Extraintestinal Manifestations and Complications of IBD

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Objectives

- To become familiar with the extraintestinal manifestations of IBD.
- To understand the physiopathology of these manifestations.
- To become familiar with the treatments available for these manifestations.

Most Common Dermatologic Manifestations

- Aphthous ulcers
- Pyoderma gangrenosum
- Erythema nodosum
- Psoriasis
- Hidradenitis suppurativa

Rare Dermatologic Manifestations

- Sweet’s syndrome
- Neutrophilic dermatosis of the dorsal hands
- Leukocytoclastic vasculitis
- Sneddon-Wilkinson disease
- Acquired epidermolysis bullosa
- Linear IgA dermatosis
- Metastatic Crohn’s disease
- Orofacial granulomatosis

Hepatobiliary Manifestations

- Sclerosing cholangitis
- Drug-induced hepatotoxicity
- Steatosis
- Cholelithiasis (gallstones)
- Granulomatous hepatitis
- Liver abscess
- Pancreatitis
- Primary biliary cirrhosis

Ophthalmologic Manifestations

- Uveitis
- Scleritis
- Episcleritis
Most Common Pulmonary Manifestations

- Parenchymal lung disease
- Interstitial lung disease
- Sarcoidosis
- Pulmonary infiltrates with eosinophilia

Rare Pulmonary Manifestations

- Necrobiotic nodules
- Serositis

Rheumatologic Manifestations

- Peripheral arthritis:
  - Joints
  - Axial episodes:
  - Sacroiliitis
  - Spondyloarthritis

Aphthous Ulcer

- Common manifestation of IBD
- 4-20% of IBD patients will present with this symptom
- Heals in 5-7 days
- Causes
  - Neutrophils and chronic inflammation (histiocytes and lymphocytes) in the superficial stroma

Treatment

- Local anesthetic
- Local and systemic corticosteroids
- Antiallergic drugs (Amlexanox 5%)
- Antibiotics (Dapsone for 3-6 months)
- Anti-inflammatory drugs (Colchicine for 3-6 months)
- 5-ASA
- Immunomodulators: Thalidomide
- Pentoxifylline

Pyoderma Gangrenosum

- Affects 1-5% of IBD patients
- Most challenging extraintestinal manifestation
- Pyoderma activity often does not parallel the intestinal inflammation
- A purplish ulcer with a well defined raised border
- Lesions are very painful
- Causes
  - Typically, a sterile abscess with significant neutrophil infiltration, hemorrhagic and necrotic areas and small vein thrombosis.
Pyoderma Gangrenosum

- Possible treatments:
  - **Mild cases**: topical therapy: corticosteroids, Tacrolimus, intralesional therapy: corticosteroids
  - **Moderate cases**: Tapering doses of prednisone per os
  - **Severe cases**: Anti-TNFs, Dapsone (ATB), corticosteroids, immunomodulators (6-MP, MTX), CellCept, immunoglobulins, cyclosporine

Erythema Nodosum

- Most common cause of inflammatory nodules on the legs
- Most common cutaneous manifestation of IBD: 10% of IBD patients have it
- Unrelated to the severity of the IBD
- Sudden onset, often accompanied by fever, synovitis and arthritis
- Multiple, bilaterally symmetrical erythematous nodules on the anterior surface of the legs, accompanied by warmth and pain
- Initially brown but progresses to blue
- No ulceration

Erythema Nodosum

- Causes
  - Subcutaneous infiltration of neutrophils, lymphocytes and histiocytes
- Treatment
  - Pressure, elevation, rest and NSAIDs (use cautiously with IBD)
  - Prednisone per os, ATB, 5-ASA, immunomodulators, anti-TNFs

Psoriasis

- The prevalence of psoriasis in the general population is 2%, 10% in patients with Crohn's disease.
- Arthritis is associated in 30% of cases.
- Causes
  - Keratinocyte hyperproliferation, hyperkeratosis, parakeratosis, abnormal dilation of and increase in the dermal veins with dermal and epidermal leukocyte infiltration resulting in the production of microabscesses
- Treatment
  - Topical corticosteroids
  - Methotrexate
  - Retinoids (Accutane)
  - Cyclosporine
  - Anti-TNFs
  - IL-12, IL-23 (Ustekinumab)

Hidradenitis Suppurativa

- 40% of patients with hidradenitis suppurativa have Crohn's disease
- A chronic, recurrent inflammation caused by occlusion of the hair follicles
- Lesions occur primarily in the armpits, anus and neck and below the breasts
**Hidradenitis Suppurativa**

- **Causes**
  - Formation of abscesses and destruction of the pilosebaceous unit with formation of sinus tracts and massive inflammatory granulomatous and suppurative infiltration and fibrosis
- **Treatment**
  - Topical ATBs, per os
  - Retinoids (isotretinoin)
  - Anti-TNFs
  - Surgery

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**Sclerosing Cholangitis**

- **Causes**
  - PSC can also occur in Crohn's disease, especially with involvement of the colon
- **Prognosis and Complications**
  - Earlier diagnosis age
  - More significant mortality
  - Liver transplantation more common
  - 10-15% lifetime risk of developing cholangiocarcinoma
  - 5% risk of developing gallbladder cancer
  - 4.8 times higher risk of developing colon cancer than UC patients with no PSC
  - Bone complications (cholestasis, vitamin ADEK malabsorption)
  - 6% risk of cholangitis
  - Increased risk of cirrhosis
  - Pruritus

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**Prevention**

- Long colonoscopy with multiple biopsy sampling at diagnosis and every 1-2 years thereafter
- Annual ultrasound to detect mass lesions in the gallbladder
- Cholecystectomy in patients with mass lesions, regardless of lesion size
- Evaluation for cholangiocarcinoma if deterioration of overall health or liver parameters (CA 19-9 tumor marker, MRI, ERCP)
- Bone density examinations at diagnosis and every 2-3 years thereafter
**Drug-Induced Hepatotoxicity**

- Most drugs used in medical therapy for inflammatory bowel disease have been associated with liver toxicity, although the overall incidence of serious complications is low.
- **Signs and Symptoms**
  - Anorexia (loss of appetite)
  - Significant weight loss
  - Right hypochondrial pain (area below the right rib cage), sometimes acute
  - Asthenia (significant fatigue)
  - Hyperthermia of about 38-39°C, sometimes lasting several months
  - Vomiting with blood
  - Allergic symptoms (skin rash, fever, joint pain, abnormally enlarged or painful lymph nodes)
  - Elevated AST, ALT, bilirubin

**Steatosis**

- Steatosis, or fatty liver disease
- 50% of liver biopsies are abnormal in IBD patients
- **Signs and Symptoms**
  - Hepatomegaly (enlarged liver)
- **Causes**
  - Malnutrition
  - Corticoids and methotrexate
  - Severity of the disease
- **Treatment**
  - Treat the causes: Malnutrition, overweight
  - Optimize IBD Tx

**Cholelithiasis**

- Gallstones are visible in 13-34% of patients who have ileitis or have undergone ileal resection.
- **Causes**
  - They are caused by bile acid malabsorption, which disturbs their enterohepatic circulation. This in turn leads to the depletion of bile salts and the production of lithogenic bile.

**Pancreatitis**

- Pancreatitis affects 1-3% of IBD patients
- **Causes**
  - Duodenal fistulas
  - Gallstones
  - Primary sclerosing cholangitis (CSP)
  - Drugs: 6-MP, azathioprine (main cause)
  - Autoimmune pancreatitis
  - Primary pancreatic Crohn's disease

**Cholelithiasis**

- Feeling of pressure and fullness in the upper abdomen, especially after drinking coffee or alcohol and consuming fatty food
- Nausea, vomiting, flatulence
- **Treatment**
  - Bile acid therapy (URSO)
  - Statins
  - Ezetimibe (cholesterol-lowering agent)
  - Cholecystectomy (if symptomatic)
Pancreatitis

- Symptoms
  - Sudden, severe, persistent, epigastric pain, often radiating to the back
  - Elevation of serum lipase or amylase levels (to three times greater than the upper limit of normal)
  - Results characteristic of acute pancreatitis on imaging (CT, MRI, transabdominal ultrasound)

- Treatment
  - Find the underlying cause
  - Supportive care: pain management, intravenous fluids and correction of electrolytic and metabolic abnormalities. Most patients do not require additional treatment.

Primary Biliary Cirrhosis

- Gradual inflammatory destruction of the interlobular and septal bile ducts through cholestasis which can progress to cirrhosis
- Multiple cases of PBC in ulcerative colitis
- Features of these two autoimmune diseases and their shared association with certain HLA haplotypes suggest a similar genetic predisposition.

- Treatment
  - Treatment of symptoms and complications resulting from chronic cholestasis
  - URSO

Anatomy of the Eye

- Ciliary body
- Sclerotic
- Iris
- Conjonctiva
- Pupil
- Vitreous humor
- Cornea
- Aqueous humor
- Crystalline lens
- Ligament

Classification of Uveitis

<table>
<thead>
<tr>
<th>Classification of Uveitis</th>
<th>Anatomical Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pars planitis</td>
<td>Ciliary body</td>
</tr>
<tr>
<td>Choroid</td>
<td>Ciliary body</td>
</tr>
<tr>
<td>Retina</td>
<td>Posterior chamber</td>
</tr>
<tr>
<td>Retina</td>
<td>Pupil</td>
</tr>
<tr>
<td>Vitreous body</td>
<td>Vitreous body</td>
</tr>
<tr>
<td>Fovea</td>
<td>Iris</td>
</tr>
<tr>
<td>Blind spot</td>
<td>Anterior chamber</td>
</tr>
<tr>
<td>Optic nerve</td>
<td>Anterior uveitis</td>
</tr>
<tr>
<td>Intermediate uveitis</td>
<td>Posterior uveitis</td>
</tr>
<tr>
<td>Blood vessels</td>
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</tbody>
</table>

Uveitis

- Occurs in 0.5-3% of patients with IBD
- Consequences are serious
- Uveitis is often bilateral,
- Posterior to the lens
- Insidious onset
- Chronic duration
- 4 times more common in women than men
- Approximately 75% of patients have associated axial and/or peripheral arthritis

- Symptoms
  - Eye pain
  - Blurred vision
  - Photophobia (light sensitivity)
  - Headache

- Causes
  - Slit-lamp examination reveals anterior chamber inflammation with perilimbal edema, cells and protein. Corneal opacification and conjunctival injection may also be present.
  - The course of the uveitis may not correlate to the IBD activity. Secondary glaucoma and, in rare cases, blindness may result.

- Treatment
  - Topical or systemic steroids
  - Scopolamine (0.25%) or cyclopentolate (1%) may help to relieve spasm
  - Infliximab may be effective in patients with refractory disease
Episcleritis/Scleritis

- **Episcleritis**
  - Episcleritis is inflammation of the episclera, a layer of vessels on the surface of the sclera, below the bulbar conjunctiva.

- **Scleritis**
  - A much more serious condition, scleritis is inflammation of the sclera itself. If severe and untreated, it could lead to scleral thinning and even ocular perforation.

Pulmonary Embolism

- IBD patients may have an increased risk of venous thromboembolism (VTE)
- It is thought that patients with IBD have several risk factors for hypercoagulability, although no particular laboratory test has sufficient predictive value to identify patients at increased risk
- IBD patients have up to a threefold risk of pulmonary embolism
- 80% of IBD patients had active disease

Type I Acute Peripheral Arthritis: Joints

- Affects men and women, adults and children equally
- 5% of IBD cases
- Coincides with or occurs before the onset of IBD
- UC + Crohn’s
- Often associated with an IBD flare
- Affects fewer than 5 joints
- Affects large joints
- Primarily affects the lower extremities: ankles, knees
- Nonerosive and nondeforming
- Average duration of flare-up: 6 weeks
- **Treatment**
  - Optimize IBD Rx

Type II Chronic Peripheral Arthritis: Joints

- Affects men and women, adults and children equally
- Affects 3-4% of IBD patients
- Occurs after IBD diagnosis
- Course does not parallel that of the IBD
- Primarily affects the hands
- Affects the small joints
- Generally nonerosive
- Duration: several months, frequent relapses (flare-ups and remissions)
- **Treatment**
  - NSAIDs: Use with care in active IBD, possible exacerbation of underlying IBD
  - Infusions
  - Rheum. Rx: Sulfasalazine, MTX, Anti-TNFs
Axial Episodes: Sacroiliitis

- Isolated sacroiliitis
- Prevalence: 5-12%

Treatment

- Exercise, physiotherapy
- NSAIDs/Coxibs (depending on IBD activity)
- Infusions
- Anti-TNFs

Axial Episodes: Spondylitis

- 1-26% of IBD patients
- 1-25% of carriers for Crohn’s disease
- 2-7% of carriers for ulcerative colitis
- Affects 3 times more men than women
- Can start several years before IBD
- Does not parallel IBD activity

Treatment

- Exercise, physiotherapy
- NSAIDs/Coxibs (depending on IBD activity)
- Infusions
- Anti-TNFs

Incidence of Selected EIMs at Baseline and Week 20 in CARE: LOCF Analysis*

<table>
<thead>
<tr>
<th>EIM</th>
<th>Baseline (N=945)</th>
<th>Baseline (%)</th>
<th>Week 20 (N=945)</th>
<th>Week 20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>445 (47.1)</td>
<td>232 (26.8)</td>
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</tr>
<tr>
<td>Arthritis</td>
<td>82 (8.7)</td>
<td>20 (2.1)</td>
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<td></td>
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<tr>
<td>One or more ulcers</td>
<td>40 (4.2)</td>
<td>20 (2.1)</td>
<td></td>
<td></td>
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<tr>
<td>Sacroiliitis</td>
<td>34 (3.6)</td>
<td>18 (2.0)</td>
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<tr>
<td>Esophageal stricture</td>
<td>22 (2.3)</td>
<td>4 (0.5)</td>
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</tr>
<tr>
<td>Ankylosing spondylia</td>
<td>16 (1.7)</td>
<td>15 (1.6)</td>
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<tr>
<td>Nephrolithiasis</td>
<td>8 (0.8)</td>
<td>8 (0.8)</td>
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<tr>
<td>Ileitis</td>
<td>7 (0.7)</td>
<td>2 (0.2)</td>
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<tr>
<td>Pyoderma gangrenosum</td>
<td>4 (0.4)</td>
<td>2 (0.2)</td>
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</tr>
<tr>
<td>Uveitis</td>
<td>3 (0.3)</td>
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<tr>
<td>Hepatic disease</td>
<td>1 (0.1)</td>
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</table>

* Percentages are calculated on nonmissing values; 3 patients had missing data at Week 20.
† p<0.001 vs. baseline (sign test).
‡ p=0.016 vs. baseline (sign test).
§ Incidence too small for comparison.

Resolution of at Least 1 of the EIMs Present at Baseline*: Stratified by HBI Remission at Week 20

In Remission at Week 20

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<tr>
<th>EIM</th>
<th>% of Patients</th>
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<tr>
<td>Arthralgia</td>
<td>85</td>
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<tr>
<td>Arthritis</td>
<td>68</td>
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<td>One or more ulcers</td>
<td>68</td>
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<tr>
<td>Sacroiliitis</td>
<td>68</td>
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<tr>
<td>Esophageal stricture</td>
<td>75</td>
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Not in Remission at Week 20

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<tr>
<td>Arthralgia</td>
<td>12</td>
</tr>
<tr>
<td>Arthritis</td>
<td>87</td>
</tr>
<tr>
<td>One or more ulcers</td>
<td>11</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>70</td>
</tr>
<tr>
<td>Esophageal stricture</td>
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Complete Absence of Any EIM: Combined Adalimumab Groups vs. Placebo (NRI Analysis)a

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<th>Patients (%)</th>
<th>Anti-TNF–Naïve</th>
<th>Infliximab–Experienced</th>
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<tr>
<td>Week 12</td>
<td>12/143</td>
<td>87/296</td>
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<tr>
<td>Week 26</td>
<td>24/143</td>
<td>23/58</td>
</tr>
<tr>
<td>Week 56</td>
<td>24/143</td>
<td>23/58</td>
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a In 495 patients. 80 mg and 40 mg. 80 mg of adalimumab induction therapy for patients who dropped out or moved to open-label therapy.

Resolution of at Least 1 of the EIMs Present at Baseline*: Stratified by Prior Infliximab Use

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CLASSIC I/GAIN: Change in CRP

**Conclusion**

- Extraintestinal manifestations of IBD affect numerous patients. It is important to assess a patient holistically, rather than just diagnostically.