Diagnosis and Mimics of Inflammatory Bowel Disease

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Pathologist’s role in IBD management

- Establishing chronicity in mucosal biopsies
- Distinguishing IBD from mimics
- Distinguishing UC from CD
- Excluding infection in IBD flares
- Distinguishing pouchitis from Crohn’s disease
- Diagnose and grade dysplasia (adenoma/DALM)
### Morphologic Features of Chronicity in mucosal biopsies

**Architectural:**
- Crypt disarray
- Crypt branching
- Crypt shortening
- Villiform transformation of colonic surface epithelium

**Inflammatory:**
- Basal lymphoid plasmacytosis
- Granulomas

**Metaplastic:**
- Paneth cell metaplasia in left colon biopsies
- Pyloric gland metaplasia
Architectural Features of IBD

Crypt Disarray & Atrophy.
Crypt branching and shortening.
Villiform mucosal surface.
Inflammatory features of IBD

Cryptitis / crypt abscesses.

**Basal lymphoplasmacytosis**, Epithelioid granulomas.
Metaplastic Epithelial Changes (Paneth cell; Pyloric gland)
Architectural Features of Chronic Ileitis
Chronic Ileitis does not always show crypt distortion
32 yr woman - 3 week history of intermittent bloody diarrhea.

“Active Colitis; no features of chronicity”
3 months later....

Early IBD can resemble infectious colitis
Common Errors at First Diagnosis

- ~5% of patients with a “diagnosis” of IBD do not have the disease!
- “Normal” in right and left colon is different:
  - Increased cellularity in lamina propria in cecum/right colon
  - Paneth cells abnormal in left colon
  - Crypt distortion often present in distal rectum
• Overdiagnosis of “chronic” colitis
  – Once chronic, always chronic is obsolete dogma
  – Diseased segments can become completely normal on treatment
  – UC and CD patients can also get an infectious colitis

• Clinical implications:
  – Perpetuate a false diagnosis
  – Give the patient a new site of disease
Focal active colitis may be a manifestation of IBD
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Differential diagnosis of IBD

- Infectious colitis: *Yersinia*, *C. difficile*, *Shigella*, *Salmonella*, *Entameba*
- Diverticular disease-associated colitis
- Diversion colitis
- Drugs: mycophenolate, Ipilumimab, NSAID
- Chronic low grade ischemic injury
- Radiation colitis
- Severe GVHD
- Isolated asymptomatic ileitis and colitis
Establishing chronicity in mucosal biopsies
• Distinguishing IBD from mimics
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• Diagnose and grade dysplasia (adenoma/DALM)
<table>
<thead>
<tr>
<th>FEATURE</th>
<th>EXCEPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confined to mucosa</td>
<td>Fulminant U.C., fissuring ulcer</td>
</tr>
<tr>
<td>Confined to colon</td>
<td>Backwash Ileitis, Upper GI</td>
</tr>
<tr>
<td>Continuous involvement</td>
<td>Cecal patch, Fulminant U.C., treatment effect</td>
</tr>
<tr>
<td>Rectal Involvement</td>
<td>Children, ASA/Steroid enema</td>
</tr>
<tr>
<td>No granulomas</td>
<td>Crypt rupture reaction</td>
</tr>
</tbody>
</table>
Variants of Ulcerative Colitis
(Often misdiagnosed as Crohn’s colitis)

- Patchy Distribution (Skip Lesions)
  - Left sided UC w/ right sided patches of mucosal hyperemia / friability (cecum; appendiceal orifice)
  - Post-therapy patchy response
  - Initial presentation in children
Cecal Patch in Ulcerative Colitis

Up to 75% of pts w/ left sided colitis (microscopically)
Variants of Ulcerative Colitis
(Often misdiagnosed as Crohn’s colitis)

- **Rectal Sparing**
  - Effect of therapy (Oral or topical; i.e., steroid enemas)
    - Up to 40% of treated patients
  - Pediatric presentation
    - Absolute rectal sparing: 3-4%
  - Rare Adult cases can present with a normal rectum
    - Relative rectal sparing: up to 30% in ones series
    - Absolute rectal sparing: 1-2%
  - Burn-out in long-standing disease
Endoscopic and/or histologic patchiness in patients with UC 38% of pts.; 11% of sequential of biopsies.
Children (<10yrs): relative rectal sparing
(patchiness 4%, rectal sparing 3%)

- Decreased inflammation at onset does not persist
- Older children (11-17): shift towards adult phenotype
Effect of medical therapy on histology

- Mixed Inflammation of the lamina propria +++
- Basal Lymphoid aggregate +++
- Basal plasmacytosis ++
- Crypt architectural abnormalities ++
- (Paneth cell metaplasia)
- (Villous surface)
Extra-Colonic Disease – As manifestation of UC

- **Gastritis**
  - Focally enhanced gastritis (FEG) thought originally to be typical of Crohn’s disease.
  - 2 studies found between 12% and 50% of UC patients had FEG (vs. 43% to 35% of CD patients).

- **Duodenitis**
  - Reports of diffuse duodenitis in pts w/ resection proven UC
    - Several of these patients also had gastritis
    - Pts tolerated endorectal pull-through procedures
Diffuse duodenitis in resection proven UC patient
• Patchy distribution is often seen once medical therapy is initiated.
  – review pre-treatment biopsies

• Rectal sparing can be seen.
  – longstanding disease; steroid enemas, and de novo UC (pediatric population)

• Skip lesions (cecal patch) can be seen.

• Extracolonic manifestations can be seen
  – Focal gastritis and diffuse duodenitis.
Distribution of CD

- Small intestine alone: 30–35%
- Small intestine and colon: 40–50%
- Colon alone: 20–25%
- Ileum/Right Colon
- Rectal sparing
- Anal/perianal disease
- All layers involved
- Discontinuous
- Fissures & fistulae
- Granulomas
The challenge of biopsy diagnoses
Terminal Ileum
Mucin granulomas in U.C.
Granulomatous gastritis
Focally enhanced gastritis (FEG)
Duodenal Involvement in Crohn’s Disease
Indeterminate colitis
(~ 5-10 % pts. with acute colitis).

- Proposed in the context of fulminant colitis. Cases w/ overlap between UC and CD (A. Price 1978)

- Features of UC or CD obscured by severe ulceration w/ superficial fissuring ulceration, transmural inflammation, and relative rectal sparing.

- Differential diagnosis
  - IBD w/ superinfection (Campylobacter, Salmonella, C. difficile, CMV)
  - Enteropathogenic bacteria
  - Amebic colitis
  - Ischemic and drug-related colitis

- Risk of pouchitis (if CD)
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Refractory Colitis or Superimposed Infection?

- **Severe disease flare:**
  - Superimposed infection complicating UC
  - Steroid Resistance (Needs colectomy)

- **Several pathogens have been implicated:**
  - CMV: 15-36%, benefit of therapy controversial
  - Enteric bacteria: 10% (*C. difficile* 5.5%, *Salmonella*, *Campylobacter*, *E. histolytica*, *P. shigeloides*, others)
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Ileal Pouch Anal Anastomosis (IPAA; J-pouch)

The diseased colon is removed while a portion of the rectum is left and is used to attach the J-pouch.

After loop is complete, a small opening is made in the lower portion.

The pouch is then sutured to the top of the anal canal.

After the end is closed a loop is formed from the ileum of the small intestine.

The short leg of the loop is attached to the ileum and an opening is created where the two are joined.
“Pouchitis”

• Symptoms similar to UC
  – 15% @ 1yr; 36% @ 5yr; 46% @ 10yrs

• How to rule out Crohn’s disease?
  – Biopsies above the pouch
  – Review previous bxs. or resection
  – Avoid using “ileitis” for pouch biopsies

• Responds to conservative management
  – Antibiotics
  – Topical mesalamine
  – Probiotics

• Pouch failure - excision
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Risk Factors for CRC in IBD

- Family history of CRC
- Primary sclerosing cholangitis (PSC)
- Extent of colitis:
  - Extensive or pancolitis: risk increases 8-10 yrs after onset of dx.
  - UC limited to rectum (proctitis): no increased risk of CRC.
- Severity of colitis

Risk increases w/ duration:
Incidence: 0.5 -1.0 % per yr
Peak of 15-20% at 30 yrs.
Risk higher if pancolitis develops in childhood

Colonoscopic Surveillance for Dysplasia in IBD

• Starts 8 yrs after dx of pan-colitis and after 12-15 yrs for left sided disease.
• Four bx at 10-cm intervals (right / transv. / desc. colon, sigmoid and rectum)
• Additional biopsies of any suspicious mucosal lesions
• 33 bxs. needed to detect dysplasia or cancer w/ 90% certainty
Effectiveness of Surveillance in IBD

3% of CRC and 11% of dysplasia found during initial colonoscopy

Choi et al, Gastroenterology 1993
Dysplasia in IBD.
Standardized classification w/ provisional clinical implications.
Riddell RH. Hum Pathol; 1983

Dysplasia distant to CRC:
74% of 50 colectomy (avg 27 blks)
92% of UC cases (76%LGD; 85% HGD)
27% to 100% of pts w/ Crohn colitis

- Negative for dysplasia
- Indefinite for dysplasia
- Low-grade dysplasia
- High-grade dysplasia
- Carcinoma
High-grade Dysplasia
DALM

- Single discrete polypoid or nodular mass
- Discrete plaque like lesion
  - Abnormal appearing mucosa
  - Raised irregular or nodular area
- Multiple polyps at a single site

- 112 pts (4 yrs FU)
- 12/112 pts w/ DALM
  - 58% carcinoma
- 27/112 pts w/ flat dysplasia
  - 4% carcinoma
- DALM=>>colectomy

Not all DALM are equal

Incidence of CRC in CUC-related DALM

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>% DALM</th>
<th>% DALM with Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blackstone, 1981</td>
<td>112</td>
<td>11%</td>
<td>58%</td>
</tr>
<tr>
<td>Rosenstock, 1985</td>
<td>240</td>
<td>5%</td>
<td>38%</td>
</tr>
<tr>
<td>Leonard-Jones, 1990</td>
<td>401</td>
<td>1.5%</td>
<td>83%</td>
</tr>
<tr>
<td>Butt, 1983</td>
<td>62</td>
<td>29%</td>
<td>83%</td>
</tr>
<tr>
<td>*Bernstein, 1994</td>
<td>1225</td>
<td>3.2%</td>
<td>43%</td>
</tr>
</tbody>
</table>

* Review of 10 studies

Varying definition; heterogenous gross types; bx vs resection; non standardized criteria for dysplasia
Macroscopic Subtypes of Dysplasia

Flat

Endoscopically Invisible

DALMs

Adenoma-like

Non-adenoma-like
### Progression of LGD to HGD or CA

<table>
<thead>
<tr>
<th>Study</th>
<th>Hospital</th>
<th>LGD (n)</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connell ('94)</td>
<td>St. Marks</td>
<td>9</td>
<td>54% @ 5 y</td>
</tr>
<tr>
<td>Ullman ('03)</td>
<td>Mount Sinai</td>
<td>46</td>
<td>53% @ 5 y</td>
</tr>
<tr>
<td>Ullman ('02)</td>
<td>Mayo Clinic</td>
<td>18</td>
<td>33% @ 5 y</td>
</tr>
<tr>
<td>Lindberg ('96)</td>
<td>Huddinge</td>
<td>37</td>
<td>35% @ 20 y</td>
</tr>
<tr>
<td>Lim ('03)'</td>
<td>Leeds, UK</td>
<td>29</td>
<td>10% @ 10 y</td>
</tr>
<tr>
<td>Befrits ('02)</td>
<td>Karolinska</td>
<td>60</td>
<td>2% @ ~10 y</td>
</tr>
</tbody>
</table>
## Progression of flat LGD to HGD & CA in UC

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>46 Patients w/ Flat LGD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Colectomy &lt;6 mo. after Dx (n=11)</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>2 (27%)</td>
</tr>
<tr>
<td>HGD</td>
<td>1</td>
</tr>
<tr>
<td>LGD</td>
<td>7</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
</tr>
</tbody>
</table>


Mean follow up: 15 months (4.5-50.5)
Colonoscopic polypectomy in chronic colitis: Conservative management after endoscopic resection of dysplastic polyps
Rubin et al. Gastroenterology 1999;117:1295-1300

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>No further polyps</td>
<td>52%</td>
<td>25</td>
</tr>
<tr>
<td>Polyps in same vicinity</td>
<td>27%</td>
<td>13</td>
</tr>
<tr>
<td>Polyps in different locations</td>
<td>21%</td>
<td>10</td>
</tr>
<tr>
<td>Dysplasia/CA in flat mucosa</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

- 48 pts (103 exams) w/ chronic colitis (mean duration: 25.4 yrs)
- 70 polyps (60 in colitic, 10 in non colitic mucosa) – F. up: 4.1 yrs
Long term outcome confirms that polypectomy is adequate treatment for adenoma-like DALMS

<table>
<thead>
<tr>
<th>Feature</th>
<th>UC patient groups</th>
<th>Non-UC patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adenoma-like DALM</td>
<td>Sporadic adenoma</td>
</tr>
<tr>
<td>No. of patients</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>82.1</td>
<td>71.8</td>
</tr>
<tr>
<td>Patients who developed additional polyps</td>
<td>15 (62.5%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Patients who developed flat dysplasia</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients who developed adenocarcinoma</td>
<td>1 (4%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Management of Dysplasia in IBD

[ Mitigating factors: age, location, activity of disease ]

DYSPLASIA (LGD – HGD)

- FLAT DYSPLASIA
  - LGD
  - HGD
  - surveillance
  - COLECTOMY

- POLYP
  - ADENOMA
  - “POLYPOID” IBD-RELATED DYSPLASIA
  - COLECTOMY

- NON ADENOMA –LIKE MASS
  - COLECTOMY

- POLYPECTOMY
  - COLECTOMY

Colectomy for HGD performed at some institutions