

Extraintestinal Manifestations of Inflammatory Bowel Disease

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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)

Orchard TR, Chua CN, Ahmad T, et al. Uveitis and erythematous nodules in inflammatory bowel disease: clinical features and the role of HLA genes. *Gastroenterology*. 2002;123:714-718.

Orchard T, Wordsworth B, Jewell D. The peripheral arthropathies of inflammatory bowel disease: their articular distribution and natural history. *Gut*. 1998;42:387-391.

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

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
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- Greenstein A, Janowitz H, Sachar D. The extra-intestinal complications of Crohn's disease and UC: a study of 700 patients. *Medicine*. 1976;55:401-412.

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

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)

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

Feature	Type 1 (Pauciarticular)	Type 2 (Polyarticular)
Frequency	35%	24%
Number of joints affected	<5	≥5
Joints affected	Mainly large joints	Mainly small joints
Joints affected	Knee > ankle > wrist > elbow > MCP > hip > shoulder	MCP > knee > PIP > wrist > ankle > elbow > shoulder
Duration of attacks	<10 wk (median 5 wk)	Months to years (median 3 yr)
Association with bowel disease activity	Parallel	Independent

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 ankylosis ("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

Answer

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

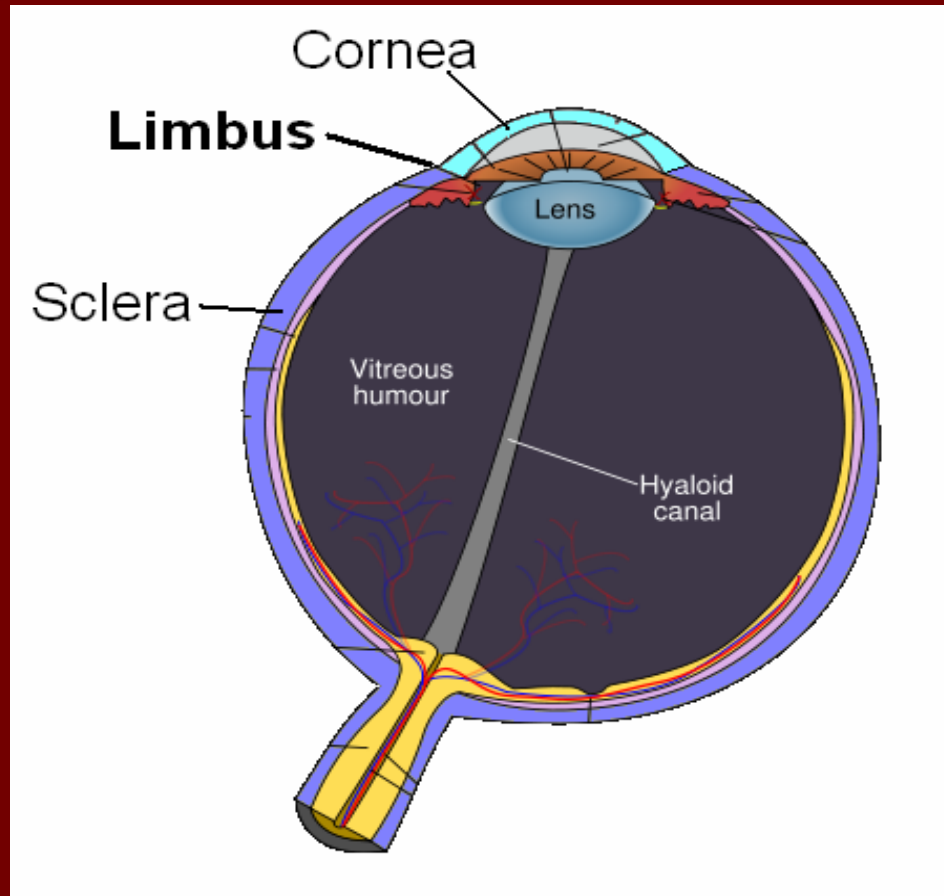
- Aphthous ulcerations in mouth
- Metastatic Crohn's (granulomatous inflammation of the skin)
- Leukocytoclastic vasculitis
- Sweet's syndrome (neutrophilic dermatosis)
- Increased rates of psoriasis

Key Points

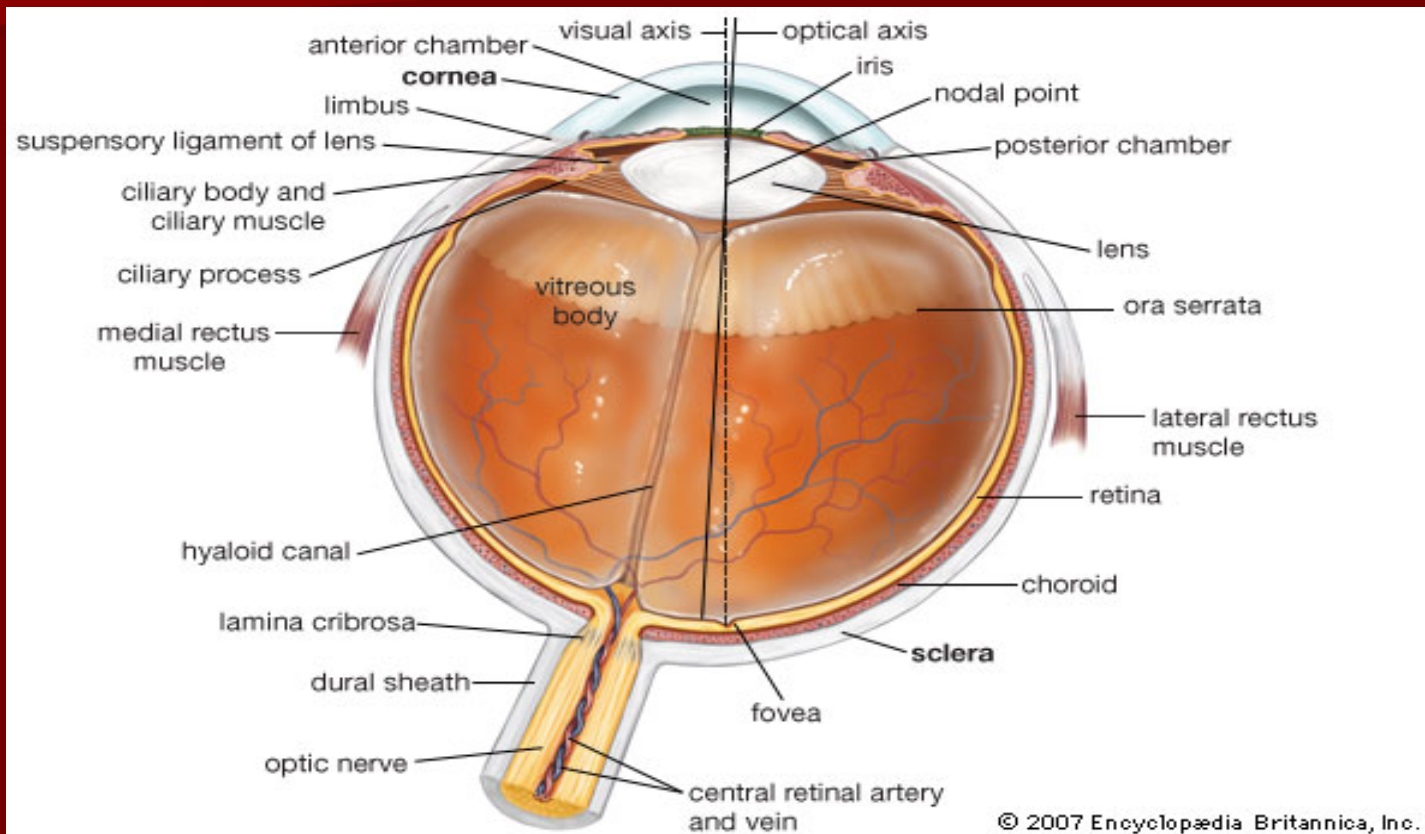
Mucocutaneous Manifestations

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

Ocular Manifestations



Ocular Anatomy



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 ophtho

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



Ciliary Flush

Uveitis

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



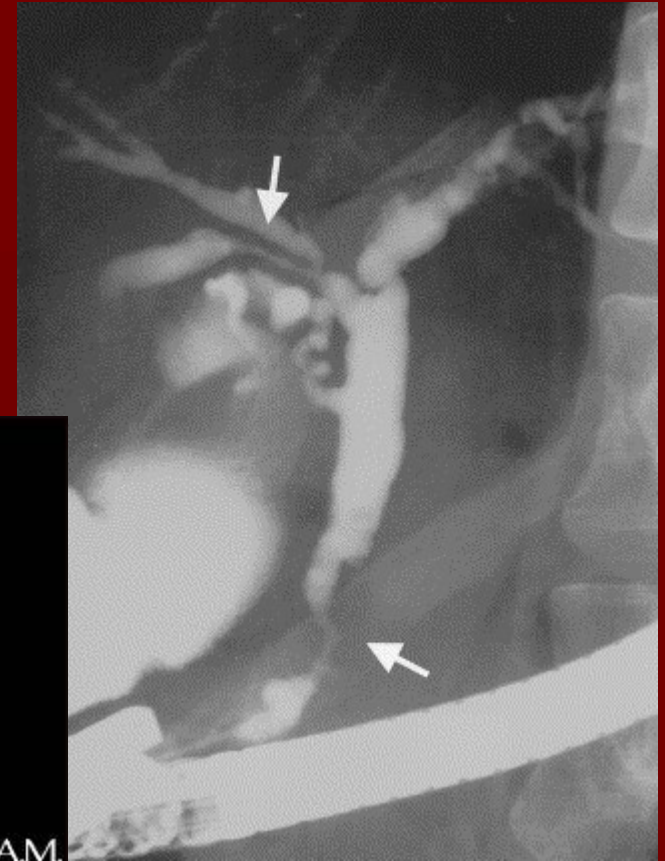
Ocular Manifestations

Diagnosis	Findings	Visual Acuity?	Association w/bowel disease?
Episcleritis	-Crohn's > UC -Scleral/conjunctival injection	Not affected	Yes
Scleritis	-Involves deeper layers of the eye	Damage if untreated	Yes
Uveitis	-Headache, eye pain, photophobia, lacrimation	* Can lead to blindness-untreated	Less predictable

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

PSC-IBD

- 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 persistently 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

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

Nephrolithiasis

- 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)
- Alkalinization 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

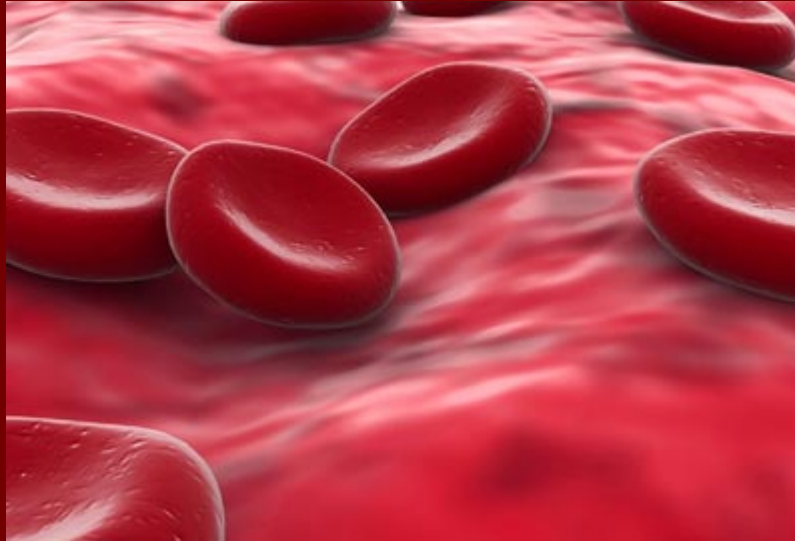
- Less Common Manifestations (21+ cases)
 - Membranous nephropathy
 - Glomerulonephritis
 - IgA nephropathy
 - Minimal change

Key Points

GU

- 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

Thromboembolism

- 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)

IBD and Fertility



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

Very Long Question

- 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 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