Microscopic colitis – It’s Back!

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Overview

• Review the clinical features and epidemiology of microscopic colitis
• Diagnostic issues
• Treatment
Clinical Features

Case Report

• 65 F with chief complaint diarrhea
• Onset 10 wk ago, slowly progressive
• 3-5 watery BM/d, 1-2 over night
• Mild pain relieved after BM, mucus but no blood
• Has lost 10 pounds
Points to Consider

• Does she have IBS?
  • New onset sx in 65 yo, nocturnal stools, weight loss
• What additional history do you want?

Clinical Features of Microscopic Colitis

• Chronic watery diarrhea
• 50+% have abdominal pain, mild weight loss
• Autoimmune associations common, sprue
• Overlap with symptoms of IBS
  • 50%-70% Olmsted County\textsuperscript{1}, 28%-65% in RCTs\textsuperscript{2}
• Association with NSAIDs and other meds

1) Limsui IBD 2007  2) Madish World J Gastro 2005
Predictors of MC vs. IBS

- Older age
- Female gender
- Shorter duration of diarrhea
- 44-46% of patients with MC had less than 12 weeks of symptoms

1) Limsui IBD 2007  2) Abboud IBD 2013

Microscopic Colitis vs. Functional Diarrhea or IBS

Macaigne G, Am J Gastro 2014
Microscopic Colitis vs. Functional Diarrhea or IBS

Macaigne G, Am J Gastro 2014

Predicting MC in Chronic Diarrhea

• Age >50, female, PPI and NSAID use, weight loss, absence of abdomen pain all a/w likelihood of MC on bx1

• High sensitivity but only modest specificity

• Clinical features alone cannot reliably distinguish MC from other causes of diarrhea

1) Kane Clin Gastro Hep 2015
Celiac sprue

- 1/3 of patients with sprue have MC-like changes on colon biopsies\(^1,2\)
- Sprue found in 2-13% or more of MC\(^3-6\)
- Celiac serologies may be less sensitive in MC\(^7\)
- Consider sprue if steatorrhea, iron deficiency, non-response to MC medications


Clinical Features

- Two subtypes
  - Collagenous and Lymphocytic colitis
- Very similar clinically and histologically
- Unclear if distinct or parts of a spectrum
Epidemiology

• 7-20% of chronic watery diarrhea
• Incidence ~5-10/100,000 each
• Most common in elderly
• Female predominance (CC > LC in most)
Age- and Gender-specific Incidence Rates
Olmsted County, MN

Incidence of Microscopic colitis,
Olmsted County 1985-2011
Case Report

• PMH: HTN, ↑cholesterol, GERD
• Meds: Olmesartan, simvastatin, omeprazole
• Denies aspirin, NSAID use
• FHx: No IBD, celiac sprue, colon cancer

Points to Consider

• Thoughts?
• Plan?
Pathophysiology

- Abnormal fluid/electrolyte secretion/absorption
- Bile acid malabsorption
- Abnormal collagen synthesis/degradation
- Infection, autoimmunity
- Reaction to luminal antigen
  - NSAIDs and other drugs

Drug-induced Microscopic colitis

- High level evidence
  - acarbose, aspirin, NSAIDs, PPI, SSRI, ticlopidine
- Intermediate level evidence
  - carbamazepine, flutamide, lisinopril, simvastatin
Drug-induced Microscopic colitis

- Collagenous colitis
  - Associated with NSAID, SSRI

- Lymphocytic colitis
  - B-blockers, SSRI, statins, bisphosphonates
  - not NSAID

- Watery diarrhea
  - SSRI, statins

Drummond
Fernandez-Banares Am J Gastro 2007

Drug-induced Microscopic colitis

- Danish population-based retrospective study
  - 3474 CC and 2277 LC diagnosed 2005-2011
  - 100 matched controls per case
  - PPI, NSAID, statin, SSRI use a/w CC and LC
  - Adjusting for a/w diarrhea weakened a/w MC but still PPI:CC and SSRI:LC

Bonderup Inflamm Bow Dis 2014
Drug-induced Microscopic colitis

• PPI + NSAID may increase risk even further
• Diarrhea persisting >3 mo after d/c or beginning after being on a drug for 1 year not likely due to that drug

Case Report

• Medications stopped for 6 weeks, no better
• Does she need a colonoscopy?
• Where to biopsy? How many biopsies?
• Right and left colon in separate bottles?
• Is flex sig adequate?
Diagnosis

Diagnostic Questions

• Where to biopsy?
  • Histology may be patchy
  • Proximal to distal gradient
  • Recommend biopsies from multiple areas
  • How many biopsies?
  • Right and left colon in separate bottles?
  • Is flex sig adequate?
Diagnostic Questions

• Where to biopsy?

• How many biopsies?
  • More is better
  • Recommend at least 8

• Right and left colon in separate bottles?
  • Is flex sig adequate?
Diagnostic Questions

- Where to biopsy?
- How many biopsies?
- Right and left colon in separate bottles?
- Is flex sig adequate?
  - Rectal biopsies may miss 40-73% of cases
  - Sigmoid may miss some too
  - Recommend biopsies from above rectum (and above sigmoid if possible)

Case Report

- Loperamide up to 16 mg/d, no improvement
- Colonoscopy: Grossly normal
- Biopsies: next slide
Treatment
Bismuth

Bismuth Subsalicylate: Open-Label Study

• 13 patients newly dx (7 CC, 6 LC)
• BiSS 262 mg tablets, 8 daily, for 8 weeks
• Response 92%
• Mean time to response 2 weeks
• 75% maintained remission for 7-28 months

Fine and Lee, Gastroenterology 1998;114:29-36
Open-Label Bismuth: Clinical Results

Stool Frequency

Stool Consistency

Fecal Weight

Fine and Lee, Gastroenterology 1998;114:29-36

Open-Label Bismuth: Histology Results

Histopathology Score

Before

After

Fine and Lee, Gastroenterology 1998;114:29-36
### Bismuth Subsalicylate: RCT

- **N=14, 9 tabs/d x 8 weeks vs. placebo**
- Response 100% vs. 0%
- BMs: 7.5/d to 2/d in BiSS; no ∆ placebo
- Histology: improved in 6/7 BiSS, 1/6 placebo
- Relapse 25%, all retreated
- Placebo patients received BiSS: 5/6 improved

Fine et al, DDW abstract (Gastro 1999;116:A880)

### Open Label Bismuth

- **N=64 (52% LC, 48% CC), 6-9 tabs/d x 8 wks**
- Complete response 48%
- Partial response 32%
- No response 20%
- Dose response: Remission 63% with 9 tabs, 35% with 6-8 tabs

Gentile N, et al. DDW 2015
### Open Label Bismuth

**Response by severity**

<table>
<thead>
<tr>
<th>Daily BMs</th>
<th>None</th>
<th>Partial</th>
<th>Complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5</td>
<td>8%</td>
<td>23%</td>
<td>69%</td>
</tr>
<tr>
<td>&gt;5</td>
<td>29%</td>
<td>32%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Gentile N, et al. DDW 2015

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**Mesalamine**
Mesalamine +/- cholestyramine

- N=64, randomized but unblinded
- 2.4 gm/d +/- cholestyramine
- Remission 85% in LC (+ or – cholestyramine)
- CC: 73% w/o vs. 100% with cholestyramine

Calabrese J Gastro Hep 2007

Mesalamine Open-label Study

- N=35
- ~3 gm/day
- Remission
  - 83.3% in LC
  - 35.3% in CC (p=0.005)

Fernandez-Banares, Am J Gastro 2003
Open Label Treatment Responses

Complete and Partial Response

<table>
<thead>
<tr>
<th>Colitis type (N)</th>
<th>(^1\text{LC (170)})</th>
<th>(^2\text{LC (199)})</th>
<th>(^3\text{CC (163)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidiarrheals</td>
<td>73%</td>
<td>70%</td>
<td>71%</td>
</tr>
<tr>
<td>Bismuth</td>
<td>73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>65 57 59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-ASA</td>
<td>42 37 35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>87 88 82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Mesalamine RCT

• Collagenous colitis, N = 92
• Budesonide vs. mesalamine 3 g/d vs. placebo
• Mesalamine no better than placebo
  • Remission (≤3 BM/d): 44% vs 60%
  • Histology 45% vs 50%

Miehlke Gastroenterology 2014;146:1222
Budesonide

Budesonide Placebo Controlled Trials

- 4 RCTs in collagenous, 2 in lymphocytic
- 9 mg/d x 6-8 weeks, +/- taper
- Response 57-100% (~85%) vs. 12-40%
- Relapse ~80%

Budesonide Induction in Collagenous Colitis: Cochrane Meta-Analysis

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Budesonide n/N</th>
<th>Placebo n/N</th>
<th>Peto OR 95% CI</th>
<th>Weight %</th>
<th>Peto OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baert 2002</td>
<td>8/11</td>
<td>3/12</td>
<td>25.04</td>
<td>6.23</td>
<td>1.26, 30.92</td>
</tr>
<tr>
<td>Bondurup 2003</td>
<td>10/10</td>
<td>2/10</td>
<td>21.13</td>
<td>23.73</td>
<td>4.15, 135.72</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.00</td>
<td>12.32</td>
<td>5.53, 27.46</td>
</tr>
</tbody>
</table>

Total events: 38 (Budesonide), 8 (Placebo)
Test for heterogeneity: Chi² = 1.25, df = 2 (P = 0.54), P = 0%
Test for overall effect: Z = 6.14 (P < 0.00001)

Case Report

- Bismuth 3 TID for 6 weeks, no better
- Budesonide 9 mg/d, sx better after 4 days, resolved after 1 week
- D/C after 8 weeks
- 3 weeks later, symptoms return
Points to Consider

• What is going on?
• Does she need repeat colonoscopy with biopsies?
• Treatment?

Natural History of Steroid-treated MC

• 80 patients rx with steroids
  • Prednisone 21%, budesonide 79%
  • Remission 76%, response 20%
  • Recurrence 70%
• Remission: 83% vs 53% (p = 0.02)
• Recurrence: HR 0.38 (95% CI 0.18-0.85)

Gentile, Pardi Am J Gastro 2013
**Budesonide Maintenance in CC**

- Two RCTs, 9 mg/d x 6 wks, remission 87-96%
  - Budesonide 6 mg/d or placebo x 6 mo
  - Relapse: 13-23% vs. 61-88%
- 3rd RCT, 4.5 mg/d vs. placebo x 12 mo
  - Relapse: 39% vs. 83%
  - Relapse: 82% after D/C
- No SAEs

- Bonderup Gut 2009
- Miehlke Gastroenterology 2008
- Munch Gut 2016

**Points to Consider**

- What to monitor for on long term budesonide?
  - Steroid related side effects
- What dose do you use?
  - Lowest effective dose
- Any special instructions?
  - Avoid grapefruit, *Echinacea*, P450 drugs
- Alternative treatments?
Azathioprine for Microscopic Colitis

- 9 patients (2.3%), 8 CC, 1 LC
- Steroid dependent, refractory, or intolerant
- Median dose 2 mg/kg/d, f/u 26 months
- 7 tapered off steroids, no-mild symptoms
- 1 intolerant to steroids responded
- 1 non-responder: colectomy


Azathioprine for Microscopic Colitis

- 46 patients (32 CC, 14 LC)
- Budesonide dependent or intolerant
- Intolerant: 67%
- Remission: 28%, non-response: 4%
- 13 intolerant pts → 6-MP, 46% remission

Munch APT 2013
**Methotrexate in Collagenous Colitis?**

- N=19, med dose 7.5-10 mg/wk\(^1\)
- Response complete in 74%, partial in 11%
- But: N=9, 15 mg/wk SQ, ↑ 25 mg/wk after 6 wks if no response\(^2\)
- D/C due to side effects in 4
- In remaining 5, remission 0%


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**Anti-TNF in Microscopic Colitis**

- N = 4 (of 372 pts, 1.1%) treated with infliximab
- Response after one dose
- 3 switched to adalimumab (2 allergic rxn, 1 loss of response)
- 3 maintained response thru 1 year
- 1 lost response to ADA → colectomy

Esteves J Crohns Colitis 2011
Anti-TNF in Microscopic Colitis

- N = 3 with CC refractory to budesonide and MTX
- Adalimumab 160/80/40
- 2 responded
- 1 d/c after 2nd dose (n/v, abdo pain)

Recommended Treatment Approach

- D/C NSAIDs, other drugs
- Bismuth subsalicylate
- Budesonide
- Azathioprine/6-MP/(MTX)
- Anti-TNF
- Surgery

Munch Scand J Gastro 2012
**Take Away Points**

- Consider celiac disease
- Consider drug-induced MC
- Bismuth or budesonide (right dose, duration)
- Maintenance budesonide is often required
  - Monitor for steroid side effects
- For steroid refractory cases, limit data for azathioprine and anti-TNF therapy

**Thank you**