, a few adjacent crypts, or small regions of mucosa across a series of multiple colorectal biopsy specimens

**46 yo man with diarrhea and normal endoscopy**

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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Adults (%) n=42</th>
<th>Adults (%) n=31</th>
<th>Children % n=29</th>
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<tbody>
<tr>
<td>Infectious</td>
<td>55</td>
<td>48</td>
<td>31</td>
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<tr>
<td>Incidental</td>
<td>40</td>
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<td>Ischemia</td>
<td>5</td>
<td>10</td>
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<td>Crohn's Disease</td>
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<tr>
<td>Hirschprung’s disease</td>
<td>0</td>
<td>0</td>
<td>3.45</td>
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</tbody>
</table>

Focal Active Colitis

- Usually normal endoscopy
- In adults interpret conservatively
- Focal active colitis is important to document in pediatric patients

Pseudomembranous Colitis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Features</th>
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<tbody>
<tr>
<td>Clostridium Difficile colitis</td>
<td>Diffuse pseudomembranes, history of antibiotic use</td>
</tr>
<tr>
<td>Ischemic colitis</td>
<td>Patchy pseudomembranes, hyalinized lamina propria</td>
</tr>
<tr>
<td>E.coli O157: H7</td>
<td>Pseudomembranes in the right colon, fibrin thrombi</td>
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</table>

Differential Diagnosis of Pseudomembranous Colitis

- Clostridium Difficile colitis
  - Diffuse pseudomembranes
  - History of antibiotic use
- Ischemic colitis
  - Patchy pseudomembranes
  - Hyalinized lamina propria
- E.coli O157: H7
  - Pseudomembranes in the right colon
  - Fibrin thrombi
**Clostridium Difficile-Induced Colitis**

- Diarrhea during a course of antibiotics or within 6–8 weeks of completing treatment
- Older adults
- Toxins produced by the bacteria cause direct tissue damage
- The diagnosis can be confirmed by the detection of C. difficile toxin in stool
- Subset of patients undergo sigmoidoscopy or colonoscopy with biopsy

**C. Difficile-Induced Colitis**

- Intercrypt necrosis
- Ballooned crypts filled with neutrophils and mucin
- Degenerated goblet cells spill into the lumen of crypts
- Laminated pseudomembrane composed of fibrin, mucin, and neutrophils

**C. Difficile Colitis**

- [Image of histological appearance of C. Difficile colitis]
Etiology
• Atherosclerosis of SMA
• Low blood flow (shock, cardiac failure)
• Thrombi/emboli
• Mechanical (volvulus, adhesions, tumors)
• Hematologic disorders (sickle cell, protein C/S deficiency)
• Drugs (OCP, vasopressin, digitalis etc)
• Lack of bowel perfusion (ex. marathon runners)
• 90% occur in patients older than 60
• Sudden onset of bloody diarrhea and abdominal pain
• E. coli O157:H7 produces ischemic colitis picture
Ischemic Colitis: Endoscopic Findings

- Geographic areas of ulceration with pseudomembranes
- Endoscopically marked submucosal edema can be prominent enough to mimic a tumor or mass lesion

Ischemic Colitis

- The watershed area around the splenic flexure is the most common site

Ischemic Colitis

- Superficial mucosal necrosis
- Hemorrhage into the lamina propria
- Withered crypts with mucin loss and reactive atypia
- Hyalinization of the lamina propria
  - Can be highlighted by trichrome stain
  - Hyalinization is absent if ischemia is recent
- Cryptitis/crypt abscesses not prominent, indicate reperfusion injury
Collagenous colitis and lymphocytic colitis

- Chronic watery diarrhea: urgency (70%), nocturnal diarrhea (50%), abdominal cramps (50%), mild weight loss (40%), fecal incontinence (40%), dehydration/electrolyte disturbances uncommon
- Normal or near normal endoscopic findings
  - Rare reports of collagenous colitis with pseudomembranes
- Usually affects middle-age or older patients

Microscopic Colitis

- Course: chronic intermittent (most common) vs continuous
- 80% response to budesonide
- 80% of cases resolve spontaneously within three years
- No known increased risk for colon cancer, IBD or increased mortality
Case

- 73 yo female with history of non small cell lung cancer on Nivolumab. Complains of watery diarrhea after initiation of Nivolumab. The examined colon appeared normal endoscopically.
Collagenous Colitis

- First described in 1976
- Female predominance, F:M 8:1
- Median age at diagnosis 55 years
- 40% have concomitant autoimmune disease
  - Rheumatoid arthritis
  - Thyroid disease
  - Celiac disease
  - Diabetes mellitus

Collagenous Colitis – Proposed Etiologies

- Idiopathic in most cases
  - Luminal antigen (Jarnerot et al, 1995)
  - Diversion of the fecal stream caused the histological changes of CC to regress
  - Reestablishing the fecal stream induced a relapse of both the abnormal collagen layer and clinical symptoms
- NSAIDs and other drugs as a possible cause

“Cat-Scratch” Colon

- Mucosal Tears on Endoscopic Insufflation Resulting in Perforation: An Interesting Presentation of Collagenous Colitis
Collagenous Colitis

- Superficial lymphocytes, plasma cells in lamina propria
- Eosinophils are often prominent (in lamina propria and intraepithelial)
- Scattered neutrophils
- Increased intraepithelial lymphocytes
- Rarely collagen seen in ileum and elsewhere in GI tract

Separation of the surface epithelium from the basement membrane beneath
Biopsies obtained from the rectum and sigmoid colon may show less thickening and may be in the normal range.

Biopsies from ascending or transverse colon preferable.

When in doubt, a trichrome stain may be helpful.

Irregular nature of the collagenous band is more important than its thickness.

Patients with long-standing IBD can develop thick collagen table.
59 year old woman with diarrhea and weight loss

Cecum biopsy

Lymphocytic Colitis - Clinical
- Described in 1989 (Lazenby et al.)
- Broad age range (mean 60-70 years)
- F=M
- Symptoms of LC more likely to be mild and to disappear (LC is a milder disease than CC)
**Lymphocytic Colitis - Proposed Causes**
- Idiopathic in 75%
- DRUGS (10%): Ranitidine, Cyclo 3 Fort, Ticlopidine, NSAIDs have been reported to cause lymphocytic colitis
- Strong association with celiac disease

**Lymphocytic Colitis**
- Surface epithelium damage with increased intraepithelial lymphocytes (CD3/CD8 positive)
  - More than 10 per 100 epithelial cells
- Superficial plasmacytosis
- Decreased goblet cells
- Crypt architecture unaltered or mild distortion
- The lamina propria has fewer eosinophils than in CC
- Neutrophils may be present

Lymphocytic colitis: superficial plasmacytosis and increased intraepithelial lymphocytes
Increased intraepithelial lymphocytes but no significant lamina propria inflammation (sometimes reported as paucicellular lymphocytic colitis)
- Resolving infectious colitis
- Brainerd diarrhea
- Crohn’s disease, CVID, immune diseases, drugs, IBS

Paucicellular lymphocytic colitis

Diversion Colitis - Mimic of IBD
- Diversion colitis develops in the bypassed or surgically isolated segments of the colon
Diversion Colitis - Clinical

- Often asymptomatic
- May present with mucoid/bloody discharge or abdominal pain
- Occurs 3 to 36 months following bypass and completely regresses within 3 months of reestablishment of the fecal stream
- Prognosis is excellent

Diversion Colitis - Pathogenesis

- A deficiency of short-chain fatty acids
- Short-chain fatty acids are the main source of energy for colonocytes
- The lack of colonocyte nutrition leads to an inflammatory reaction
- The inflammation can be reversed by giving short-chain fatty acids via enemas several times a week, or by reestablishing the fecal stream

Diversion Colitis

- Grossly apparent nodularity, which corresponds to large lymphoid aggregates with prominent germinal centers
- Chronic inflammation of the lamina propria
- Patchy cryptitis may be present
- It is imperative that the pathologist knows that he/she is looking at material from a diverted segment of colon
Diversionitis: mucosal erosion, reactive lymphoid hyperplasia and crypt distortion

Diversion Colitis

Diverticular Disease-Associated (Segmental) Colitis

- Chronic active colitis limited to area with diverticulosis
- Restricted to the mucosa
- Pathogenesis is unknown
- It is not a diverticulitis
Hematochezia and cramping abdominal pain.
Colonoscopic evaluation reveals patchy or confluent hyperemia, often accentuated on the crests of mucosal folds
Rectal sparing

Lymphoplasmacytic inflammation in the lamina propria
Basal lymphoid aggregates
Acute cryptitis
Crypt abscesses
Distorted crypt architecture
Paneth cell metaplasia
Diverticular disease-associated colitis

Iatrogenic Colitis
- Radiation colitis
- NSAIDs-induced injury
- Mycophenolate-associated colitis

Radiation Colitis/Proctitis
- Acute
- Chronic
  - Hyalinization of the lamina propria
  - Crypt architecture disarray
  - Cytologic atypia, but low N/C ratio
  - Atypical fibroblasts
  - Dilated vessels parallel to epithelial surface
Acute radiation colitis: erosion, lamina propria hemorrhage, mucin depletion

Radiation atypia

Chronic radiation colitis: crypt distortion, gland atrophy, hyalinized lamina propria, telangectasia
Radiation colitis: atypical fibroblasts

- May be associated with focal active colitis/ileitis or ulcers throughout the colon
- Abrupt ulcers with no significant inflammation in the adjacent mucosa
- Circumferential strictures
- Submucosal fibrosis
- Associated with microscopic colitis

**NSAIDs-Induced Injury**

- May be associated with focal active colitis/ileitis or ulcers throughout the colon
- Abrupt ulcers with no significant inflammation in the adjacent mucosa
- Circumferential strictures
- Submucosal fibrosis
- Associated with microscopic colitis

**Case**

- 50 year old woman with watery diarrhea who is status post renal transplant
Drug inhibits the de novo pathway of purine synthesis, leading to enterocyte injury
- Chronic watery diarrhea
- Increased apoptosis
- Crypt disarray
- Crypt dropout
- Mild inflammation