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

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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>
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</tbody>
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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?"*


General Classification of Inflammatory Disorders of the Colon

- **Chronic Idiopathic IBD**
  - Ulcerative colitis
  - Crohn’s
- **Infectious**
- **Motor Disorders**
  - Diverticulitis
  - Prolapse/SRUS
- **Ischemia**

- **Iatrogenic**
  - Drug associated
  - Radiation
  - Diversion colitis
  - GVHD
  - Neutropenic colitis

- **Other**
  - Collagenous colitis
  - Lymphocytic colitis
  - Eosinophilic colitis
  - Diverticular-disease associated colitis

![Diagram of Chronic colitides](ASLC_AITC_FAC_CIBD)

**CHRONICITY**
- Architectural distortion
- Basal plasmacytosis
- Left sided Paneth cells
- Pyloric metaplasia

**Variant** chronic colitides
- Tic-associated segmental colitis
- Diversion colitis
- Lymphocytic colitis
- Collagenous colitis

**ASLC**
- Infection
  - NSAID
- Rarely Crohn’s

**AITC**
- Infection
  - NSAID
- Rarely Crohn’s

**FAC**
- Infection
  - NSAID

**CIBD**
- Crohn’s
- UC
The “Atypical” or Variant Colitides

- Heterogeneous group of colitides
  - NOT UC or Crohn’s
- Often lack constitutional symptoms
- Often lack definite laboratory abnormalities
- Often included are:
  - Collagenous colitis
  - Lymphocytic colitis
  - Diversion colitis
  - Diverticular disease-related segmental colitis

30 year old man with sudden onset of bloody diarrhea - right colon bx

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!

- Apthous ulcers
- Cryptitis
- Superficial hemorrhage
- Apoptotic debris at surface
Are there any snakes like this one in Pennsylvania?

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

Crohn’s disease - note submucosal infiltrate
Crohn's disease
Pyloric-type metaplasia
Only if you’ve been living right…

Important Clinical/Endoscopic Information

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

Clinical
• Family hx, PSC, symptoms/signs, serology, prior surgery, perianal disease

Radiologic
• Segmental vs diffuse, SB involvement, strictures, fistulas, wall thickness

Endoscopic
• Type/appearance of ulcers, distribution of disease, appearance of ileum

Pathologic
• Prior biopsies (and resections), ideally pre-treatment

Courtesy Dr. Rob Odze

Indeterminate Colitis

• Not a distinct entity/disease
  – No diagnostic criteria

• Should be regarded an interim diagnosis

• “CIIBD, unclassified” or a comment is preferred
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 CIIBD, 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

This lecture has worn me out. When is the break?

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!

Diverticular-Disease Associated Colitis - Histology

- Mimics chronic idiopathic inflammatory bowel disease:
  - Cryptitis and crypt abscesses
  - Increased LP mixed inflammatory infiltrate
    - Often basal plasmacytosis
  - Crypt distortion (mimics CIIBD)
  - Granulomas (Crohn’s-like variant)
  - Ulceration
Mucosal lymphoid aggregates are common in DDASC.

Cryptitis in DDASC.

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

Diversion Colitis

Histology

- Aphthous ulcers
- Prominent lymphoid follicles
- Increased inflammation in lamina propria
  - Including neutrophils; granulomas rare
- Cryptitis and crypt abscesses
- Crypt architecture usually preserved
Prominent lymphoid follicles in diversion colitis

Aphthous ulcer overlying prominent lymphoid follicle in diversion colitis

Courtesy Dr. Nathan Lee
Cryptitis, crypt abscesses, and focal mild architectural distortion in DC.
Diversion Colitis
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
• Methyl dopa
• Flucytosine
• Cellsept (mycophenolate)
• 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 true distortion
- Ddx: Crohn’s, infection, other drug reactions
Mycophenolate mofetil (Cellsept)

- 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

Mycophenolate mofetil
Microscopic Features

- Prominent apoptosis
- Crypt atrophy/dropout
- Crypt distortion
- Dilated crypts with neutrophils, eosinophils
  - Marked neutrophilic activity, diffuse mixed inflammation usually absent
Mycophenolate toxicity

Significant architectural distortion may be present, mimicking CIIBD

Iplimumab colitis
Infectious mimics of chronic idiopathic inflammatory bowel disease

- Yersinia
- Aeromonas
- Shigella
- Salmonella
- CMV
- Amoebiasis
Yersinia species
Infections superimposed on CIIBD

- CMV
- *C. difficile*
- Food-borne enterics

*Aeromonas:* common food and water-borne pathogen
Utility of CMV Stains in Evaluation of Biopsies from UC Flares

• Kambham et al, AJSP 2004
  – Case control study of UC patient with refractory disease
  – 25% of patients with refractory UC had CMV inclusions on immunostain
  – 60% of these had been missed on H&E
  – Recommend using CMV IHC in evaluation of biopsies in these patients

CMV commonly superinfects both Crohn’s disease and UC patients
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

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
- Viral enterocolitis
- Crohn’s
- Resolving bacterial infection
Lymphocytic Colitis
Diagnostic Pitfalls

• Failure to integrate with clinical and endoscopic data
• Other entities featuring colonic epithelial lymphocytosis:
  – Drug-related colitis (especially NSAID)
  – Celiac disease
  – Crohn’s disease
  – Infectious diarrhea (Brainerd diarrhea)
  – Resolving bacterial infection

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.
How to stay out of trouble

- Find out history
- Know macroscopic findings (e.g., if colitis limited to segment with diverticula or bx from diverted segment)
- Be aware of drugs and infections that mimic CIIBD

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

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
Report

- Colon, left, bx: Chronic, active colitis
- Comment:
  - Description, emphasizing chronicity
  - Features compatible with _____ type of CIIBD, depending on clinical/colonoscopic information
  - Dysplasia designation

Report

- 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

Colitis-unacceptable reporting

- “cryptitis” with no comment
- Chronic inflammation
- Acute inflammation
- “moderate colitis”
- “colitis with a few erosions”
- Not giving a category of disease, and/or recommendations
Let's go grill!