Extraintestinal Manifestations of Inflammatory Bowel Disease

Lauren C. Briley M.D.
University of Louisville
Department of Gastroenterology/Hepatology
Extraintestinal Manifestations

- Common – affect 21-36% of IBD patients
- Includes:
  - Disorders of the skin, eyes, and joints – parallel disease activity (some exceptions)
  - Complications or direct extensions of the bowel disease (kidney stones, obstructive uropathy, malabsorption, and gallstones)
  - Nonspecific extraintestinal manifestations: osteoporosis, hepatic diseases, and amyloidosis
Prevalence

- 25-40% of IBD patients will exhibit extraintestinal manifestations of the disease
- Virtually 100% of patients will have disease outside the GI tract if “secondary effects” of the disease are considered
- In large series, EIMs more common in CD than UC
Pathophysiology

- Multiple theories
  - Immune complex type hypersensitivity to a colonic antigen – would explain why patients with colonic disease are more likely to have pathology
  - Cytotoxic antibodies
  - Delayed type hypersensitivity reaction
  - Cross-reacting colon protein that affects eyes, joints and skin
Association with Disease Activity

- EN associated with active disease in over 90% cases
- Ocular inflammation in 78%
- Arthropathy depends on clinical characteristics of the arthropathy:
  - Type I peripheral arthropathy (large joint acute arthropathy) associated with active disease in 80%
  - Type II (symmetrical small joint arthropathy) is more independent of disease activity (similar to axial arthropathy)


Take Home Point #1

Parallel disease activity:
- Peripheral arthritis (Large joint>small joint)
- Erythema nodosum
- Pyoderma gangrenosum (in UC)
- Episcleritis

Independent of disease activity:
- PSC
- Uveitis
- Axial arthropathy
The presence of EIMs increases the risk of developing subsequent EIMs

- CD patient without any EIM has 2% risk of developing EN – risk increases to 24% if they have Type I arthropathy
- Risk of developing ocular manifestations increases from 2 (no EIMs) to 17% (one EIM)
- Similar increases seen with UC

Walker D, Orchard, T. Do extraintestinal manifestations predict disease course, severity, and/or activity in IBD? Inflammatory Bowel Disease; 14(S2): S200-201.
EIMs more common with colonic disease

- In general – colonic involvement means more likely to have extraintestinal manifestations.
- In a study of 700 patients, Colonic disease (42%) had a higher association with extraintestinal manifestations than small bowel (23%) disease alone.

Musculoskeletal Manifestations
Which of the following patients symptoms are more likely to be associated with active bowel disease?

1. 28 yo with CD who complains of morning stiffness and low back pain
2. 32 yo with CD and tender, hyperpigmented nodules on his shins and joint pain
3. 40 yo with CD and pain and swelling of his MIP and wrist joints
Which of the following patients symptoms are more likely to be associated with active bowel disease?

1. 28 yo with CD who complains of morning stiffness and low back pain
   Axial arthropathy-independent of IBD

2. 32 yo with CD and tender, hyperpigmented nodules on his shins and joint pain
   Erythema nodosum – parallels IBD activity

3. 40 yo with CD and pain and swelling of his MIP and wrist joints
   Polyarticular peripheral arthritis - independent
Peripheral Arthropathy

- 5-20% patients with IBD
- Crohn’s > UC
- More likely with disease affecting the colon in CD and with more extensive colonic involvement in UC

DDSEP Version 5.0; Feldman: Sleisenger & Fordtran's Gastrointestinal and Liver Disease, 8th ed
Peripheral Arthropathy

- Risk increases in patients with complications of their IBD (i.e., abscesses in Crohn’s) and with other extraintestinal manifestations (skin, eye, etc.)

- Seronegative (RF negative)

- No permanent joint deformity

- Usually responds to treatment of colitis (medical or surgical)

DDSEP Version 5.0; Feldman: Sleisenger & Fordtran’s Gastrointestinal and Liver Disease, 8th ed
Peripheral Arthropathy

Classification

- **Type I - Pauciarticular** (4 or fewer joints)
  - typically large joints
  - 20-40% will have recurrent episodes
  - associated with increased incidence of EN and uveitis
  - Parallels disease activity

- **Type II - Polyarticular** (5+)
  - typically small joints
  - persistent symptoms
  - increased risk uveitis but not EN
## Peripheral Arthropathy

**Feldman: Sleisenger & Fordtran’s Gastrointestinal and Liver Disease, 8th ed**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Type 1 (Pauciarticular)</th>
<th>Type 2 (Polyarticular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>35%</td>
<td>24%</td>
</tr>
<tr>
<td>Number of joints affected</td>
<td>&lt;5</td>
<td>≥5</td>
</tr>
<tr>
<td>Joints affected</td>
<td>Mainly large joints</td>
<td>Mainly small joints</td>
</tr>
<tr>
<td>Joints affected</td>
<td>Knee &gt; ankle &gt; wrist &gt; elbow &gt; MCP &gt; hip &gt; shoulder</td>
<td>MCP &gt; knee &gt; PIP &gt; wrist &gt; ankle &gt; elbow &gt; shoulder</td>
</tr>
<tr>
<td>Duration of attacks</td>
<td>&lt;10 wk (median 5 wk)</td>
<td>Months to years (median 3 yr)</td>
</tr>
<tr>
<td>Association with bowel disease activity</td>
<td>Parallel</td>
<td>Independent</td>
</tr>
</tbody>
</table>
Axial Arthropathy

- Less common than peripheral (3-5%)
- Spondylitis and Sacroilitis
- Presents as low back pain and morning stiffness
- Disease does not parallel bowel activity
Axial Arthropathy
Spondylitis

- 5-10%
- Most HLA-B27 positive
- Positive Schober’s test (limited spinal flexion)
- Progressive course - permanent skeletal damage
- Advanced cases - characteristic squaring of vertebral bodies and anklyosis ("bamboo spine")
Axial Arthropathy
Sacroilitis

- May be asymptomatic
- Majority HLA-B27 negative
- Most do not progress to spondylitis unless bilateral
Key Points

IBD Associated Arthropathy

- Peripheral arthropathy most common
- Pauciarticular arthropathy, mostly large joints – parallels bowel activity
- Polyarticular peripheral arthropathy and axial arthropathy do not parallel bowel disease activity (both are more chronic)
- Spondylitis is associated with HLA-B27
Osteopenia/Osteoporosis

- 30-60% patients with Crohn’s
- Low bone density is associated with Crohn’s (malabsorption of calcium and vitamin D +/- effects of pro-inflammatory cytokines and osteoblasts)
- Exacerbated by chronic steroid use
Osteopenia/Osteoporosis

- Low BMD is a risk factor for these disorders, but IBD patients are still at higher risk even with normal BMD.
Question

Which of the following statements is true regarding DEXA screening in patients with IBD?

A. Patients who do not have joint pain do not need DEXA
B. All patients with CD and UC should undergo DEXA at diagnosis
C. Patients who are not currently treated with steroids do not need DEXA
D. Patients with IBD who are older than 60 yrs or postmenopausal women should undergo DEXA
E. Patients with IBD who are older than 50 yrs should undergo DEXA
D. Patients with IBD who are older than 60 yrs or postmenopausal women should undergo DEXA
Osteoporosis/Osteopenia

DEXA Testing Guidelines

AGA and ACG guidelines – DEXA recommended with any of the following risk factors:

- Age > 60
- Low BMI (< 20)
- Hypogonadism (postmenopausal or low testosterone in men)
- Steroid treatment for at least 3 months
- Recurrent steroid courses
- Family history of osteoporosis
- History of heavy smoking
- Personal history of osteoporotic fracture
Musculoskeletal Manifestations

Less common

- Septic joint (as a complication of psoas abscess extension)
- Amyloidosis
- Pseudoarthrosis due to withdrawal of steroids
- Aseptic necrosis of the hip due to steroids
Mucocutaneous Manifestations
Which of the following is least likely to assist in healing this IBD associated lesion?

1. Infliximab
2. Local wound care
3. Antibiotics
4. Debridement
Which of the following is least likely to assist in healing this IBD associated lesion?

1. Infliximab
2. Local wound care
3. Antibiotics
4. Debridement – Pyoderma Gangrenosum exhibits PATHERGY
Pyoderma Gangrenosum

- Approximately 5% UC patients – Less common with Crohn’s
- Most often on the leg or around a stoma – can occur on face, trunk or upper extremities
- Exhibits pathergy (worsens with trauma and debridement)
Pyoderma Gangrenosum

- Begins as a papule, pustule or nodule and progresses to ulceration
Pyoderma Gangrenosum

- Often occurs without flare in bowel symptoms in Crohn’s but parallels disease activity in UC
Erythema Nodosum

- Female > Male
- Tender, red subcutaneous nodules
- Usually pretibial
- Strongly associated w/arthropathy
- Occurs with flares of bowel symptoms
Mucocutaneous Manifestations

Less Common

- Apthous ulcerations in mouth
- Metastatic Crohn’s (granulomatous inflammation of the skin)
- Leukocytoclastic vasculitis
- Sweet’s syndrome (neutrophilic dermatosis)
- Increased rates of psoriasis
Key Points
Mucocutaneous Manifestations

- EN and PG (EN>PG) parallel bowel activity
- PG exhibits pathergy – do not debride!
Ocular Manifestations
Ocular Manifestations

- < 10% with IBD will have ocular manifestations
- Can lead to permanent vision loss
- Important to know when to refer to ophtho
Which of the following patients needs urgent referral to an ophthalmologist?

1. 28 yo CD patient with active bowel disease and a burning, red left eye
2. 36 yo with CD and severe right eye pain with ocular exam notable for a diffusely red eye
3. 40 yo with UC and new onset visual blurring and photophobia in his right eye which is also somewhat painful
4. 42 yo CD patient with history of steroid dependent disease requiring multiple courses of steroid in the past few years
Which of the following patients needs urgent referral to an ophthalmologist?

1. 28 yo CD patient with active bowel disease and a burning, red left eye - **Episcleritis**
2. 36 yo with CD and severe right eye pain with ocular exam notable for a diffusely red eye – **Scleritis** – requires urgent referral
3. 40 yo with UC and new onset visual blurring and photophobia in his right eye which is also somewhat painful – **Uveitis** – requires referral due to risk of longterm complications
4. 42 yo CD patient with history of steroid dependent disease requiring multiple courses of steroid in the past few years – needs regular eye exams due to increased risk of cataract formation
Eye Findings in IBD

- Tearing
- Burning
- Itching
- Ocular Pain
- Photophobia
- Conjunctival/Scleral Hyperemia
- Blurred Vision
- Loss of Visual Acuity
Episcleritis

- Acute redness of one or both eyes
- Symptoms of irritation and burning
- Characteristically flares with disease flares
- Pain is common
- Not associated with loss of vision, photophobia, or loss of normal pupillary response to light
Episcleritis

- Ocular exam – focal or diffuse patches of redness within which white patches of sclera can be seen between the dilated episcleral vessels
- Symptoms usually improve with treatment of underlying IBD
Scleritis

- More severe than episcleritis
- Severe eye pain
- Eye is more diffusely red than in episcleritis with pink areas between dilated blood vessels (as opposed to white with episcleritis)
Scleritis

- Can lead to vision impairment
- Can lead to retinal detachment or optic nerve swelling
- Must be treated with systemic steroids, NSAIDs, or immunosuppressants to prevent vision loss
- Requires urgent referral to ophthalmologist
Uveitis

- Present with painful eye with visual blurring and photophobia
- Serious cases feature miotic pupils and abnormal pupillary response to light
- “Ciliary flush” – intense redness at the limbus and radiates outward for a short distance
Uveitis

- Long-term complications include intraocular adhesions that can lead to cataracts and secondary glaucoma.
- Treatment – cycloplegics and topical steroids.
# Ocular Manifestations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Findings</th>
<th>Visual Acuity?</th>
<th>Association w/bowel disease?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episcleritis</td>
<td>- Crohn’s &gt; UC</td>
<td>Not affected</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>- Scleral/conjunctival injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scleritis</td>
<td>- Involves deeper layers of the eye</td>
<td>Damage if untreated</td>
<td>Yes</td>
</tr>
<tr>
<td>Uveitis</td>
<td>- Headache, eye pain, photophobia, lacrimation</td>
<td>* Can lead to blindness-untreated</td>
<td>Less predictable</td>
</tr>
</tbody>
</table>
Ocular Manifestations

Key Points

- If the patient present with a red eye + pain or visual changes, REFER to ophtho (scleritis/uveitis can lead to permanent visual loss)
- All IBD patients should have routine eye exams
Hepatobiliary Manifestations
PSC

- Most common hepatobiliary complication of IBD
- 70-80% PSC patients have concomitant IBD
- 1.4-7.5% IBD patients will develop PSC
Distinct pattern of clinical findings in IBD patients with PSC:
- higher prevalence of rectal sparing
- more backwash ileitis
- more likely to have pancolitis
- higher incidence of colorectal neoplasia (risk persists after OLTx)
- poorer survival overall

Navaneethan, U; Shen, B. Hepatopancreatobiliary Manifestations and Complications Associated with Inflammatory Bowel Disease. Inflamm Bowel Dis 2010
Hepatobiliary

- PSC – UC (85-90%) > Crohn’s
  - 7.5 % of patients with UC
  - Cholangiocarcinoma 20-30X more likely in UC patients
  - Seen in Crohn’s disease with colonic involvement (colitis/ileocolitis)
  - Independent of the course of bowel disease
  - Should be excluded in patients with persistantly elevated LFTs or evidence of chronic liver disease
Pancreatitis

- Increased risk of both acute and chronic pancreatitis in IBD
- May be gallstone associated, medication related (5-ASA, steroids, imuran, 6-MP), or idiopathic
- Most cases clinically silent
- CD>UC (risk slightly higher)
Gallstones

- 17-34% of patients with CD
- Does not appear to be an increased risk in UC
- CD of the colon does not increase the risk for gallstone formation

DDSEP Version 5.0
Gallstones in CD
Pathophysiology

- Decreased bile salt pool due to decreased resorption in terminal ileum (due to active inflammation or previous resection)
  - Causes cholesterol supersaturation and nucleation with subsequent gallstone formation
- Decreased gallbladder motility
- Prolonged hospitalizations and use of TPN also associated
Genitourinary Manifestations
Nephrolithiasis

- 7-10% patients with IBD
- Uric acid and calcium oxalate most common types
Nephrolithiasis

- Calcium oxalate stones (80%)
  - Fat malabsorption leads to luminal binding of fatty acids by calcium
  - Decreased calcium available to bind and clear oxalate
  - Causes increased oxalate absorption and stone formation
Nephrolithiasis

- Calcium oxalate stones
  - Because the absorption of sodium-bound oxalate occurs in the colon, the increased risk of stones is present only with an intact colon
Uric acid stones
- Due to volume depletion (diarrhea/ileostomy output) and hypermetabolic state
- Kidneys respond to fluid loss by forming concentrated acidic urine which favors uric acid crystal precipitation
- Patients with ileostomy are at highest risk
Prevention of Nephrolithiasis

- Adequate hydration
- With known hyperoxaluria, decreased dietary oxalate and fat and cholestyramine (4 gm tid – binds bile salts and oxalate in the gut) may help
- Potassium citrate reduced calcium stones (especially in hypocitraturia)
- Calcium supplementation may help (increased calcium to bind oxalate and form insoluble complex excreted in stool)
- Alkalization of the urine is used for uric acid stones (oral citrate or bicarbonate)
Secondary Systemic Amyloidosis

- Very rare – CD > UC (0.9% vs. 0.07%)
- Often affects the kidney
- Proteinuria → Nephrotic Syndrome → CRI
- Fat pad biopsy most sensitive test for diagnosis in IBD patients
Obstructive Uropathy

- Classically right sided in pts with distal ileal CD
- Left sided can be seen with jejunal CD
- Almost always occurs at the level of the pelvic brim
- Mechanism is obstruction due to inflammation, abscess, or scarring
Fistula

- Almost exclusively seen in CD
- Estimated incidence 8%
  - Bladder (colovesicular/enterovesicular)
  - Also urethra, vagina, or ureter
- Most common are ileovesicular and occur on the right side of the bladder
- M>F (posterior bladder wall protected by uterus)
Fistula

- Symptoms begin with dysuria/increased frequency and can progress to pneumaturia and fecaluria once the fistula is complete.
- 1/3 present with sepsis.
- Uncommonly can have associated abscess.
Genitourinary Manifestations

Less Common Manifestations (21+ cases)
- Membranous nephropathy
- Glomerulonephritis
- IgA nephropathy
- Minimal change
Treat calcium oxalate stones with calcium supplementation to prevent new stones

Uric acid stones more common with ileostomy; Ca oxalate needs intact colon

Right (think TI) sided hydroureter in CD

Proteinuria/CRI in IBD – think amyloid!

Increased gallstones in CD of SB
Hematologic Manifestations
True or False

Both UC and CD are prothrombotic
Both UC and Crohn’s disease are prothrombotic

Venous thromboembolism > arterial

In > 50% with thrombosis, no precipitating factor found

Associated factors include - thrombocytosis; increased levels of fibrinogen, fibrinopeptide A, factor V, and factor VIII; antithrombin III deficiency; and free protein S deficiency

- All are related to active bowel inflammation.
Anemia

- Multifactorial
  - GI Blood loss
  - B12 malabsorption in CD patient with ileal inflammation or resection
  - Iron malabsorption with CD of the duodenum
  - Folate malabsorption with inflammation in the jejunum
  - Bacterial overgrowth due to strictures or resection (low B12, nml/high folate b/c bacteria produce folate)

DDSEP Version 5.0
IBD and Fertility
Evidence shows that females with Crohn’s have somewhat impaired fertility
- Mechanisms vary – (dyspareunia, perineal disease, impaired ovulation, etc)

Males with Crohn’s may have reversible infertility due to sulfasalazine

No difference in fertility in UC patients
Pregnancy and IBD

- Patients in remission are likely to remain in remission throughout the pregnancy.
- Patients with active disease at the time of conception have poorer outcomes.
- EGD, ERCP, flex sig safe in pregnancy if needed (with lead protection) – c-scope should be avoided unless life threatening situation.
General Recommendations for Patients with IBD

- Annual eye exams if significant history of steroid use (increased cataract formation) and early referral for visual symptoms
- Baseline DEXA, calcium and vitamin D supplementation with consideration for bisphosphonate in Crohn’s patients
Which of the following statements is false?

A. Peripheral arthritis is the most common extraintestinal manifestation in pts, occurring in 5-20%. The risk increases as the extent of colonic involvement increases.

B. Uveitis usually manifests as an acute/subacute painful eye with visual blurring, photophobia, headache and iridospasm. The temporal relationship of uveitis with bowel disease activity is very predictable. Uveitis classically parallels bowel activity.

C. Sacroilitis may be isolated and asymptomatic. SI joint changes are often present on MRI. Most are HLA-B27 negative and do not progress to AS.

D. Episcleritis is characterized by painless hyperemia of the sclera and conjunctiva without loss of vision. This parallels the disease activity.

E. PG occurs in 1-4% of IBD pts and seems more common in pts with UC than CD. Four distinct variants exist – pustular, bullous, ulcerative and vegetative. The vegetative is most common and is classically seen in IBD patients.
Answer

B. Uveitis usually manifests as an acute/subacute painful eye with visual blurring, photophobia, headache and iridospasm. The temporal relationship of uveitis with bowel disease activity is very predictable. Uveitis classically parallels bowel activity.

- The temporal relationship is actually not very predictable
Management of EIMs
Biologic Therapy in the Management of EIMs

- 3 small studies have shown improvement in joint symptoms in IBD patients with active intestinal inflammation and peripheral arthritis (N=4/4; N=36/59; n=7/11)
- All were treated with infliximab 5 mg/kg
- Axial arthritis also shown to respond to infliximab and adalimumab
Biologic Therapy in the Management of EIMs

- Few clinical trials have studied effect of biologics on IBD-associated skin diseases
- Largest study (Brooklyn et al) – multicenter, randomized, placebo-controlled (N=30 with 19/30 having IBD)
  - 46% of treatment arm had symptom improvement after initial infusion (within first 2 weeks)
- Only case reports regarding the use of biologics for the treatment of EN
Biologic Therapy in the Management of EIMs

- Few clinical trials have studied the effect of biologics on IBD-associated ocular diseases
  - Very small studies have shown suppression of symptoms with biologics
  - Pediatric literature regarding uveitis showed a positive response with infliximab
Take Home Points

1. EN, PG, Episcleritis and Peripheral Arthropathy (large joint > small joint) parallel disease activity
2. Axial arthropathy, Uveitis, and PSC are independent of bowel activity
3. EIMS are more common with colonic disease
4. PG exhibits pathergy
5. Refer painful, red eyes +/- vision changes for ophthalmologic evaluation