Thinking Outside the Bowel: Extra-Intestinal Manifestations
“Disease vs Drug Related”
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No disclosures.
Objectives

• Recognize common extra-intestinal manifestations of IBD
• Identify extra-intestinal manifestations that correlate with IBD disease activity and those that correlate with drug
• Describe workup of medication induced symptomatology
• Describe treatment of extra-intestinal manifestations of IBD and drug reaction
Most Common Extra-intestinal Manifestations of IBD

- Musculoskeletal
- Dermatologic
- Other
  - Hepatobiliary
  - Ocular

EIM can involve any organ system
Extra-intestinal Manifestations of IBD

- Most patients colonic involvement
- May precede onset of luminal symptoms
- More likely to develop another EIM
Case #1

45 yof UC diagnosed 2007 with bloody diarrhea, severe tenesmus x 1 month with 20+ loose BM/day with nocturnal symptoms. Malaise. Joint pains in right knee and both elbows.
- C diff negative
- Flex sig with mod-severe proctitis with moderate to severely active chronic colitis, CMV neg.
- Admitted with no response to IV steroids by day 3
- Inpatient infliximab with improved symptoms after 1st dose – dismissed
- Second dose = worsening joint pains in right wrist, left ankle, both knees and jaw with low grade fever. 1-2 formed BM/day.
Case #1: Differential Diagnoses

1. Type I IBD related peripheral arthritis
2. Type II IBD related peripheral arthritis
3. Serum sickness
4. Systemic Lupus Erythematosus
5. Rheumatoid Arthritis
6. Septic arthritis
7. Other infections with migratory arthritis
Peripheral Arthritis

Peripheral arthritis – 5-20% of IBD patients
RF negative
No destructive changes
Treatment – sulfasalazine

<table>
<thead>
<tr>
<th>TYPE 1</th>
<th>TYPE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pauciarticular &lt;5 joints</td>
<td>Polyarticular</td>
</tr>
<tr>
<td>Associated with IBD activity</td>
<td>Independent of IBD activity</td>
</tr>
<tr>
<td>Large joints</td>
<td>Small joints</td>
</tr>
<tr>
<td>Associated with other EIM</td>
<td>Not associated with other EIM (except uveitis)</td>
</tr>
<tr>
<td>Self Limited – treat IBD</td>
<td>Chronic</td>
</tr>
</tbody>
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Serum Sickness

- Reaction similar to an allergy
- Classic presentation: fever, rash, polyarthritis or polyarthralgias
- Onset: 1-2 weeks after exposure
- Treatment: remove offending agent
## Infliximab-Related Infusion Reactions

<table>
<thead>
<tr>
<th>Immediate (during- &lt;24hr)</th>
<th>Late (&gt;24hr-weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–23% of patients</td>
<td>1-3% of patients</td>
</tr>
<tr>
<td>• Pruritus [22.1%]</td>
<td>• Serum sickness-Like</td>
</tr>
<tr>
<td>• Flushing [9.9%]</td>
<td>• Type III immune-cmplx hypersensitivity</td>
</tr>
<tr>
<td>• Dyspnea [6.2%]</td>
<td>• IFX (Ag)- ATI (Ab) complex</td>
</tr>
<tr>
<td>• Chest discomfort [5.9%]</td>
<td>• blood vessels, skin and joint tissue</td>
</tr>
<tr>
<td>• Hypertension [5.9%]</td>
<td>• Acute inflammatory response</td>
</tr>
<tr>
<td>• Myalgia [5.0%]</td>
<td>• 7–14 days after initiation of offending agent</td>
</tr>
<tr>
<td>• Nausea [4.7%]</td>
<td>• Fever, Urticaria, Arthralgias, Myalgias, Lymphadenopathy, mild proteinuria</td>
</tr>
<tr>
<td>• Urticaria [4.7%]</td>
<td>• Jaw pain common symptom</td>
</tr>
<tr>
<td>• Headache [4.0%]</td>
<td>• Self limited</td>
</tr>
<tr>
<td>• Rash [3.4%]</td>
<td>Increased risk:</td>
</tr>
<tr>
<td>• Dizziness [2.8%]</td>
<td>• Episodic</td>
</tr>
</tbody>
</table>

**Antibodies toward infliximab [ATI]:**
- 2-fold risk of acute reactions
- 6-fold risk of serious acute reactions

**Increased risk:**
- Episodic
- Resumed after break
- High ATI

Lichtenstein et al. Journal of Crohn's and Colitis, 2015, 806–815
True Rheumatologic Etiology

- Systemic Lupus Erythematosus
  - Can also be drug induced
  - Symptoms: fever, malaise, joint pains, skin rash on areas exposed to light
  - Serologic markers: positive
  - Etiology: anti-TNF
  - Timing!

- Rheumatoid Arthritis

- Septic Arthritis
Case Continued

• Labwork
  • ANA: 1.7 (weak positive)
  • RF, CCP, Complements and anti-dsDNA: negative
  • Parvo, CMV, EBV, HIV: negative
  • Infliximab:
    • Drug level: 1.7 mcg/mL
    • Antibodies to Infliximab: 218 U/mL
Other Musculoskeletal Manifestations

1. Axial arthritis – up to 26% of IBD patients
   - Males > females
   - Independent of IBD disease activity
   - Colectomy will not improve symptoms
   - Includes SI joints

2. Ankylosing spondylitis – up to 6% of IBD patients
   - “bamboo spine”
   - HLA B27 positive
   - Treatment – Anti-TNF

3. IBD arthropathy
   1. Inflammatory – can precede, synchronous or after IBD dx
   2. Morning stiffness
   3. Peripheral or axial
   4. Seronegative
42 year old man, HLA B27-, with CUC presents with lower back pain for 6 months. Pain is worse in the morning and improves as the day goes on. Having 2 soft stools a day with blood occasionally in the last 4 months. Currently using oral mesalamine 2.4 g daily. Physical exam reveals slightly limited spinal flexion. What is the etiology of his back pain.

A. Ankylosing spondylitis
B. Axial arthritis
C. IBD arthropathy
D. Mesalamine drug induced arthropathy
Case #2 continued

A. Ankylosing spondylitis
B. Axial arthritis
C. IBD arthropathy
D. Mesalamine drug induced arthropathy

What treatment is recommended for the back pain?
A. Ibuprofen 600 mg QID
B. Physical therapy
C. Colectomy
D. Anti-TNF
E. Hydrocodone/acetaminophen
Case #2 continued

A. Ibuprofen 600 mg QID
B. Physical therapy
C. Colectomy
D. Anti-TNF
E. Hydrocodone/acetaminophen

Key points:
- Optimize IBD therapy
- Address discomfort in non pharmacologic management
Musculoskeletal Manifestations Pearls

• **Disease mediated**
  • Serologic markers generally negative
  • Treatment – treat IBD

• **Drug Induced**
  • **Timing** of medication and manifestation of symptoms
  • Etiologies: antibodies (serum sickness), drug itself
  • Resolves when drug removed
An 18 year old woman recently diagnosed with Crohn’s colitis develops an increase in bowel frequency (8 BM/day), associated with urgency and nocturnal bowel movements. Two weeks prior to these symptoms she developed painful red nodules on her shins, and pain in her right knee and left wrist. Her right knee is swollen and warm to touch. She is started on a medrol dose pack and while her rash improves her joint pains are preventing her from getting a good night’s sleep. Which of the following treatments is the most likely to address her arthropathy?

A. Oxycodone
B. Budesonide
C. Mesalamine
D. Infliximab
E. Vedolizumab
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B. Budesonide  
C. Mesalamine  
D. Infliximab  
E. Vedolizumab
Dermatologic Manifestations of IBD

Prevalence 2-34% of IBD patients

1. Erythema Nodosum
   - 10-20%
   - Deep, tender nodules on extensor surfaces
   - Correlates with IBD activity
   - Treat underlying disease
   - Other conditions:
     - TB
     - Histoplasmosis
     - Yersinia
     - Bechet syndrome
     - Sarcoidosis
   - Medication Induced:
     - Sulfonamides, iodides, bromides, estrogen
Case #4

A 54 year old morbidly obese woman with Crohn’s colitis undergoes total proctocolectomy with end ileostomy. One year later she develops the following rash. Which treatment is most likely to be effective in preventing recurrence of this rash?

A. Diflucan
B. Cephalexin
C. Weight loss
D. Sulfasalazine
E. Stoma revision
Case #4 continued

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C. Weight loss
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E. Stoma revision
Dermatologic Manifestation of IBD

- **Pyoderma gangrenosum**
  - Pustule, papule breaks down into ulcer with violaceous undermined borders on lower extremities or peristomal
  - May or may not parallel disease activity
- **Treatment**
  - Avoid trauma
  - Underlying IBD (azathioprine and/or anti-TNF)
  - Oral corticosteroids
  - Topical tacrolimus (*)
  - Dapsone (*)

*off label use
Dermatologic Manifestations of IBD

• Sweet Syndrome
  • Raised, tender nodules on face, arms and trunk with fever and constitutional symptoms
  • Histology: neutrophilic infiltrates without vasculitis
  • Treatment
    • Corticosteroids
    • Underlying IBD
Dermatologic Manifestations of IBD

• Psoriasis
  • Well-defined plaques with scaling on scalp and/or extensor surfaces
  • May be associated with anti-TNF and some cases with ustekinumab
  • Mechanism not well understood
• Treatment
  • Stop offending agent
Dermatologic Manifestations Pearls

• **Collaboration**
  - Working closely with dermatology for biopsy and confirmation for best targeted therapies

• **Treat underlying disease**
  - Pyoderma gangrenosum and Erythema Nodosum

• **Consider drug induced psoriasis**
  - Onset, duration
Other Extra-intestinal manifestations of IBD

• Hepatobiliary
  • Pancreatitis
    • Drug induced: azathioprine, mercaptopurine, 5ASA, corticosteroids
    • Crohn’s disease of duodenum
  • Primary Sclerosing Cholangitis (PSC)
    • Inflammation, stricturing and fibrosis of medium and large intra- and extrahepatic bile ducts that does not parallel disease activity
    • 75% PSC have UC, usually extensive colonic involvement
    • 5-10% PSC have CD
    • 5% of UC and 2% of CD have PSC
    • Need annual surveillance colonoscopy after diagnosis
• Portal Vein Thrombosis
Other Extra-intestinal manifestations of IBD

Ocular - Up to 5% often concurrent with other EIM

- **Episcleritis**
  - Acute erythema in one or both eyes with irritation and burning and no change in vision

- **Scleritis**
  - Similar presentation but may impair vision and needs immediate evaluation

- **Uveitis**
  - Associated with skin and MSK EIM
  - Pain, erythema, blurring, photophobia, headaches requiring immediate referral
  - No parallel with disease activity
Summary

• Extra-intestinal manifestations can occur in any organ system
  • Most common: Musculoskeletal, dermatologic, hepatobiliary, ocular

• Some correlate with IBD activity
  • Musculoskeletal: IBD arthropathy, Type 1 peripheral arthritis
  • Dermatologic: Erythema nodosum, pyoderma gangrenosum

• Drug induced – Timing is everything; mechanism not well understood
  • Serum sickness/anti-drug antibodies
  • Lupus like reaction
  • Drug induced psoriasis
  • Pancreatitis
Questions?

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