Microscopic colitis

Case

• 68yo Caucasian female, no significant PHx, has complaints of bloating, gas and increased stools x 3 months.
  – No blood in stool
  – No wt loss, no other new problems /alarm sx. No travel.
  – Had a screening colonoscopy 2 years ago, told it was “normal.”
  – BMs are 8x per day, also with bloating and gas.
  – She has since limited going out, given the unpredictable nature of her urgency and diarrhea.
• PHx: HTN, hypothyroidism
• Meds:
  – HCTZ 25, Synthroid 0.125mg, ASA 81mg
  – Imodium prn prior to going out
• Soc: Smoked 1 pp week x 30 years (quit 5 yrs ago). No illicit drugs. Social alcohol once a week.
• FHx: negative for CRC or IBD.
• ROS, exam unremarkable
• Labs normal (CBC, CMP, celiac screening, stool for C diff, culture)
• Assessment and Plan:
  – Chronic Diarrhea: IBS-d vs. microscopic colitis vs…

Should you do a colonoscopy?

– 25% of all colonoscopies <50 and 10% of all colonoscopies in the U.S. are performed for the evaluation of IBS symptoms.
– Why?
  • Reassurance for MD and patient, improved functional symptoms with reassurance.
    – Study: No differences in quality of life measures or a sense of reassurance in patients regardless of colonoscopy.
  • Could be missing something (cancer, IBD, etc.)
    – Study: Prospective study looking at colonoscopy for suspected IBS-d symptoms (466 patients)
      » Adenoma 7.7% (26.1% controls)
      » Cancers: none
      » IBD: 2 (0.4%)
      » Microscopic colitis: 7 (1.5%), 2.3% if >35 years old.

Colonoscopy

- Normal colonic mucosa throughout.
- Terminal ileum was intubated to approx 20cm proximal to the IC valve. Normal mucosa.
- Random colon biopsies taken in the R and L colon.

Microscopic colitis

- A common cause of chronic watery diarrhea, especially in older adults.
- Incidence has been increasing over the past 20 years.
  - Increased awareness of the disease.
  - Increase in utilization of colonoscopy with biopsies.
**History of microscopic colitis**

- 2000-: Immunology, pathophysiology.
- 2003: 1st RCT of Collagenous colitis
- 2002: Microscopic colitis manuscripts
- 1995: Epidemiology, natural history
- 1989: 1st report of Lymphocytic colitis
- 1980: 1st report of Microscopic colitis
- 1976: 1st report of Collagenous colitis

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**Microscopic colitis: Once rare, now more common**

- **Incidence increase in CC and LC**
  - Sweden
  - United States (MN)
  - Canada
  - Denmark

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Microscopic colitis: how common?

- **Microscopic colitis**
  - 1985-2001 (Mayo):
    - CC 3.1/100,000
    - LC 5.5/100,000
  - 1997-2001
    - CC 6.2/100,000
    - LC 12.9/100,000

- **IBD**
  - 1984-1993 (Mayo)
    - UC 8.3/10,000
    - Crohn’s 6.9/100,000

Microscopic colitis: epidemiology

- Population-based studies in US and Europe
  - Incidence has doubled from 1985-2001.
  - These numbers approach or surpass the incidence rates for both ulcerative colitis and Crohn’s disease

- Mean age 60s
- Women> men (~3:1)
Is it microscopic colitis, or is it IBS?

• 11-33% of patients with MC are initially given a diagnosis of IBS

• Up to 56% of patients with MC fulfill Rome criteria for IBS.
  • Rome III criteria:
    – Recurrent abdominal pain or discomfort at least 3 days per month during the previous 3 months that is associated with 2 or more of the following:
      » Relieved by defecation
      » Onset associated with a change in stool frequency
      » Onset associated with a change in stool form or appearance

Limsui D et al, IBD 2007;13:175-81

Microscopic colitis: natural history

• Diarrhea can be severe, incontinence common
  – 66% have 4-9 BMs per day
  – 22% have >10 BMs per day
  – 27% have nocturnal diarrhea

• Relapses are common:
  – 60-80% relapse within 2-8 weeks of stopping treatments.

• Quality of life poor for untreated disease
  – Scores worse than anal fissure, incontinence, severe constipation, GERD requiring surgery.

Bodenre JK et al. Gut 2009;58.68
Hjortswang H et al. Dig Liver Dis 2010;43:102
Microscopic colitis

- MC associated with other autoimmune disease
  - Rheumatoid arthritis
  - Thyroid dysfunction
  - Psoriasis
  - Very rarely ulcerative colitis/Crohn’s (1/642 in our cohort)

- Common overlap with celiac disease.
  - United States & Canada: MC seen 50-72x more commonly in celiac vs. general population.

Celiac disease and Microscopic colitis

- Celiac disease patients
  - 1/3 have histologic changes in the colon that may represent MC.
  - Suspect MC if not getting better on a gluten-free diet. (a more common scenario than below)

- Microscopic colitis patients
  - Small bowel inflammation, villous atrophy in 20%.
  - Inconsistent reports of celiac serologies
  - Consider doing small bowel biopsies if you are suspicious for celiac disease in MC patients. (steatorrhea, iron def anemia, non-response to MC therapy)
Smoking and Microscopic colitis

• Former or current smoking is associated with MC: OR 2.1
• Association greater in current smokers:
  – OR CC 5.4, LC 3.8 and all MC 4.4
• Effect of smoking same regardless of type of MC and gender.
• Diarrhea onset >12 years prior in smokers vs. non-smokers with MC.

Medication-induced MC?

• Controversial: some medications reported to increase risk of MC.
• Small case reports, case series (mixed results).
  – Proton pump inhibitors
  – NSAIDs (34-71% of patients with MC)
  – SSRIs
  – HMG-CoA reductase inhibitors (Statins)
• Largest study: Denmark (n=5751 patients) – population-based vs. random national controls.
  – Association found with above meds and MC diagnosis.
  – Strongest associations:
    • PPI and collagenous colitis (adjusted OR 2.03, 95% CI: 1.77-2.33)
    • SSRIs and lymphocytic colitis (adjusted OR 1.77, 95% CI: 1.42-2.21)
  – Recall bias?, More endoscopy in MC group?


“Benign colonic mucosa with increased intraepithelial lymphocytes”

- Is it lymphocytic colitis?
- Differential diagnosis (your pathologists generally cannot help you with this).
  - Gluten sensitive enteropathy
  - Autoimmune diseases
    - Thyroid, DM
  - Drug reactions
    - Problems with nomenclature: Medication-induced increase IELs not MC.
- Bottom line:
  - Take a good medication history
  - Discuss potential risks of meds with MC
  - Encourage alternatives to NSAID use


Diagnosis

- Normal-appearing colonic mucosa
  - Rarely get proximal mucosal tears
- Histology
  - No crypt architectural distortion (different from other forms of IBD).
  - Increased intra-epithelial lymphocytes (normal 4-5 per 100 epith cells)
  - Collagenous colitis: Thickened subepithelial collagen layer (>10mm)

Rare mucosa tears
Lymphocytic colitis
Collagenous colitis
Diagnosis

- Do you need a colonoscopy?
  - First small case series: Biopsies limited to the rectum and rectosigmoid would have missed MC cases.
    - Lymphocytic infiltration and collagen band thickening scattered, higher likelihood to be positive in the R colon.
  - Two larger studies: Non-rectal biopsies should get you the diagnosis (flex sig or colonoscopy).
    - Denmark: n=168 (LC), n=270 (CC)
      » 95% of CC and 98% of LC fulfill criteria in the R and L colon
    - Our center: n=76 with MC
      » Sigmoid or L colon biopsies +100% in CC, 95% in LC.
      » 20-25% of cases of LC or CC missed if rectal biopsies alone.


Lymphocytic colitis = collagenous colitis?

- Are they different entities (like Crohn’s and UC)?
  - Unlikely, CC and LC should be considered one clinical entity.
  - Clinical characteristics, risk factors are indistinguishable between the two subgroups.
- Does LC convert into CC (and vice versa)?
  - One can often see mixed histologic features of both conditions on the same colonoscopy

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CC</th>
<th>LC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of diagnostic colonoscopies</td>
<td>1741</td>
<td>981</td>
</tr>
<tr>
<td>Diagnostic for MC in right and left colon</td>
<td>95% (91-98)</td>
<td>98% (93-100)</td>
</tr>
<tr>
<td>MC in left colon, not in right colon</td>
<td>72 (4-28)</td>
<td>1** (1-6)</td>
</tr>
<tr>
<td>MC in right colon, not in left colon</td>
<td>70 (1, 0-3)</td>
<td>1** (1-6)</td>
</tr>
<tr>
<td>CC with abnormal intraepithelial lymphocytes</td>
<td>48% (40-55)</td>
<td>-</td>
</tr>
<tr>
<td>&gt;5/100 cells</td>
<td>-</td>
<td>24% (18-31)</td>
</tr>
<tr>
<td>LC with an abnormal collagenous layer &gt;5 and &lt;10 μm</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Treatment for microscopic colitis

Mild-moderate MC cases

- Smoking cessation
- Review meds: NSAIDs, PPIs, SSRIs, statins
- OTC antidiarrheals: Loperamide, Bismuth subsalicylate
- Cholestyramine ~60% response in retrospective studies
  - Bile-acid malabsorption a potential mechanism of MC
  - ~40% of MC patients have abnormal histology in TI.

**Budesonide randomized trials**

**Collagenous colitis**

<table>
<thead>
<tr>
<th>Ref</th>
<th>N</th>
<th>Endpoint</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baert 2002</td>
<td>Budesonide 9mg qd x 8 wks (14) vs placebo (14)</td>
<td>50% decreased BMs</td>
<td>8/14 vs 3/15 (p=0.05)</td>
</tr>
<tr>
<td>Miehlke 2002</td>
<td>9mg qd x 6 wks (26) vs placebo (25)</td>
<td>3 or less BMs/ day</td>
<td>20/26 vs 3/26 (p&lt;0.001)</td>
</tr>
<tr>
<td>Bonderup 2003</td>
<td>9mg x 4 wks, 6mg x 2 weeks, 3mg x 2 weeks (10) vs placebo (10)</td>
<td>50% decreased BMs</td>
<td>10/10 vs 2/10 (p&lt;0.001)</td>
</tr>
<tr>
<td>Sum of the 3</td>
<td></td>
<td></td>
<td>38/50 (76%) vs 8/51 (16%) placebo</td>
</tr>
</tbody>
</table>

**Lymphocytic colitis**

| Miehlke 2009      | Budesonide 9mg qd x 6 wks (21) vs placebo (21) | 3 or less BMs/day          | 18/21 (86%) vs. 10/21 (48%) placebo |

Miehlke S et al. Gastroenterology 2009 Jun;136(7):2092-100

**Mesalamine in MC**

- Uncontrolled studies: 40-50% response.
- Open label
  - Mesalazine vs. Mesalazine + cholestyramine – both arms effective
- RCT in collagenous colitis – no difference between 5-ASA and placebo.

Miehlke S et al. DDW 2012
Other therapies for MC

• Azathioprine, 6-mercaptopurine
  – Case series: n=46
    • Clinical remission in 28%
    • Stopped in 67% due to intolerance.

• Anti-tumor necrosis factor agents (infliximab, adalimumab)
  – Effective but should be a very small % of your patients.
  – Study: 5/372 (1.3%) of all MC patients got anti-TNF.
    4/5 responded


Maintenance therapy for MC

• Budesonide
  – 2 RCTs of maintenance therapy (6mg per day x 6 months)- 77-96% remain in remission. (NNT=2)
  – 60-80% relapse within 2-8 weeks of stopping therapy.
  – Indefinite/intermittent Budesonide?
    • Safety a concern
    • Older, more female patients with MC (compared to other forms of IBD)

• More studies needed!

Microscopic colitis treatment

- Stop non-steroidal anti-inflammatory drugs (NSAIDs), other drugs or dietary factors that might contribute to diarrhea

- Mild symptoms
  - Loperamide or Diphenoxylate

- Moderate symptoms
  - Bismuth subsalicylate or Cholestyramine or Aminosalicylates

- Severe symptoms
  - Budesonide
    - Prednisone
    - Azathioprine/6-Mercaptourine/Methotrexate
    - Surgery


Conclusions

- Microscopic colitis is a common cause of chronic diarrhea, particularly older individuals.

- Incidence appears to be increasing to levels comparable to Crohn’s and ulcerative colitis.

- More research is needed to better understand the natural history, pathogenesis and maintenance therapy for microscopic colitis.
Thank you!