The Pathology of Inflammatory Bowel Disease

Objectives

- Normal colon
- Pathology of IBD
  - Mimics of IBD
  - Indeterminate colitis
- Dysplasia

Anatomy of colon

Normal colonic mucosa
Normal colonic mucosa--
Site and inflammatory cells

Left colon  Right colon

Normal colonic mucosa--
Site and Paneth cells

• Inflammatory cells: right > left, surface > base
• Paneth cells: cecum to hepatic flexure
  The presence of Paneth cells beyond the hepatic flexure is considered a sign of chronic injury
• Slight crypt irregularity in rectum

Endoscopic preparations--
effect or noise

• Hypertonic enema: edema and hemorrhage in lamina propria, damage to surface epithelium
• Oral sodium phosphate solution: apoptosis, neutrophils on surface epithelium, active cryptitis (“focal active colitis”), aphthoid ulcer
Normal colonic mucosa

- Inflammatory cells: right > left, surface > base
- Paneth cells: cecum to hepatic flexure
  
  The presence of Paneth cells after hepatic flexure is considered a sign of chronic injury
- Slight crypt irregularity in rectum
- Effect due to bowel preparation

--The most difficult dx to make in colorectal bx is normal or no significant abnormality.
--Avoid “nonspecific chronic colitis”

Interpretation of GI pathology

- Limited reaction patterns of GI tract to insults: morphologic pattern versus specific disease
- Clinical-pathologic correlation essential

Interpretation of GI pathology

- Include relevant clinical and endoscopic information
- Submit different sites separately
  
  inflammation in LP, Paneth cells, small focus of dysplasia/cancer
- Label the specimen site (site versus cm)

Multiple biopsies in one specimen-- potential pitfall
Pathology of IBDs--chronic active colitis

- Two morphologic expressions
  - Chronicity: essential for diagnosis
  - Activity

Acute self-limited colitis versus IBD

- ASLC: lacks crypt architectural changes
- UC: shows crypt architectural changes

Chronic active colitis

- Architectural distortion
- Metaplasia
- Inflammation
- Stromal changes

Chronic active colitis

- Architectural distortion
  1. Variation in crypt size, shape, and orientation (crypt branching)
  2. Crypt shortening and dropout (mucosal atrophy)
  2. Villous blunting in small intestine
Chronic active colitis

• Metaplasia
  1. Paneth cell metaplasia: after hepatic flexure
  2. Gastric pyloric metaplasia

• Inflammation
  1. Basal plasma cells
  2. Granulomas in Crohn’s

• Stromal changes
  1. Hyperplasia of m. mucosae and submucosal nerves
  2. Fibrosis of submucosa

• Neutrophilic epithelial damage
  1. Cryptitis & crypt abscess
  2. Neutrophils in LP
  3. Ulceration
Distinguishing gross features for IBDs

<table>
<thead>
<tr>
<th>Feature</th>
<th>Ulcerative colitis (UC)</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal involvement</td>
<td>Yes</td>
<td>Variable</td>
</tr>
<tr>
<td>Isolated R-sided</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Distribution</td>
<td>Diffuse</td>
<td>Focal or diffuse</td>
</tr>
<tr>
<td>Upper GI involvement</td>
<td>No</td>
<td>Common</td>
</tr>
<tr>
<td>Fistulas</td>
<td>No</td>
<td>Occasional</td>
</tr>
<tr>
<td>Thickened bowel wall</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Stricture</td>
<td>Rare</td>
<td>Occasional</td>
</tr>
<tr>
<td>“Creeping” serosal fat</td>
<td>No</td>
<td>Frequent</td>
</tr>
</tbody>
</table>
**Microscopic features for IBDs**

<table>
<thead>
<tr>
<th></th>
<th>UC</th>
<th>Crohn’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation confined to mucosa &amp; submucosa</td>
<td>Yes</td>
<td>Usually no</td>
</tr>
<tr>
<td>Transmural inflammation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fissuring ulcers</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Fistulas</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Granulomas</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Submucosal fibrosis</td>
<td>Occasional</td>
<td>Common</td>
</tr>
<tr>
<td>Distribution of inflammation</td>
<td>Diffuse</td>
<td>Focal or diffuse</td>
</tr>
<tr>
<td>in mucosal specimens</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pathology of ulcerative & Crohn’s colitis**

Ulcereative colitis

Crohn’s colitis

**Granulomas in Crohn’s**

- Only in ~1/3 of mucosal bx
- Earlier in the disease
- More frequent in younger pts
- More common & numerous in colon than in small bowel
- ? A marker of more aggressive disease with more areas of involvement and more frequent recurrences

Granulomatous rxn around inflamed/damaged crypts: not specific, may be seen in classic UC

**Crohn’s disease**

- Villous blunting
- Gastric metaplasia
- Hypertrophy of m.m.
- Submucosal fibrosis
- Transmural inflammation
Crohn’s disease

- Focal active colitis without crypt architectural distortion or granulomas: common in bx of Crohn’s disease
- Dx of Crohn’s disease limited to colon and without granulomas: almost impossible based on bx alone

(Focal) active colitis-- ddx

- Infection (acute self-limited colitis)
- NSAID use
- Incidental (including bowel preparation)
- Ischemia
- Crohn’s disease

Variants of ulcerative colitis

- May be patchy or focal
- Granulomatous rxn associated with ruptured crypts
- Mural changes
  -- thickening and/or scar of m. mucosae
  -- submucosal fibrosis
  -- transmural inflammation below deep ulcers
- Rectal sparing
- Backwash ileitis
- Upper GI involvement

Mimicry of IBD on mucosal bx--
Chronic active colitis pattern

- Chronic infection
- Diverticulosis
- Chronic NSAID use
- Endometriosis
- Underlying colorectal mass (lymphoma, primary or metastatic ca)
- Chronic ischemia (including serosal adhesions)

Importance of clinical-pathologic correlation
Indeterminate colitis—a pathologist’s perspective

- A preliminary descriptive term when a definite dx of UC or Crohn’s disease cannot be established
- Prevalence: 1-20% (average 5%)
- No characteristic histologic features
- ? Not a distinct disease entity
- Dx based on thorough examination of a resection specimen, not on mucosal biopsies

Indeterminate colitis—pathologic features

- Fulminant UC
- Insufficient clinical, radiologic and pathologic information
- Attempt to distinguish UC or Crohn’s on mucosal bx
- Failure to recognize unusual variants of UC
- Confusion of backwash ileitis in UC as ileal involvement in Crohn’s
- Failure to use “hard” criteria (granulomas, transmural inflammation) as Crohn’s
- Other forms of colitis: chronic ischemic or infectious colitis


Colon cancer arising in IBD

Who will develop CRC?
Risk factors for CRC in IBDs

- Clinical disease duration
- PSC
- age of onset
- anatomic extent
- family history of CRC
- degree of activity
- Dysplasia: best marker

Dysplasia in IBD-- gross features

- Flat
- Raised adenoma-like
  DALM
- Unifocal
- Multifocal

Dysplasia in IBD

- Unequivocal neoplastic process, precursor of carcinoma
- Standard classification scheme
  - Negative for dysplasia
  - Indefinite for dysplasia
  - Positive for dysplasia
    Low-grade dysplasia (LGD)
    High-grade dysplasia (HGD)

**Dysplasia in IBD**

- Distinction between reparative and dysplastic change can be difficult

**Can pathologists reliably assess dysplasia?**

- Inter-observer agreement in grading dysplasia
  - HG dysplasia/carcinoma: substantial ($\kappa = 0.65$)
  - Negative: moderate to substantial ($\kappa = 0.58$)
  - LG dysplasia: fair ($\kappa = 0.32$)
  - Indefinite: slight ($\kappa = 0.15$)


**Diagnosis of dysplasia in IBD**

- Adjunct objective tests
- Flow cytometry for DNA aneuploidy
- Molecular markers by IHC
  - p53, racemase
- Digital image analysis

Low sensitivity and specificity
Not clinically validated

Diagnosis of dysplasia should be confirmed by an expert gastrointestinal pathologist.

**Can pathologists distinguish colitis-associated dysplasia from sporadic adenomas?**

- No pathologic features to reliably separate the two
**Distinction between colitis-associated dysplasia and sporadic adenomas?**

- Pathologic features: not reliable
- Molecular genetic markers?
- Clinical features
- Endoscopic appearance: most important

**Evaluation of dysplasia in IBD**

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IBD
   Flat dysplasia
       Adenoma-like
           Outside colitis
               Sporadic adenoma (SA)
       Non adenoma-like
           Inside colitis
               DALM
```

**Colon biopsy--**

**Dx: Adenomatous/LG dysplastic lesion; see note.**

- 70 y/o
- IBD 2 yrs
- Base & adjacent mucosa: no dysplasia, no colitis

- Likely SA

**Colon biopsy--**

**Dx: Adenomatous/LG dysplastic lesion; see note.**

- 70 y/o
- IBD 2 yrs
- Base & adjacent mucosa: no dysplasia, no colitis

- Likely SA

- 35 y/o
- IBD 15 yrs
- Base or adjacent mucosa: positive for dysplasia and chronic colitis

- Likely DALM
Conclusion I

- Pathology of IBD is characteristic but not specific
- Correlation with clinical and endoscopic findings is important
- Provide relevant information and specimen labeling
- Treatment may alter the “classic” pathology
- Review of prior biopsies and resection may be helpful
- A small percentage of IBD remains indeterminate

Conclusion II

- Interobserver agreement is poor in diagnosing LG dysplasia and indefinite for dysplasia
- Confirm difficult cases by an expert GI pathologist
- Use an integrated approach to evaluate raised dysplastic lesions in IBD
**Backwash ileitis**

- Diffuse process, contiguous from cecum, short distance
- Mucosal-based, no chronic changes

**Colitic dysplasia vs. Sporadic adenoma**

- Younger age (<40)
- Longer duration of IBD
- Inside colitis
- Endoscopy: plaque-like or sessile
- Adjacent and remote mucosa: dysplastic

- Older age (>40)
- Shorter duration of IBD
- Outside colitis
- Endoscopy: polypoid adenoma-like
- Adjacent and remote mucosa: non-dysplastic