Biopsy Evaluation of Non-Neoplastic Diseases of the Large Bowel: an algorithmic approach

Laura W. Lamps, MD
Godfrey D. Stobbe Professor and Director of Gastrointestinal Pathology

Medical (lung, GI, liver, kidney, skin) pathology has different challenges from tumor pathology.

- Nonspecific by definition
  - Infinite variety of insults cause finite variety of tissue reactions
    - Cirrhosis
    - Interstitial fibrosis
    - Lichenoid dermatitis
    - Villous blunting

Biopsy Diagnosis of Colitis
Clinically Relevant Diagnosis vs. Description

- 68% of biopsy specimens obtained for non-neoplastic colonic disease showed an abnormal inflammatory process
- 75% of these could be classified into specific types of colitis based on morphology + available clinical data
- BUT, 59% were originally given only descriptive diagnoses; reclassified upon review

Biopsy Diagnosis of Colitis
Clinically Relevant Diagnosis vs. Description

<table>
<thead>
<tr>
<th>Description</th>
<th>Clinically Relevant Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammation</td>
<td>Active colitis, suggestive of acute infectious-type colitis</td>
</tr>
<tr>
<td>Chronic nonspecific inflammation</td>
<td>Chronic, active colitis, consistent with.....</td>
</tr>
<tr>
<td>Unspecified colitis, acute/subacute, etiology undetermined</td>
<td>Histologic changes consistent with ischemia</td>
</tr>
</tbody>
</table>

Components of a useful “medical” colitis report

- Diagnosis or at least useful description
  - Normal vs. inflamed
  - Chronic or not
- Description
  - They like to know what we see
- Avoid “clinical correlation required”
- Comment/implications
  - Even if there is no specific diagnosis, it’s helpful to give them a category of disease, a differential, and something to do

General Evaluation of Intestinal Mucosal Biopsies:
the question oriented approach
(made easier by the advent of widely accessible EMRs)

- Why was the biopsy done?
- What are the nature and duration of the patient’s symptoms?
- From EXACTLY where was the biopsy taken?
- What were the endoscopic findings?
Fear not the normal biopsy!

“One of the most common complaints that endoscopists have...is that pathologists label all cases ‘mild chronic inflammation.’ The intestinal tract...is constantly bombarded with antigenic stimulation, and thus always contains mild chronic inflammation. The real question is, ‘is enough inflammation seen to explain the patient’s symptoms?’”


<table>
<thead>
<tr>
<th>General Classification of Inflammatory Disorders of the Colon</th>
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<tbody>
<tr>
<td><strong>Chronic Idiopathic IBD</strong></td>
</tr>
<tr>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>Crohn’s</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
</tr>
<tr>
<td><strong>Motor Disorders</strong></td>
</tr>
<tr>
<td>Diverticulitis</td>
</tr>
<tr>
<td>Prolapse/SRUS</td>
</tr>
<tr>
<td><strong>Ischemia</strong></td>
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<tr>
<td><strong>Iatrogenic</strong></td>
</tr>
<tr>
<td>Drug associated</td>
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<tr>
<td>Radiation</td>
</tr>
<tr>
<td>Diversion colitis</td>
</tr>
<tr>
<td>GVHD</td>
</tr>
<tr>
<td>Neutropenic colitis</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Collagenous colitis</td>
</tr>
<tr>
<td>Lymphocytic colitis</td>
</tr>
<tr>
<td>Eosinophilic colitis</td>
</tr>
<tr>
<td>Diverticular-disease associated colitis</td>
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<th><strong>Colitis</strong></th>
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<tbody>
<tr>
<td><strong>CHRONICITY</strong></td>
</tr>
<tr>
<td>Architectural distortion</td>
</tr>
<tr>
<td>Basal plasmacytosis</td>
</tr>
<tr>
<td>Left sided Paneth cells</td>
</tr>
<tr>
<td>Pyloric metaplasia</td>
</tr>
<tr>
<td>“Variant” chronic colitides</td>
</tr>
</tbody>
</table>

Infection
NSAID
Ranney-Colitis
Crohn’s UC

Ischemia
NSAID
FAC
ALLC

Infection
NSAID
Diverticular-disease associated colitis

Drug associated
Radiation
Diversion colitis
GVHD
Neutropenic colitis
Collagenous colitis
Lymphocytic colitis
Eosinophilic colitis
Diverticular-disease associated colitis

Collagenous colitis
Lymphocytic colitis
Eosinophilic colitis
Diverticular-disease associated colitis
30 year old man with sudden onset of bloody diarrhea right colon biopsies.

**Focal Active Colitis**

Often has:
- Lamina propria neutrophils
- Focal cryptitis
- Surface injury

Should not have:
- Architectural distortion
- Basal plasmacytosis
- Paneth cell metaplasia (left)
Implications of FAC

- Infection
- NSAID
- Nothing
- Occasionally Crohn’s (less than 10% in adults; around 30% in kids)


Remember the bowel prep artifacts!

- Aphthous ulcers
- Cryptitis
- Superficial hemorrhage
- Apoptotic debris at surface

Courtesy Dr. Joel Greenson
Are there any snakes like this one in Florida?
43 year old male, 3 month history of diarrhea, crampy abdominal pain; left colon and rectosigmoid bx

Chronic idiopathic inflammatory bowel disease: UC vs. Crohn’s

Clinical info
Imaging
Macroscopic findings
Pathologic features

Ulcerative colitis

Crohn’s disease

Classic Features of Untreated Ulcerative Colitis and Crohn’s Disease

**Ulcerative colitis**
- Diffuse continuous disease
- Rectal involvement
- Disease worse distally
- Usually limited to mucosa
- Ileum spared (except backwash)
- If granulomas, associated with ruptured crypts

**Crohn’s disease**
- Segmental disease +/- upper tract involvement
- Variable severity
- Transmural lymphoid aggregates, other mural changes
- Granulomas
- Pyloric metaplasia
- Perianal disease
Crohn’s disease—note submucosal infiltrate.
Important Clinical/Endoscopic Information

- insuffcient clinical/radiographic info is most common cause of error in the Crohn’s vs. UC scenario

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Family hx, PSC, symptoms/signs, serology, prior surgery, perianal disease</th>
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<tr>
<td>Radiologic</td>
<td>Segmental vs diffuse, SB involvement, strictures, fistulas, wall thickness</td>
</tr>
<tr>
<td>Endoscopic</td>
<td>Type/appearance of ulcers, distribution of disease, appearance of ileum</td>
</tr>
<tr>
<td>Pathologic</td>
<td>Prior biopsies (and resections), ideally pre-treatment</td>
</tr>
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Ulcerative Colitis Variants (things we used to call Crohn’s Disease)

- Patchy Distribution
  - Left sided UC with peri-appendiceal disease (the cecal 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
- Upper tract involvement
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

Crohn’s Disease
Can you diagnose it in biopsies?

- Small bowel ulcers/erosions
  - NSAIDs, Ischemia

- Pyloric gland metaplasia
  - NSAIDs

- Patchy or focal distribution
  - UC, especially after treatment

- Granulomas
  - Not due to mucin, TB, Yersinia

UC vs. Crohn’s on biopsy: how far can you go?

- Depending on quality of other information, may get to UC or CD
- If not, if you can get to CIBD, then the drugs are the same
  - Most cases of indeterminate disease end up acting like UC, and do well treated as such
  - Don’t use “indeterminate colitis” as a disease entity
**Indeterminate Colitis**

- Not a distinct entity/disease
  - No diagnostic criteria
- Should be regarded an interim diagnosis
- “CIIBD, unclassified” or a comment is preferred

**A few words about dysplasia: current management**

- **Polypoid adenoma in noncolitic mucosa: sporadic**
- **Flat/invisible dysplasia in colitic mucosa:**
  - High grade: colectomy
  - Low grade: surveillance vs. colectomy
- **Polypoid adenoma in colitic mucosa: endoscopic resection and sampling of flat mucosa**
- **These things get a colectomy:**
  - Unresectable lesions
  - HGD in flat mucosa
  - Extra CRC risk factors


**Polypoid LGD: Looks like adenoma**
Mucin may be columnar rather than well-formed goblet cells.

UC: polypoid LGD

Flat LGD: well delineated from surrounding mucosa.

Flat LGD: looks like adenoma, loss of goblet cells, delineated from surrounding mucosa, changes extend to surface.
LGD: apoptotic cells, dystrophic goblet cells, most nuclei within lower half of epithelium

Even with inflammation, the architecture is too complex to explain as reactive.

UC: HGD

Loss of nuclear polarity, dystrophic goblet cells, apoptotic cells.
Definitely dysplastic—but what grade?

My approach to "indefinite for dysplasia"

- "You can’t put it back"
- Be wary of markedly inflamed and/or fragmented specimens
- Be wary of biopsies where all of the pieces look atypical
- Be wary of biopsies from the edges of frank ulcers
- Most people regard serrated lesions as indefinite, at least for now

Indefinite—I’m worried, but there is too much inflammation
Indefinite: very inflamed, only one crypt, fragmented specimen

Negative for dysplasia

Crohn's disease-negative for dysplasia
This lecture has worn me out. When will be done?

The “Atypical” or Variant Colitides

- Heterogeneous group of colitides
  - NOT UC or Crohn’s
- Often lack systemic symptoms
- Often lack definite laboratory abnormalities
- Often included are:
  - Collagenous colitis
  - Lymphocytic colitis
  - Diversion colitis
  - Diverticular disease-related segmental colitis
65 year old man with diarrhea, crampy abdominal pain; sigmoid biopsies

**Diverticular-Disease Associated Segmental Colitis**

- Primarily elderly patients
- Hematochezia, mucus, cramps
- Colonoscopy:
  - Patchy or confluent hyperemia
    - Accentuated on crests of mucosal folds
  - Mucosal granularity
  - Distribution
    - Descending colon and sigmoid, in area of tics
    - Rectum is virtually always spared!
Mucosal lymphoid aggregates are common
Note architectural distortion and crypt abscesses

Architectural distortion, crypt abscesses, and basal lymphoid aggregates in DDASC
**Diverticular-Disease Associated Colitis-Differential Diagnosis**

- Crohn’s
  - Involvement of other segments of bowel (upper and lower)
  - Gross features
- Ulcerative colitis
  - Contiguous disease with rectal involvement
- DDASC
  - Patients have diverticula
  - Colitis limited to segment of bowel with tics
  - Rectum spared

**Diversion Colitis**

- Found in segments of bowel diverted from the fecal stream
  - Eventually occurs in almost all diversions
- Cured by surgical reversal of diversion
- Symptoms occur with increasing duration of diversion:
  - Bloody/mucoid discharge
  - Abdominal pain
  - Tenesmus
Diversion Colitis

- Mimics IBD
- Need to know that it’s diverted, and need to know why they were diverted

It’s the Surgeon’s Fault!

Courtesy Dr. Nathan Lee
Prominent lymphoid follicles in diversion colitis

Aphthous ulcer overlying prominent lymphoid follicle in diversion colitis

Active inflammation and basal lymphocytosis
Cryptitis, crypt abscesses, and focal mild architectural distortion in DC

Differential Diagnosis

- Differential from Idiopathic IBD:
  - History of diversion!
  - Disease in remainder of bowel
  - Histology
    - Lack of significant architectural distortion
    - Milder inflammatory changes
    - May be very difficult if not impossible
  - Resolution of symptoms with surgical correction, fatty acid enemas
Drug and Chemical Related Colitis

Antibiotics
Chemotherapeutic agents
Gold
NSAIDS
Methyldopa
Flucytosine
Cellsept
(myophenolate)

Carbamazepine
Cimetidine
Retinoids
Detergents, etc:
Herbal remedies
Hydrogen peroxide
Sodium hydroxide
Alcohols
Formalin

NSAID-Associated Colitis

• May occur after only weeks of use
• Abdominal pain, cramping, bloody stool
• Commonly involves ileum but can be any area of colon
  – Mucosal erythema, friability, ulcers
  – Strictures/diaphragms
  – Massive bleeding, perforation
• Risk increases with patient age, duration of use, and use of other concomitant medications

NSAID-Associated Colitis
variable histology

• Patchy colitis with mixed inflammation, including neutrophils
• Intraepithelial lymphocytes
• Superficial erosions
• Regenerative mucosal changes
• May be focal architectural disarray but not well-developed distortion
Mycophenolate mofetil (Cellcept)

- Maintenance immunosuppression, primarily in solid organ transplants
- Most common side effect is GI toxicity (diarrhea)
- Mimics GVHD, CIIBD
- GI toxicity does not appear to be dose-dependent
  - More severe if drug started later in the course
  - More toxicity with higher creatinine
Apoptotic colonocytes

Crypt abscesses

Significant architectural distortion may be present, mimicking CIIBD
Enterocolitis due to Immunotherapy

Ipilimumab (CTLA-4 for melanoma)
Pembrolizumab (anti-PD-1, everything)
Nivolumab (anti-PD-1, everything)
Idelalisib (CLL and follicular lymphoma)
Dasatinib (Tyrosine kinase for CML)

Immunotherapy-associated colitis

Ipilimumab can cause skin, GI, liver and endocrine toxicities. GI often takes 5-10 weeks to develop.
Up to 1/3 of patients have diarrhea
Combo with anti-PD-1 increases odds of diarrhea to 44%
1% with life threatening perforations
Typically involves colon, but small bowel and stomach can also be affected.
Responds to steroids and infliximab

Immunotherapy colitis

Pathological Features

- Ipilimumab colitis shows both neutrophilic and lymphocytic crypt injury
  - Cryptitis and crypt abscesses
  - Base of crypts with lymphocytic and apoptotic injury resembling autoimmune enterocolitis.
  - May mimic IBD
- Anti-PD-1 drugs seem to cause milder damage with two distinct patterns:
  - Active colitis with apoptosis
  - Lymphocytic colitis
What about “microscopic colitis?”

- The presence of histologic abnormalities in the context of an unremarkable colonoscopic examination (“microscopic” disease).
- Don’t use “microscopic colitis” as diagnosis
  - Collagenous colitis
  - Lymphocytic colitis
- Both patterns associated with olmesartan
What about “microscopic colitis?”

- You need:
  - History of long-term chronic watery diarrhea
  - Appropriate histology
  - Normal colonoscopy

If any of these don’t fit, back off the diagnosis!!

Collagenous Colitis

- Chronic, watery diarrhea
  - Often lasts for years
- Crampy abdominal pain
- Normal colonoscopy and radiographs
- Primarily a disease of middle aged women
  - Male:female ratio 9-20:1
- Often coexistent autoimmune disorder
  - ?association with NSAIDS
Collagenous Colitis
Histology

- **Collagen**
  - Thickened subepithelial collagen band
    - No numerical cutoff!
    - May abate with treatment
  - Variable, shaggy, with entrapped capillaries

- **Colitis**
  - Intraepithelial lymphocytosis
  - Increased mixed LP inflammatory infiltrate
    - Neutrophils should be rare
  - Surface epithelial damage

Yield of Biopsy Specimens Diagnostic of Collagenous Colitis

70%
83%
78%
66%

From: Offner et al, Hum Pathol 30:451-7

Courtesy Dr. Joel Greenson
Collagenous Colitis
Diagnostic Pitfalls

- Failure to consider inflammatory component
- Sole reliance on numerical quantitation of collagen band
- Misinterpretation of normal structures or other types of fibrosis
  - Tangential orientation
  - Hyperplastic polyps
  - Fibrosis of ischemia, Crohn’s
- Site within colon

Lymphocytic Colitis

- Symptoms are similar to collagenous colitis
- Unremarkable colonoscopy
- Equal male to female distribution

Lymphocytic Colitis

Histology

- Increased intraepithelial lymphocytosis
  - Usually greater than 10/100 enterocytes
  - Surface and crypts involved
- Surface epithelial damage
- Increased LP inflammatory component
  - Plasma cells common; neutrophils should be rare
- No abnormal subepithelial collagen band
Other things that cause a lymphocytosis:

- NSAIDs, Olmesartan, checkpoint inhibitors
- Viral enterocolitis
- Crohn’s
- Resolving bacterial infection
- Celiac Disease
  - 15% of LC patients have Celiac disease.
  - 5-31% of Celiac patients have LC/CC and up to 67% of refractory sprue patients have LC

Collagenous vs. Lymphocytic Colitis

- **Similarities:**
  - Watery diarrhea
  - Mean age at dx
  - Normal colonoscopy
  - Intraepithelial lymphocytosis

- **Differences:**
  - Female to male ratio
  - HLA antigens
  - Increased subepithelial collagen
  - Autoantibodies

Alys ponders the diagnostic nuances of inflammatory bowel disease.

Components of a useful “medical” intestinal biopsy report

- **Diagnosis**
  - Normal vs. inflamed
  - Chronic or not
  - How active is it

- **Description**
  - They like to know what we see

- **Comment/implications**
  - Even if there is no specific diagnosis, we need to give them a category and something to do

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**Report**

- Colon, right, bx: Focal active colitis; sc

**Comment:**

- Description
- There are no features of chronicity
- These features are most commonly seen with self-limited processes such as infection, adverse drug reaction; can recommend drug history, infectious workup
Colon, left, bx: Chronic, active colitis

Comment:
- Description, emphasizing chronicity
- Features compatible with _____ type of CIIBD, depending on clinical/colonoscopic information
- Dysplasia designation

• Colon, left, bx: Chronic, active colitis; see comment
  - Give description
  - Note that per endoscopist colitis is present only in region of tics
  - Consistent with DDASC

Let's go grill!