Systemic Complications in IBD Patients

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Presentation of a Case

• 24 year old Caucasian woman with perforating ileocolonic Crohn’s disease.
• She underwent an ileocecal resection one year after diagnosis secondary to perforating disease.
• Six months after surgery, she underwent a surveillance colonoscopy which showed moderate recurrence (Rutgeert’s II endoscopic score) at the IC anastomosis.
• IFX 5 mg/kg was restarted and continued every 8 weeks.
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Case presentation (cont.)

• 10 months after re-starting IFX, she develops severe pain in her hands, L knee and L ankle.
• Her physical examination is notable for tenderness of the R 2\textsuperscript{nd} and 3\textsuperscript{rd} MCP, 2\textsuperscript{nd} PIP, 2\textsuperscript{nd} DIP, L knee, and tenderness and swelling of the L ankle and L Achilles tendonitis.
• The albumin is 3.3 g/dL, ESR is 34 mm/hr, CRP is 18.5 mg/L, ANA is 1:640 in a homogenous pattern and dsDNA is positive.
• Imaging of the hands, feet and pelvis are normal.
• IFX 10 mg/kg is given x 1 without improvement

Rankin, GB et al. Gastroenterology 1979
Extraintestinal manifestations depending on disease activity in CD and UC

Vavricka, SR et al. Am J Gastroenterol 2010

Enteropathic arthritis

- Joint complaints are the most common form of EIM
  - Occur in 10-20% of patients with IBD
  - More common in CD than UC

- Pathogenesis
  - HLA-DRB*103 and HLA-B*27 associated with pauciarticular arthritis
  - HLA-B*44 associated with polyarticular arthritis
  - Increased gut permeability to bacterial antigens may induce arthritis
    - HLA-B27 transgenic mice raised in germ free environments do not develop gut or joint inflammation

Types of joint EIM

• Arthralgias without frank arthritis
• Pauciarticular
• Polyarticular
• Axial
  – Sacroileitis
  – Ankylosing spondylitis

Arthralgias without frank arthritis

• Occur in 8-16% of IBD patients
  – More common in CD
• Can affect any joint
• Usually coincides with active disease and emerges with relapses
• Should resolve with treatment of disease flare
  – If not consider pseudorheumatism, other drug side effects or other forms of arthritis

Pauciarticular arthritis-associated with IBD

- More common than polyarticular
- Usually acute and self-limited (<10 weeks)
- Involves less than 5 joints including 1 weight bearing joint
- Usually coincides with active disease
- Associated with EN and uveitis
- Lasts a mean of 5 weeks
  - 10-20% have chronic symptoms
  - Recurs in 25-40%
- X rays are normal

Orchard, TR et al. Gut 1998

Polyarticular arthritis-associated with IBD

- Affects 5 or more joints
  - Commonly the small joints in the hands, particularly the MCP joints
- Usually does not correlate with underlying bowel activity
  - Can occur prior to the diagnosis
- Mean duration of symptoms is 3 years
- Associated with uveitis

Lyons, JL and Rosenbaum, JT. Arch Ophthalmol 1997; Paredes, JM et al. Gastroenterol Hepatol 2005
Immunogenicity is common with anti-TNF therapy

*IFX 5 and 10 mg/kg groups during 54 weeks study, ANA ≥ 40 IU/mL, dsDNA +ANA plus +crithidia assay
ADA 40 mg EOW; results at week 56, ANA ≥ 80 IU/mL ds DNA ≥ 3.6 IU/mL
CTZ results at 26 weeks


Therapy for peripheral arthritis

• Rest
• Analgesics
  – COX II inhibitors?
• Type I
  – Treat underlying disease flare
  – Intra-articular steroid
  – Sulfasalazine
• Type II
  – Sulfasalazine
  – Low dose oral steroids
  – Methotrexate
  – Anti-TNF?

**Isolated sacroileitis**

- Diagnosis by clinical symptoms, plain x-ray, CT, or MRI
  - Iliac erosions followed by fusion of the SI joint
- Present with stiffness and/or pain in the buttocks, worse in the morning or after rest
  - Improves with exercise
- Occurs more commonly in CD
  - CT detects SI in 32% of patients
- More likely to have peripheral arthritis
- HLA-B*27 + patients more likely to progress to AS


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**Ankylosing spondylitis**

- Strong genetic susceptibility
  - 50-80% of IBD patients are HLA-B*27 +
- Present with thoracic or lumbar pain, alternating buttock pain or chest pain
- Morning stiffness, changes in posture and loss of flexibility
- Low trauma fractures
- Restrictive lung disease and dilation of aortic root
- Radiographically, syndesmophytes are seen between vertebral bodies
- Usually occur years before IBD is detected and are independent from disease course

Therapy for SI and AS

- Analgesia
  - NSAIDs are drugs of choice but may flare IBD
  - COX II inhibitors?
- Physical Therapy
- Disease modifying-drugs
  - Sulfasalazine
  - Corticosteroids
  - Methotrexate
  - Biologics

Ocular inflammation

- First described by Crohn in 1925
- Affects 2-13% of patients
  - Women affected more than men (3:1)
- 30% of cases are recurrent
- Iritis (60%)
- Episcleritis (30%)
- Uveitis (10%)
- Association with
  - HLA-B*07
  - HLA-B*58
- HLA-DRB*103
- Autoimmune reaction to a form of tropomyosin expressed in both gut and eye

Clinical features of ocular inflammation

- Gritty feeling in the eye
- Perikeratic (corneal) injection
- Painful red eye
- Blurred vision
- Floaters
- Light sensitivity
- Usually unilateral
- Associated with IBD activity in 70% of cases
- May result in blindness if left untreated

Diagnosis and treatment of ocular inflammation

- Early referral for full ophthalmological exam
- Treatment usually involves a 6-8 week course of topical steroids
  - Cycloplegics can be added to prevent posterior synechiae
- Periocular or oral steroids may be needed
- Topical NSAIDs
- Immune suppressants and biologics can be used for patients with a poor response or recurrent symptoms
  - 59% of patients have decrease in episodes of inflammation and 94% decrease need for topical steroids

Erythema nodosum

- Characterized by tender, red or violet subcutaneous nodules usually in the pre-tibial location
- Can appear on thighs, trunk, and upper extremities but absence of leg involvement is unusual
- May be associated with fever, malaise, and elevated ESR
- Associated with other EIMs and active disease
- More common in CD than UC
- Pathogenesis is unclear but thought to be a hypersensitivity reaction to antigens associated with infections, drugs, and other diseases


Treatment of EN

- Usually self-limited and/or resolves with treatment of underlying IBD
- Analgesics
  - NSAIDs (COX II inhibitors?)
- Potassium iodide
- Steroids

Pyoderma gangrenosum

- Single or multiple lesions
  - Begin as tender papules, pustules or vesicles
  - Lower extremities or trunk most common location
- Often preceded by a local trauma
- Can be peristomal, genital, and post-operative
- Necrosis of the dermis with deep ulcerations containing purulent material, which is typically sterile on culture
- 14-34% of cases associated with IBD
- In IBD exacerbation parallels in 50% with disease activity

Farhi, D et al. Medicine 2008
Diagnosis of PG

- **Major criteria:**
  - Rapid progression of painful, necrolytic cutaneous ulcer
  - Other causes of ulceration excluded

- **Minor criteria:**
  - History suggestive of pathergy
  - Systemic disease associated with PG present
  - Sterile neutrophilic dermatosis on biopsy
  - Responsive to steroids


### Treatment of 103 PG cases in a referral hospital 2000-2007

<table>
<thead>
<tr>
<th>Drug Systemic (all patients)</th>
<th></th>
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<tbody>
<tr>
<td>3 or more systemic drugs</td>
<td>28%</td>
</tr>
<tr>
<td>Steroids</td>
<td>73%</td>
</tr>
<tr>
<td>Cyclosporine, mycophenolate, azathioprine</td>
<td>36%</td>
</tr>
<tr>
<td>Anti-TNF (Infliximab, adalimumab, etanercept)</td>
<td>25%</td>
</tr>
<tr>
<td>Doxycycline, minocycline</td>
<td>23%</td>
</tr>
<tr>
<td>Other</td>
<td>28%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Topical (100 of 103 patients)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>38%</td>
</tr>
<tr>
<td>Steroid intralesional</td>
<td>25%</td>
</tr>
<tr>
<td>Tacrolimus/cyclosporine</td>
<td>24%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other Treatment (59 of 103 patients)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Debridement, Skin graft</td>
<td>37%</td>
</tr>
</tbody>
</table>

IFX in the treatment of PG

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Remission</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>PG Duration &lt;12 weeks (n=14)</td>
<td>13 (93%)</td>
<td>4 (31%)</td>
</tr>
<tr>
<td>PG Duration &gt;12 weeks (n=15)</td>
<td>7 (47%)</td>
<td>2 (13%)</td>
</tr>
</tbody>
</table>

Brooklyn, TN et al. Gut 2006

PSC

• Progressive disorder resulting in cholestasis and liver failure
• Median survival without transplant ~12 years from time of diagnosis
  – Worse in symptomatic patients
• Up to 90% of PSC patients have IBD; conversely on 5% of IBD patients develop PSC
• Patients present with no symptoms, fatigue, pruritus, and cholangitis
  – 50% do not have symptoms at diagnosis
• PSC-colitis may be a distinct form of IBD

**Diagnostic algorithm for PSC**

- **Suspicion of PSC**
  - Elevation of cholestatic enzymes or transaminases

- **Bilirubin elevated**

- **MRCP**
  - No PSC and high suspicion or PSC with strictures and cholestasis
  - ERCP +/- dilation and brushing of strictures

- **PSC without significant strictures**
  - if ERCP negative and high suspicion

- **Liver Biopsy**

**Complications and management of PSC**

**Malabsorption of fat soluble vitamins**
- Periodically check vitamin A, D and E

**Osteoporosis**
- Perform bone density testing q 2-3 years
- Calcium and vitamin D supplementation

**Pruritus**
- Dominant strictures should be excluded if pruritus worsens with evidence of cholestasis

**Cholangiocarcinoma**
- 10-15% lifetime risk
- Some suggest annual US or MRCP and Ca 19-9

Bergquist, A et al. J Hepatol 2002
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**Risk factors for colorectal cancer in UC**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio (OR)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSC</td>
<td>6.9</td>
<td>1.2-40</td>
</tr>
<tr>
<td>Chronic active disease*</td>
<td>3.2</td>
<td>1.2-8.6</td>
</tr>
<tr>
<td>Colorectal cancer in first degree relative</td>
<td>1.4</td>
<td>0.3-5.9</td>
</tr>
</tbody>
</table>

*Period of >1 year with continuous symptoms

- CRC in PSC patients has been reported to occur early in the course of the disease
- If PSC and chronic colitis, surveillance should be performed annually from the time of PSC diagnosis


**Ursodeoxycholic acid and chemoprevention in UC**

<table>
<thead>
<tr>
<th>Treatment Assignment</th>
<th>Probability</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>Low-dose UDCA (8-15 mg/kg)</td>
<td>Placebo</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>UDCA</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>UDCA</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>UDCA</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>UDCA</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>UDCA</td>
<td>1.0</td>
</tr>
<tr>
<td>High-dose UDCA (28-30 mg/kg)</td>
<td>Placebo</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>UDCA</td>
<td>0.2</td>
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<td>UDCA</td>
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n=52

- Proportion of patients free of dysplasia or cancer according to initial treatment assignment

Summary

• EIMs commonly occur in patients with IBD
  – Arthritis, EN and ocular disorders most common
• Educate your patients on EIMs
• Identify a rheumatologist, ophthalmologist, and dermatologist in your institution and/or area to refer patients with complicated EIMs
• Identify one or two common EIMs that you feel comfortable managing