Beyond the Bowel: Extraintestinal Manifestations of Inflammatory Bowel Disease

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Learning Objectives

- Review manifestations of inflammatory bowel disease outside of the luminal digestive tract
  - Bones and joints
  - Skin disease
  - Eye inflammation
  - Oral lesions
  - Psychiatric disorders
  - Miscellaneous

- Understand current management of extraintestinal manifestations (EIMs)

- Review symptoms that indicate intestinal inflammation is not controlled

- Know when and where to seek expert consultation for non-digestive symptoms
Introduction
Extraintestinal Manifestations

• Up to 50% of patients with inflammatory bowel disease suffer from EIMs
  • Some can precede the diagnosis of inflammatory bowel disease
  • Symptoms and presentation can be seen in other conditions
    • E.g. joint pain and swelling due to rheumatoid arthritis

• Risk factors for development of EIMs
  • Duration of inflammatory bowel disease
  • Other EIMs
  • Crohn’s disease (CD) > ulcerative colitis (UC); especially colonic CD

• Causes of EIMs poorly understood
Extraintestinal Manifestations

- Skin and mucosae
  - Aphthous stomatitis
  - Cheilitis
  - Peristomatitis vegetans

- Dermatologic
  - Erythema nodosum
  - Pyoderma gangrenosum
  - Metastatic Crohn's disease
  - Psoriasis
  - Epidermolysis bullosa acquista
  - Sweet's syndrome
  - Perianal disease
  - Polyarteritis nodosa
  - Acrodermatitis enteropathica

- Neurologic
  - Peripheral neuropathy
  - Meningitis/abscesses
  - Vestibular dysfunction
  - Thromboembolic disease

- Ocular
  - Uveitis/iritis
  - Episcleritis
  - Chorioretinitis
  - Retinal vascular disease

- Cardiac
  - Pericarditis
  - Cardiomyopathy
  - Myocarditis
  - Endocarditis

- Hepatobiliary and pancreatic
  - Primary sclerosing cholangitis
  - Steatosis
  - Cholelithiasis
  - Cholangiocarcinoma
  - Autoimmune hepatitis
  - Pancreatitis
  - Pancreatic insufficiency

- Bronchopulmonary
  - Reduced CO2 diffusing capacity
  - Pulmonary vasculitis
  - Fibrosing alveolitis
  - Eosinophilic pneumonia

- Renal and genitourinary
  - Nephrolithiasis
  - Obstructive hydropnephrosis
  - Enterovesical fistula
  - Glomerulonephritis
  - Amyloidosis

- Hematologic
  - Iron deficiency anemia
  - Folate deficiency
  - Vitamin B12 deficiency
  - Autoimmune hemolytic anemia
  - Anemia of chronic disease
  - Coagulation abnormalities
  - Thrombocytosis/thrombocytopenia

- Musculoskeletal
  - Colitis arthritis
  - Sacroiliitis
  - Ankylosing spondylitis
  - Hypertrophic osteoarthropathy
  - Osteoporosis/osteomalacia
  - Granulomatous synovitis
  - Rheumatoid arthritis
  - Osteonecrosis
  - Steroid-induced myopathy

- Endocrine and metabolic
  - Delayed growth/ puberty
  - Thyroiditis
Why do EIMs matter?

• EIMs can affect quality of life
  • Some EIMs can lead to disability or death

• Need to differentiate from an alternative diagnosis or medication side effects

• Many EIMs become active when the intestine is inflamed
  • Warning sign that GI symptoms may be coming or that inflammation is not controlled

• Need for alternative or additional medical therapy, specialist referrals (beyond gastroenterology)
Joint and Bone Disease

Who needs a weather report when you have arthritis?
Arthritis and Arthropathy

- Joint involvement by inflammatory bowel disease
  - Axial (spine)
  - Peripheral

- Symptoms based on location of inflammation
  - Low back pain, stiffness, and decreased mobility
  - Pain, stiffness, and swelling of various joints
  - Symptoms classically noticeable after resting / sitting still and can improve with movement or stretching

- Medications used to treat inflammatory bowel disease can also lead to joint pain
  - Anti-TNF alpha therapy, drug-induced lupus

- One of the most common EIMs
  - 5-14% of those with UC and 10-20% of those with CD
  - Evidence of inflammation on imaging may be more common
Arthritis and Arthropathy

- Axial arthropathy
  - Sacroiliitis
    - Inflammation of the sacroiliac joint
    - Can cause low back pain / stiffness
    - Common
      - Seen in 20-50% of IBD patients on MRI
  - Ankylosing spondylitis
    - Inflammation of the spine
    - Can cause stiffness, pain, limited mobility
      - If progressive can fuse the vertebra of the spine
    - Less common
      - Seen in 1-10% of patients
    - Unrelated to bowel inflammation

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Arthritis and Arthropathy

- Peripheral arthropathy
  - Type I (pauciarticular)
    - Affecting \( \leq 5 \) joints
    - Most common in the lower extremities (knee)
    - Tracks with gut inflammation
    - Resolves within 10 weeks or less
    - No permanent joint damage
  - Type II (polyarticular)
    - Affecting \( >5 \) joints, symmetric inflammation
    - Often affects the upper extremities (hands)
    - Can last for months to years
    - Independent of gut inflammation
    - No permanent joint damage typically

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Arthritis and Arthropathy

- **Treatment**
  - **Axial**
    - Referral to Rheumatologist recommended
      - Risk for progressive damage to the spine
    - Physical therapy, short-term, low dose NSAIDs (COX-2 selective)
    - Anti-TNF alpha therapy
  - **Peripheral**
    - Treatment of gut inflammation helpful for Type I
    - Rheumatology referral may be needed for Type II
    - Short course of NSAIDs, prednisone, steroid injections, sulfasalazine, anti-TNF alpha

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Bone Mineral Density

- Low bone mineral density and osteoporosis are common in IBD
  - 20-50% of patients
- Osteoporosis can increase risk of fractures, which can be disabling
- Risks can be related to the underlying disease or medications needed for treatment
  - Chronic inflammation
  - Corticosteroids (prednisone)
  - Small bowel inflammation
  - Smoking
  - Nutritional deficiency
  - Age
  - Low physical activity

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Bone Mineral Density

- Diagnosis is made by dual-energy X-ray absorptiometry (DEXA)
- Screening recommended if
  - Steroid use for >3 months
  - Family history of osteoporosis
  - Malnourished or thin
  - All post-menopausal women
- Vitamin D levels checked intermittently as deficiency is common
  - Vitamin D replacement may reduce risk of disease flares
Bone Mineral Density

- **Treatment**
  - Osteoporosis can be treated safely with bisphosphonate therapy
  - Control of inflammation can help in normalizing bone density
- **Prevention**
  - Calcium and vitamin D supplements should be used when prednisone is prescribed
    - Calcium 500-1000mg/day, vitamin D3 800-1000 units per day
  - Correction of low vitamin D levels
  - Avoidance of excess alcohol and smoking, weight bearing exercise, maintain healthy nutritional status
Skin Disease

"Now what seems to be the problem?"
Skin Disease

- Inflammatory bowel disease associated with skin lesions and rashes
  - Classic IBD lesions
    - Erythema nodosum and pyoderma gangrenosum
    - Metastatic Crohn’s disease
  - Medication side effects
    - Anti-TNF alpha, methotrexate, sulfasalazine, antibiotics
  - Vitamin and mineral deficiencies
  - Infections
  - Rashes associated with higher prevalence of IBD
    - Hidradenitis suppurativa and psoriasis
Skin Disease

- **Erythema nodosum (EN)**
  - Painful red or violet nodules 1-5cm in diameter
  - Typically found on the front of the legs, below the knee
  - Seen in 4-7.5% of patients
  - No permanent scarring, bruising can be seen as lesions heal
  - Tracks with bowel inflammation

- **Treatment**
  - Leg elevation, rest, compression stockings
  - Management of associated bowel inflammation
  - Potassium iodide, NSAIDs
  - Prednisone effective as well as azathioprine and anti-TNF alpha agents

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Skin Disease

- **Pyoderma gangrenosum**
  - Skin pustule which can become a burrowing ulcer 1-8in, with purple border.
  - Most common on the legs and around stomas
    - Often arises at sites of trauma (pathergy)
  - More common in ulcerative colitis (0.6-2.1%) than CD
  - Does not track with bowel inflammation
  - Can lead to scarring, infection, and exposure of muscle and tendons
  - Treatment: Urgent
    - Wound care /ostomy nurse, dermatologist, surgeon
    - Avoidance of ongoing trauma to the area
    - Topical or systemic corticosteroids
    - Anti-TNF alpha therapy
    - Ostomy revision
Eye Disease

Islets of Humor

If only we had our regular eye exams.
Eye Disease

Several parts of the eye can become inflamed in association with inflammatory bowel disease
  - Fairly common, 4-12% of IBD patients

Symptoms can range from asymptomatic or mild irritation to severe pain and blindness

Diseases of the eye can also be seen with medications used for inflammatory bowel disease
  - Prednisone: Glaucoma, cataracts

Routine eye exams recommended

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Eye Disease

- **Episcleritis**
  - Inflammation of the outer layer of the eye
  - Symptoms: Red conjunctiva, mild pain / “grittiness”, no vision changes
  - Tracks with bowel inflammation
  - Treatment
    - Management of underlying bowel inflammation
    - Addition of eye drops (NSAID, corticosteroids)

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Eye Disease

- **Uveitis**
  - Inflammation of the inner eye
  - Symptoms: Typically both eyes involved. Eye pain, blurred vision, headache, and worsening pain with light
  - Independent of bowel inflammation
  - Treatment
    - Urgent referral to an ophthalmologist recommended given possibility of loss of sight
    - Treatments for IBD often effective for uveitis
      - Anti-TNF alpha therapy, azathioprine, methotrexate
  - Other rare forms of eye disease have been associated with inflammatory bowel disease. Any rapid change in vision should prompt urgent referral to an ophthalmologist
Oral Lesions
Oral Lesions

- **Oral lesion**
  - Common in IBD
    - Seen in 20-50% of patients with CD
    - Seen in 8% of patients with UC
    - Aphthous stomatitis and angular chelitis seen in both conditions (and in the general population)
    - Angular chelitis often related to vitamin deficiencies
    - Lesions typically unrelated to bowel inflammation

- **Specific lesions seen in Crohn’s disease due to direct Crohn’s inflammation**
  - Cobblestone appearance to the oral mucosa
  - Deep ulcers
  - Swelling of lips, cheek
  - Inflamed gums
  - Fissures

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Oral Lesions

Treatment

- Specific oral lesions in CD often treated with medications used for the bowel disease
  - Additional topical therapy can be added to improve inflammation, pain, and to prevent infection of the lesions
    - Topical corticosteroids, topical NSAIDs, anesthetics, antiseptic mouthwash,
- Aphthous stomatitis typically treated with topical therapy
- Angular chelitis treated by correction of vitamin/minearl deficiency (iron, B12, folate, zinc) and exclusion of infection
- Multidisciplinary care with an ENT specialist and dentist may be needed
Liver Disease
Liver Disease

- Primary sclerosing cholangitis
  - Chronic scarring of the bile ducts
    - Symptoms: itching, malaise, fevers, abdominal pain in right upper quadrant
    - Seen in 4-5% of those with inflammatory bowel disease
      - UC>CD
    - 70-80% of patients with PSC have IBD
  - No effective medical therapy
  - Disease complications
    - Liver failure / cirrhosis, cholangitis, liver and bile duct cancer, colon cancer (4x increased risk)
  - 12-20 year survival without liver transplant
Psychiatric Disease
A Common Problem

- Using structured diagnostic interviews:
  - 65% lifetime prevalence of mood disorder in IBD
    - 42% in controls
  - 12 mo depression prevalence of 12-14% in IBD

- Higher levels of depression/anxiety in IBD than colon cancer
  - Similar to rates for RA or DM

- 17% with major depression and IBD considered suicide in the last 12 mo
Mood in IBD Management

- Higher depression scores have been associated with higher CD Activity Index scores
- Depression level at baseline correlates with total number of relapses
- Median time to relapse was shorter in those with depression (97 days vs. 362 days)
- Major depression and higher anxiety symptoms less likely to achieve remission with infliximab
Managing Psychiatric Comorbidities

• Watch the steroids
  • >25% may have adverse psychiatric events, 6% of these serious
    • Dose-dependent effect
    • No clear association with underlying psychiatric disease
  • Manic symptoms tend to occur early (even 1st week)
  • Depressive symptoms tend to occur later in treatment / during taper

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Managing Psychiatric Comorbidities

- Most vulnerable times
  - Disease onset, disease diagnosis, and during flares

- Anti-depressant therapy
  - Typical therapy (SSRI, SNRI) works.
    - Side effects can include digestive symptoms such as diarrhea

- Consider psychological treatment
  - Cognitive behavioral therapy with most support
Miscellaneous
Miscellaneous EIMs

• Kidney stones
  • Calcium oxalate and uric acid stones more common, particularly with CD
    • Impaired calcium absorption due to fat in stool
      • More oxalate is absorbed
      • Weakened gut barrier allows
    • Acidosis and concentrated urine due to diarrhea
  • Affects 10% of CD patients
    • 4-7 years after diagnosis
    • Particularly with multiple or long ileal resection or small bowel disease
  • Prevention and treatment
    • Control of diarrhea, adequate hydration, dietary calcium
    • Medical treatments for specific stone types
    • Surgical treatments for complicated stones

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Miscellaneous EIMs

- **Gallstones**
  - Risk increased 2x in CD (no increased risk in UC)

- **Blood Clots**
  - 2.5x increased risk with IBD
  - Associated with active inflammation and hospitalization
    - Smoking, oral contraceptives, surgery, genetic conditions as other risks
  - 1/3 recur within 5 years
  - Prophylactic and therapeutic anticoagulation when appropriate
    - Lifelong anticoagulation recommended if clots arises without flare of disease

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Thanks for your attention!

• Questions?