Clinico-Pathologic Discussion of Dilemmas in Inflammatory Bowel Disease

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Disclosures

• Dr. Lewin has no disclosures
• Dr. Comerford
  UCB – Consultant
  UCB – Research Support
  Abbott – Research Support
  Centocor – Speakers Bureau
Additional Disclosures

• My wife is more attractive than I am

• None of my children listen to me

• I just submitted my 2010 taxes
Case-based presentation

#1 - Differentiating Ulcerative Colitis from Crohn’s Colitis

#2 – Ileal Lesions – Crohn’s Disease?

#3 Dysplasia in Inflammatory Bowel Disease
Case #1 UC vs CD

21 year-old female college student presents with diarrhea (loose bowel movements daily) mild crampy abdominal pain, rectal bleeding for 2 months.

No recent travel or antibiotic use; Non-smoker

Mildly anemic Hg 11; Stool cultures are negative for enteric pathogens, *C. difficile*, and ova and parasites
Differential Diagnosis

- Infectious colitis
- Inflammatory Bowel Disease
- Ischemic colitis
- Microscopic colitis
- SCAD
- Radiation colitis
- Drug-induced colitis
- Solitary rectal ulcer syndrome
<table>
<thead>
<tr>
<th></th>
<th>Acute Infections</th>
<th>IBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration symptoms</td>
<td>&lt;2 weeks</td>
<td>&gt;4 weeks</td>
</tr>
<tr>
<td>Onset of symptoms</td>
<td>abrupt</td>
<td>insidious</td>
</tr>
<tr>
<td>Platelets</td>
<td>normal</td>
<td>&gt;450,000</td>
</tr>
<tr>
<td>Hct</td>
<td>normal</td>
<td>low</td>
</tr>
<tr>
<td>Biopsy</td>
<td>neutrophils predominate</td>
<td>mixed infiltrate, abnormal crypt architecture, lymphoid aggregates, basal plasmacytosis</td>
</tr>
</tbody>
</table>
Endoscopy

• Colonoscopy: Diffuse ulcerated and friable mucosa throughout entire colon; < inflammation in rectum
• Unable to intubate terminal ileum
• Upper endoscopy normal
UC - Extent of Disease

- Extensive
- Left-sided
- Pancolitis
- Proctosigmoiditis
- Proctitis
UC - Spectrum of Disease

Normal

Mild

Moderate

Severe
Endoscopic Features

Distribution

- Involves the rectum
- Continuous pattern; no skip lesions
- More severe distally
- May have a Cecal patch
- Backwash ileitis
Crohn’s Disease

- Chronic inflammation potentially involving any location of the alimentary tract
- 30% small bowel only, 40% ileocolic, 30% colon only
- Inflammatory Bowel Disease (IBD), ileitis, regional enteritis, granulomatous enterocolitis
- Skip pattern, transmural (from mucosa to serosa)
- Stricture, fistula, abscess
- Unknown etiology
- No cure - Yet
Anatonic Distribution

Freq. of involvement
most          least

Small bowel alone 33%
Ileocolic 45%
Colon alone 20%
Crohn’s Disease
CD - Clinical Patterns

Inflammation

Fistulization

Obstruction

Microperforation (appendicitis-like)
Perirectal fistula
Crohn’s endoscopy

• Rectal sparing
• Skip patterns
• TI involvement
• Cobblestoning, ulceration
Endoscopic Features

Rectal involvement  UC > CD
Skip lesions  CD > UC
Cobblestoning CD > UC
Pseudopolyps UC > CD
TI involvement CD > UC (Backwash)
More severe distally UC > CD
Who are these guys?

Dr. Crohn with 2 Mt. Sinai gastroenterologists at 1928 ACP meeting
Etiology of Inflammatory Bowel Disease

- Prevalence differs among ethnic groups
- Concordance rate for monozygotic twins (44%) > dizygotic twins (3.8%)
- Link to genetically susceptible hosts (e.g. NOD 2/CARD 15)

- Cytokine Imbalance
- Immunosuppressant and anti-TNF-α therapy can be effective.

- Antigen Trigger (Bacteria, food Ag, or toxins)
- Hygiene or Urban Areas
- Smoking
- NSAIDS

IBD - Global Prevalence

Key:
- **High**
- **Intermediate**
- **Low**
Estimated 1 Million Americans with IBD

- Ulcerative Colitis: 50%
- Crohn’s Disease: 50%
- Indeterminate Colitis: 10%

<table>
<thead>
<tr>
<th></th>
<th>Cases per 100,000 persons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence (range)</td>
</tr>
<tr>
<td>Ulcerative Colitis</td>
<td>2.2 – 15.6</td>
</tr>
<tr>
<td>Crohn's Disease</td>
<td>3.6 – 15.6</td>
</tr>
</tbody>
</table>

Loftus EV. Gastroenterology. 2004;126:1504-1517.
Indeterminate colitis

• “IC” restricted to resected specimens
• “IBD Unclassified” - patients who appear to have IBD colitis but who cannot be readily classified when all clinical, radiological, endoscopic, histologic, and serologic data are taken into account
Indeterminate colitis

- Approximately 10% of cases
- 5 year Norway study of 40 IC cases\(^1\):
  18/40 UC  7/40 CD  8/40 non-IBD
- Diagnostic problems common in early & severe disease

\(^1\) Moum B., Scand J Gastroenterol 1996;31:362-366
Indeterminate colitis

CD vs UC

Radiology: SBFT, CTE, MRE
Small bowel endocapsule
Serology markers
Histology
Tincture of time
Potential Roles for IBD Serologic Testing

• Assist in the initial diagnosis of IBD
  – Presence of diagnostic uncertainty
  – To assess need for endoscopy (esp. pediatrics)

• Differentiate Ulcerative Colitis (UC) from Crohn’s Disease (CD)
  – Indeterminate colitis
  – Strengthen diagnosis prior to surgery

• Helps identify patients at risk for aggressive disease
PROMETHEUS® IBD Serology 7

- ELISA tests (Enzyme Linked Immunosorbent Assay)
  - ASCA IgA
  - ASCA IgG
  - Anti-CBir1⁺ IgA
  - ANCA IgG
  - Anti-OmpC* IgA
- IIF tests (Indirect Immunofluorescence)
  - pANCA
  - DNAse-sensitive pANCA*
pANCA

- Identified in 60-70% of UC patients
- Identified in 40% of Crohn’s disease patients
- pANCA (+) CD have phenotype similar to left sided UC
- CBir-1 is (+) 44% of pANCA (+) CD patients
- CBir-1 is (+) 4% of pANCA (+) UC patients

Targan SR, Gastroenterology 2005;128:2020-8
PROMETHEUS® IBD Serology 7 Performance Characteristics

- Sensitivity:
  - IBD: 74%
  - CD: 71%
  - UC: 51%

- Specificity:
  - IBD: 86%
  - CD: 93%
  - UC: 92%
Indeterminate colitis

Correct diagnosis important:

Surgical decisions (IPAA)

Medical treatment
“Sometimes we have to save lives, not colons.”
Ulcerative Colitis
Surgical Options

- Conventional ileostomy (Brooke)
- Continent ileostomy (Kock pouch)
- Ileo-anal anastomosis with reservoir
Indeterminate colitis

Severe Pouch complications
CD 30-45%   IC 20%   UC 10%

Pouches requiring surgical correction
IC 50%   UC 3%  (n=235)

1 Geboes G. Inflamm Bowel Dis 2008;14:850-857
ASLC V UC

• Plasmacytosis in the lamina propria extending to the mucosal base and mucosal distortion were present in all cases of UC and absent in all cases of ASLC.
  – Histopathologic features always distinguished UC and ASLC

• Biopsy specimens are only diagnostic when obtained within the first 4 days

Nostrant et al. Gastroenterology 1987;92:318
## ASLC V ACUTE ONSET IIBD

<table>
<thead>
<tr>
<th>Findings</th>
<th>ASLC</th>
<th>IIBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Architecture</td>
<td>44 (85)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Distorted Crypt Architecture</td>
<td>0</td>
<td>34 (65)</td>
</tr>
<tr>
<td>Branched Glands</td>
<td>5 (10)</td>
<td>41 (79)</td>
</tr>
<tr>
<td>Villiform Surface</td>
<td>0</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Crypt Atrophy</td>
<td>1 (2)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Goblet Cell Mucin Depletion</td>
<td>36 (70)</td>
<td>48 (92)</td>
</tr>
<tr>
<td>Reactive Epithelial Hyperplasia</td>
<td>37 (73)</td>
<td>48 (92)</td>
</tr>
</tbody>
</table>

### ASLC V ACUTE ONSET IIBD

<table>
<thead>
<tr>
<th>Findings</th>
<th>ASLC</th>
<th>IIBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute and chronic inflammation</td>
<td>16 (31)</td>
<td>49 (94)</td>
</tr>
<tr>
<td>Crypt abscess</td>
<td>24 (37)</td>
<td>47 (90)</td>
</tr>
<tr>
<td>Basal plasmacytosis</td>
<td>3 (6)</td>
<td>40 (77)</td>
</tr>
<tr>
<td>Basal lymphoid aggregates</td>
<td>1 (2)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>Isolated giant cells</td>
<td>1 (2)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Granulomatous crypt abscess</td>
<td>8 (15)</td>
<td>19 (37)</td>
</tr>
</tbody>
</table>

*Surawicz et al. Gastroenterology 1994;107:755*
## Histologic Features For Ulcerative Colitis v CD

<table>
<thead>
<tr>
<th>Feature</th>
<th>K</th>
<th>UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelioid granulomas</td>
<td>.41</td>
<td>-.41</td>
</tr>
<tr>
<td>Langhan’s giant cells</td>
<td>.4</td>
<td>-.28</td>
</tr>
<tr>
<td>Crypt distortion</td>
<td>.38</td>
<td>.34</td>
</tr>
<tr>
<td>Crypt architecture</td>
<td>.36</td>
<td>.35</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>.32</td>
<td>.31</td>
</tr>
<tr>
<td>Crypt branching</td>
<td>.3</td>
<td>.30</td>
</tr>
<tr>
<td>Paneth cell metaplasia</td>
<td>.29</td>
<td>.23</td>
</tr>
<tr>
<td>Villous mucosal configuration</td>
<td>.26</td>
<td>.29</td>
</tr>
<tr>
<td>Crypt atrophy</td>
<td>.24</td>
<td>.28</td>
</tr>
<tr>
<td>Focal inflammation</td>
<td>.05</td>
<td>-.18</td>
</tr>
</tbody>
</table>

Diffuse (UC) v Patchy (CD)
### IBD SCORING SYSTEM

<table>
<thead>
<tr>
<th>Feature</th>
<th>IBD/normal</th>
<th>UC/CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophilic infiltration</td>
<td>1</td>
<td>-1</td>
</tr>
<tr>
<td>Epithelioid granulomas</td>
<td>1</td>
<td>-6</td>
</tr>
<tr>
<td>Crypt architecture abn</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Mucin depletion</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Paneth cell metaplasia</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diffuse inflammation</td>
<td>1</td>
<td>-2</td>
</tr>
<tr>
<td>Villous configuration</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

#### UC/CD score

<table>
<thead>
<tr>
<th></th>
<th>&lt;= -3</th>
<th>-2 to 2</th>
<th>=&gt; 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;= 1</td>
<td>-</td>
<td>&quot;Normal&quot;</td>
<td>-</td>
</tr>
<tr>
<td>2 to 4</td>
<td>CD</td>
<td>Possible IBD</td>
<td>UC</td>
</tr>
<tr>
<td>=&gt; 5</td>
<td>CD</td>
<td>IBD</td>
<td>UC</td>
</tr>
</tbody>
</table>

Granulomas in Crohn’s Disease

• One of the best discriminating factors v UC
• Types of Granulomas
  – Well-formed, non-necrotizing granuloma
    • Diagnostic of CD
      – Rule out TB and sarcoid
  – Pericryptal microgranuloma
    • Occasionally seen in UC and other colitides
  – Mucin Granuloma
    • Ruptured crypt with associated giant cells, non-specific
    • Can be seen with ulcerative colitis
• Granulomas only seen in 20 - 30% of Crohn’s biopsies
Summary of Causes of Unusual Patterns of Disease in UC

- Treatment effect
- Low-grade disease in remission
- Appendiceal involvement as a skip lesion
- Cecum/ascending colon inflammation in left-sided colitis
- Pediatric UC (initial presentation)
- “Backwash” ileitis
- Rare upper gi involvement (e.g., duodenitis)
- Fulminant colitis

Before considering a pouch, make sure it is UC and not Crohn’s

GI pathologist to review the biopsies
Evaluate small bowel
IBD serology
Rectal exam
Case #2: Ileal Lesions

- 53 year old male
- Chronic diarrhea
- Multiple terminal ileal ulcers
- History of NSAIDs
Ileal Lesions

• Screening endoscopy (6,408 with terminal ileal intubation of 30,000 screening exams)
  – Gross lesions in 1% (68)
    • Ulcer (29), Lymphoid hyperplasia (23), Erythema (8), other (8)
  – Histopathology in 0.3% (22)
    • Acute ileitis (17)
    • Chronic active ileitis (5)
      – Four had a change in management

• Conclusion: Ileal intubation not required in screening colonoscopy

Ileal Lesions

• Normal (Abdominal pain, screening, constipation, rectal bleeding)
  – 15/138 (11%) had changes
    • No Crohn Disease
    • Nonspecific Ileitis 2 (2.2%)
    • Nodular lymphoid hyperplasia 13 (14.3%)

• Chronic Nonbloody diarrhea
  – 47/138 (34%) had changes
    • Crohn Disease 9 (6.5%)
    • Nonspecific Ileitis 18 (13%)
    • Nodular lymphoid hyperplasia 33 (24%)

Chronic Diarrhea Patient

• Distinguish backwash ileitis of UC vs CD
  – BWI: Activity level correlates with the level of cecal UC
  – CD: Focal isolated ileal erosions, mucous gland metaplasia (27%), patchy edema with mild inflammation

• Isolated chronic ileitis
  – Crypt distortion, inflammation, plasmacytosis of lamina propria, ulceration, pyloric metaplasia
    • 54% will develop CD on follow-up
      – 36% will have focal enhanced gastritis

Goldstein N. AJCP 2006;126:365
Petrolla AA. J Gastro 2008;43:524
Ileal Lesions

• Symptomatology and indication for endoscopy predict the likelihood that ileitis will progress to Crohn disease
  – Asymptomatic ileitis (11 of 14 with features of chronicity)
    • None progressed to CD
  – Symptomatic ileitis
    • 8/10 with features of chronicity progressed
    • 2/5 with focal active ileitis progressed

Courville EL et al. AJSP 2009;33:1341
Case #3 – Dysplasia in IBD

• 42 year female with history of Crohn Disease
• Originally diagnosed in 2009
• Treatment with prednisone, azathioprine, and adalimumab
  – All discontinued due to side effects
• Currently on no medications
  – 10 bowel movements per day
• Repeat colonoscopy performed
Endoscopic Findings

- The ICV was narrowed: could not intubate TI
- Proximal ascending colon, 5 cm distal to ICV large 4 cm sessile polyp surrounded in a field of inflamed mucosa concerning for a DALM lesion.
  - Multiple biopsies taken of the polyp and placed in a separate jar.
  - Biopsies were also taken of the adjacent mucosa and placed in a separate jar.
- Flat nodular area in the ascending colon a few centimeters distal to the polyp
  - Biopsied and placed in the random right colon jar.
- Flat polyp 2 cm in size in the transverse colon.
- Patchy disease throughout colon; normal rectum
- Surveillance biopsies were taken in each of 4 quadrants every 10 cm throughout the colon.
5 cm Proximal Ascending Colon Lesion
Biopsy Adjacent to 5 cm Lesion
Random Right Biopsies (Includes Flat Nodular Area)
Random Right Biopsies (Includes Flat Nodular Area)
Flat Polyp Transverse Colon
Random Left Colon
Random Left Colon
Rectal Biopsy
Colorectal Neoplasia in IBD

• UC and CD have an increased risk of developing colorectal carcinoma
  – Ulcerative colitis (UC)
    • Risk 2% at 10 years, 8% at 20 years, 18% at 30 years
  – Crohn disease (CD)
    • Standardized incidence ratio for CRC 2.5 (95% CI, 1.7-3.5)
    • Relative risk 4.5 (95% CI, 1.3-14.9)
Risk Factors

- Disease duration
- Extent of disease
- Association of PSC
- Family history of sporadic CRC
- Colonic strictures (in UC), multiple pseudopolyps
- Increased degree of macroscopic and histologic inflammation
Screening/ Surveillance

• UC
  – Screening at 8 to 10 years disease duration
  – Surveillance
    • 1-2 years in extensive colitis (proximal to splenic flexure) and left-sided (descending colon)
    • Standard (non-uc) CRC surveillance in proctosigmoiditis (limited to rectum and sigmoid)
      – No increase risk of colorectal cancer

• IBD + PSC
  – Screening and surveillance (yearly) at time of PSC diagnosis
Biopsies

• Polyps (mass lesions)
  – Resection of polyp if possible
  – Biopsy of the mucosa next to the polyp in separate jar

• Random biopsies
  – No specific # recommended in guidelines, “sufficient”
    • Studies show minimum of 33 with extensive disease
    • 4-quadrant biopsies every 10 cm
Gross Features of DALMs

- Adenoma-like (endoscopically resectable)
  - Sessile/pedunculated
  - Well circumscribed
  - Smooth surface
  - Visible borders
  - Nonulcerated
  - No stricture
  - No mucosal tethering

- Non-adenoma-like (not endoscopically resectable)
  - Usually sessile (broad based)
  - Poorly circumscribed
  - Irregular surface
  - Indistinct border
  - Ulceration/necrosis
  - Stricture
  - Tethering

Farraye FA et al. Gastroenterology 2010;138:746–774
Adenoma-like DALM

Non-adenoma-like DALM

ACG Practice Guidelines

• “From a practical perspective, therefore, it matters little whether a mass lesion is called an adenoma-like mass, or dysplasia-associated lesion or mass; the important issue is to determine whether the lesion is completely resectable and the rest of the colon is free of dysplasia.”
DMSG CLASSIFICATION

- Negative for dysplasia (Neg)
- Indefinite for dysplasia (Indef)
- Low-grade dysplasia (LGD)
- High-grade dysplasia (HGD)
- Carcinoma (CA)
Follow-up

• At resection:
  – Partial colectomy (Crohn disease)
• Multiple polyps with low grade dysplasia and multifocal flat low grade dysplasia
  – No invasive carcinoma
Resection Specimen: Villous Lesion
Flat Dysplasia: Resection Specimen
Flat Dysplasia: Resection Specimen
Summary
Clinico-pathologic Information

#1 - Differentiating Ulcerative Colitis from Crohn’s Colitis

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#3 Dysplasia in Inflammatory Bowel Disease