Extraintestinal Manifestations of Inflammatory Bowel Disease

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Objectives

1. Discuss the major EIM’s by organ system
2. Discuss the treatment of each EIM
3. Discuss epidemiology
4. Briefly discuss pathogenesis
3 major groups

**Group 1** - Reactive manifestations of IBD

**Group 2** - IBD related complications secondary to metabolic or anatomic abnormality

**Group 3** - Non-IBD specific autoimmune diseases (hemolytic anemia, thyroid disease, vitiligo, type 1 diabetes, bechet’s disease)
Group 1
Reactive EIM organ systems

• Musculoskeletal
• Dermatologic
• Ocular
• Hepatobiliary
Group 1
Reactive EIM in relation to GI inflammation

Diseases divided into those that parallel bowel inflammation and those that are independent
Parallel Disease Activity

- Peripheral arthritis type 1
- Erythema nodosum
- Apthous stomatitis
- Episcleritis

✧ Respond to IBD specific medical / surgical therapy
Inflammation Independent

- Pyoderma gangrenosum
- Uveitis
- Axial arthritis
- Primary sclerosing cholangitis (PSC)

✧ May require disease specific treatment
Group 2
IBD related complications

- Bone - Osteoporosis, Osteonecrosis
- Renal - Nephrolithiasis, Obstructive Uropathy, Fistulization of the urinary tract
- Secondary Amyloidosis
- Hematologic - Thromboembolic events
- Pulmonary - Chronic bronchitis, bronchiectasis, ILD secondary to sulfasalazine
Shared Clinical Features

• More common in Crohn’s disease than ulcerative colitis
• More common with extensive colitis
• 25% of patients with one EIM will have at least one other (presence of one increases risk)
• Familial predisposition - clear linkage to several HLA loci
Associations with HLA loci

- Crohn’s EIM’s - Associated with HLA-A-2, HLA-DR-1, HLA-dq-W5
- UC - Associated with HLA-DR2
- Genome wide association studies have found several genes linked to PSC
Pathogenesis - Shared antigens

- Likely some common pathogenic pathway
- Autoimmune reaction to an isoform of tropomyosin

\[ \text{Tropomyosin related peptide 1} \]

- Expressed in eye (non-pigmented ciliary epithelium)
- Skin (keratinocytes)
- Joints (chondrocytes)
- Biliary epithelium
- GI tract

Bhagat S, Das KM. A shared and unique peptide in the human colon, eye and joint detected by a monoclonal antibody. Gastroenterology 1994
Frequency and Risk Factors for Extraintestinal Manifestations in the Swiss Inflammatory Bowel Disease Cohort

Stephan R. Vavricka, MD\textsuperscript{1,6}, Lionel Brun\textsuperscript{1,6}, Pierluigi Ballabeni\textsuperscript{2}, Valéorie Pittet\textsuperscript{2}, Bettina Mareike Prinz Vavricka, MD\textsuperscript{3}, Jonas Zeitz, MD\textsuperscript{1}, Gerhard Rogier, MD\textsuperscript{1}, Alain M. Schoepfer, MD\textsuperscript{4,6} and the Swiss IBD Cohort Study Group\textsuperscript{7}

OBJECTIVES: Data on the frequency of extraintestinal manifestations (EIMs) in Crohn's disease (CD) and ulcerative colitis (UC) and analyses of their risk factors are scarce. We evaluated their prevalence and risk factors in a large nationwide cohort of inflammatory bowel disease (IBD) patients.

METHODS: IBD patients from an adult clinical cohort in Switzerland (Swiss IBD cohort study) were prospectively included. Data from validated physician enrolment questionnaires were analyzed.

RESULTS: A total of 950 patients were included, 580 (61\%) with CD (mean age 41 years) and 370 (39\%) with UC (mean age 42 years). Of these, 249 (43\%) of CD and 113 (31\%) of UC patients had one to five EIMs. The following EIMs were found: arthritis (CD 33\%, UC 21\%), aphthous stomatitis (CD 10\%, UC 4\%), uveitis (CD 6\%, UC 4\%), erythema nodosum (CD 6\%, UC 3\%), ankylosing spondylitis (CD 6\%, UC 2\%), psoriasis (CD 2\%, UC 1\%), pyoderma gangrenosum (CD and UC each 2\%), and primary sclerosing cholangitis (CD 1\%, UC 4\%). Multiple logistic regression identified the following risk factors for ongoing EIM in CD: active disease (odds ratio (OR) = 1.95, 95\% confidence interval (CI) = 1.17–3.23, \(P = 0.01\)), and positive IBD family history (OR = 1.77, 95\% CI = 1.07–2.92, \(P = 0.025\)). No risk factors were identified in UC patients.

CONCLUSIONS: EIMs are a frequent problem in CD and UC patients. Active disease and positive IBD family history are associated with ongoing EIM in CD patients. Identification of EIM prevalence and associated risk factors may result in increased awareness for this problem and thereby facilitating their diagnosis and therapeutic management.

\textit{Am J Gastroenterol} 2011; 106:110–119; doi:10.1038/ajg.2010.343; published online 31 August 2010
Prevalence

• Prospective study of Swiss cohort of 950 IBD patients, 43% CD and 31% UC patients had at least one EIM
• 15% CD, 8% UC patients had two or more EIM’s
• Peripheral arthritis single most common EIM in both CD and UC patients
• All EIM’s (except pyoderma gangrenosum and PSC) more common in CD
Musculoskeletal

• Most common organ system affected
• Broadly grouped into 2 categories
  A. Peripheral arthritis – 2 types
  B. Axial manifestations – Sacroiliitis, Ankylosing Spondylitis

All of these subtypes are broad class of musculoskeletal disease called SERONEGATIVE SPONDYLOARTHROPATHIES (rheumatoid factor negative)
Sacroiliitis

- Milder of two forms of axial disease
- Often asymptomatic or presents with mild lower back pain
- Spanish prospective cohort study looked at 62 IBD patients without axial symptoms undergoing MRI, 24% had radiographic changes consistent with disease

Ankylosing Spondylitis

• Spinal pain: moves from the lumbar to cervical spine
• Alternating buttock or chest pain, worse in morning or after rest
• Physical exam: limited spinal flexion, reduced chest expansion
• Independent of gut inflammation
• Axial symptoms often precede bowel disease by many yrs.
• Nearly 100% IBD patients with HLA B27 go on to develop AS
Gut Inflammation in patients with spondyloarthropathy and no GI symptoms

- Retrospective studies of patients with AS and no GI symptoms → 67% had evidence of inflammation (ileal) on colonoscopy

- *Chronic* inflammatory gut lesions found in 52% of patients with classic AS → 10% developed IBD after 2 to 9 years of follow-up (9 Crohn’s and 2 UC)

Axial arthritis treatment

- Early referral to physical therapist for back and neck exercises
- NSAID’s, particularly Cox-2 inhibitors
- Responsive to Anti-TNF therapy (remicade best studied, smaller studies with adalimumab)
- Etancercept (Enbrel) has no effect on gut inflammation
Peripheral Arthritis

• Most common EIM in both Crohn’s and UC
• Type 1 (classic arthritis) mirrors gut inflammation and responds to treatment
• Type 2 much less common, sometimes independent of gut inflammation
# Peripheral Arthritis

<table>
<thead>
<tr>
<th></th>
<th>Type 1 (Pauciarticular)</th>
<th>Type 2 (Polyarticular)</th>
</tr>
</thead>
<tbody>
<tr>
<td># Joints Affected</td>
<td>&lt; 5</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>Joints Affected</td>
<td>Mainly Large</td>
<td>Mainly Small</td>
</tr>
<tr>
<td>Duration of Attacks</td>
<td>&lt; 10 weeks</td>
<td>Months to Years</td>
</tr>
<tr>
<td>Association with Bowel Disease Activity</td>
<td>Parallels</td>
<td>Independent</td>
</tr>
<tr>
<td>Relationship to Others</td>
<td>Associated with EN and Uveitis</td>
<td>Only with Uveitis</td>
</tr>
</tbody>
</table>
Medical Management of IBD Related Arthropathy

**General**

- Rest
- Physiotherapy
- Splints
- Intra-articular corticosteroids
Medical Management of IBD Arthropathy Safety of selective cyclooxygenase-2 Inhibitors

Methods

• Retrospective chart review of 27 patients with Crohn’s and UC receiving celecoxib or rofecoxib
• Median Duration of therapy = 9 months (1wk-22 months)
  17 inactive IBD
  6 mild disease
  4 moderate activity

Mahadevan et al. AJG 2006;97: 910-914
Medical Management of IBD Arthropathy
Safety of selective cyclooxygenase-2 Inhibitors

Results

• 22/27 no change in IBD activity
• 14 improved Arthralgias/myalgias
  8 partial improvement
  5 no benefit

Conclusions

• Selective COX-2 inhibitors safe

Mahadevan et al. AJG 2006;97: 910-914
Medical Management of IBD Related Arthropathy

• Sulfasalazine

Meta-analysis of 5 placebo controlled trials-500 mg BID, titrated to a maximal dose of 1500 TID

Ferraz et al. J Rheumatology 1990;17:1482-1486

• Mesalamine

Used but no good placebo controlled trials

If 5-ASA’s ineffective, methotrexate, 6-mp and anti-TNF agents can be effective
Osteoporosis

• Reduction in bone mineral and bone matrix resulting in normal composition of bone but abnormally low density

• Defined as 2 standard deviations below the mean of age-adjusted controls
Bone Disease in IBD

• Prevalence of osteoporosis ($T \leq -2.5$) using DEXA: 15 - 35%

• Prevalence of osteopenia ($T -1.0$ to $-2.49$): 16 - 77%

• Corticosteroid use is strongly associated with osteoporosis

AGA medical position statement. Gastroenterology 2003
Risk Factors for Osteoporosis: IBD

- Corticosteroid therapy
- Reduced physical activity
- Inflammatory factors (IL1, IL6, TNF)
- Calcium and magnesium malabsorption
- Vitamin D deficiency
- Hypogonadism
- Poor dietary calcium intake (lactose intolerance)
- Malnutrition
- Decreased serum albumin
- Ileal resection
Fracture Risk and Dose of Corticosteroids

Relative risk of fracture compared with control

- 2.5 mg/d
- 2.5-7.5 mg/d
- >7.5 mg/d

- Hip Fracture
- Vertebral Fracture
IBD Medications and Bone Loss

- Cyclosporine, methotrexate, TPN, IV heparin cause bone loss
- Budesonide better than prednisone in corticosteroid naïve patients
- Azathioprine does not affect the bones
- Infliximab may increase BMD

AGA Recommendations for Managing Osteoporosis

IBD patient:
Any of:
- Prolonged steroid use (>3mo consec or recurrent courses)
- Low trauma, fragility fracture
- Postmenopausal or male age >50
- Hypogonadism

T score >-1
- Basic Prevention:
  - Ca/Vit D
  - Exercise
  - Smoking cessation
  - Avoid alcohol
  - Minimize corticosteroids
  - Treat hypogonadism

T score -2.5 to -1
- DXA
- Prevention and:
  - Repeat DXA 2 years
  - Prolonged CS consider BP and DXA 1 year

T score <-2.5
- Vert Fracture Regardless of DXA
- Prevention and:
  - Screen other causes low BMD
  - Bisphosphonate therapy or
  - Refer to bone specialist

Gastroenterology 2003;124:795-841
Osteonecrosis

- Death of osteocyte, adipocytes and eventual bone collapse
- Pain: aggravated by motion; joint swelling
- Bilateral and multifocal
- Hips > knees and shoulders
- Steroids: in one series, 4.3% patients developed osteonecrosis within 6-month of steroid use
- Diagnosis: bone scan or MRI
- Treatment:
  - early identification is essential
  - medical management, core decompression biopsy, arthroplasty

Dermatologic manifestations

- Erythema nodosum
- Apthous stomatitis
- Pyoderma gangrenosum
- Sweet’s syndrome
- Metastatic Crohn’s disease
Erythema Nodosum

- Most common skin manifestation
- 15% of CD patients, female predominance
- Deep tender nodules, usually 1-5 cm
- Anterior tibial area most common-can occur on arms and trunks
- Inflammation occurs in subcutaneous fat (panniculitis) and can occur wherever present
Erythema Nodosum (cont.)

• DDX: TB, histoplasmosis, Yersinia, Salmonella

• Sarcoidosis, Bechet’s disease, connective tissue disease

• Medications-Sulfonamides, OCP, Bromides,

• Iodides
Erythema nodosum treatment

- Usually responds to IBD treatment
- EN precedes initial presentation of IBD in 2-3%
- Idiopathic EN patients should be evaluated for IBD
Aphthous stomatitis

- Shallow round ulcers with fibrinous membrane and erythematous halo
- Cannot be clinically differentiated from oral apthae occurring in other conditions
- DDX: Late stage HSV, Bechet’s Disease, Cocksackie virus, HIV
Pyoderma ganrenosum

- Ulcerated skin lesions begin as tender papules or vesicles - develop into painful ulcers with ragged, purple overhanging edges and surrounding erythema and induration, usually on the lower extremities
- Ulcer base contains necrotic tissue, granulation tissue or purulent exudate
- Lesions heal with cribiform scars
- Pathogenesis unknown
Pyoderma ganrenosum
Pyoderma ganrenosum
## Associated Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>PG Frequency</th>
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<tbody>
<tr>
<td>Ulcerative Colitis</td>
<td>14.1%</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>12.5%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>14.1%</td>
</tr>
<tr>
<td>Non-rheumatoid arthritis</td>
<td>4.7%</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>10.9%</td>
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Pathergy

- Exaggerated physiologic response to minor trauma
- Pathergy seen in PG and Bechet’s disease
- Characteristic of PG-NEVER BIOPSY!
Local Therapies

- Dressings
- Topical corticosteroids
- Intralesional corticosteroids
- Topical tacrolimus
- Topical/intralesional cyclosporine
- Debridement - contraindicated
Systemic Therapies

- Anti-inflammatory therapy – Anti-TNF’s first line, steroids and/or azathioprine or 6-mercaptopurine
- Antibiotics for superinfection
- Alternative therapies for refractory cases - Cyclosporine, Dapsone, Hyperbaric oxygen, Heparin, Cyclophosphamide, Chlorambucil, Thalidomide, Mycophenolate, Tacrolimus, IV immunoglobulins, Clofazamine
Sweet's Syndrome

- Acute febrile neutrophilic dermatosis
- Tender or erythematous plaques or nodules
- Arms, legs, trunk, hands, face
- Leukocytosis
- Histologic findings of neutrophilic infiltrate
- Associated with arthritis, fever, ocular symptoms
- Responds to steroids
Metastatic CD

- Most commonly in skin
- Cutaneous lesions appear as ulcerating nodules
- Classically in anterior abdominal wall, submammary areas
- Usually parallels active gut inflammation
- Responds to mesalamine or systemic steroids
Hepatopancreatobiliary

- PSC
- Cholelithiasis
- Portal vein thrombosis
- Drug induced hepatotoxicity (6-MP, AZA)
- Drug induced pancreatitis
PSC

- 60-75% of PSC patients have co-existing UC, 5% with Crohn’s
- Only 5% of UC patients will develop PSC
- 1-2% of all Crohn’s patients
- UC patients with pancolitis more at risk than left sided disease only
- 2:1 male prevalence
PSC and Colon cancer risk

Patients with PSC and IBD at significantly higher risk of colorectal CA proximal to splenic flexure compared to IBD patients without PSC

- Alterations in concentration and composition of bile acids exposed to the colon
- AASLD recommends patient with PSC and IBD get surveillance colonoscopy every 1-2 years from diagnosis of PSC with random biopsies
PSC and Ursodiol

- Controversy remains over use of Ursodeoxycholic acid
- Some studies using low dose ursodiol (13-15mg/kg) show modest chemopreventive effect, others show no effect
- Some studies show higher risk of colorectal CA using high dose UDCA (17-23mg/kg).


✧ AASLD practice guidelines specifically recommend against the use of UDCA at any dose (2010 recommendations)
Cholelithiasis

- Interruption of the enterohepatic circulation secondary to ileal disease or resection
- Present in 15-34% of patients with ileal disease
Drug induced hepatotoxicity

- Thiopurines
- Methotrexate
- Sulfasalazine
- Cyclosporine
- Anti-TNF’s
Episcleritis and Uveitis

- **Episcleritis**: painless hyperemia of the scleritis
  - parallels IBD activity and responds to IBD therapy, cool compresses/local steroids as needed
  - rarely progresses to vision loss if untreated
- **Uveitis**: acute or subacute painful eye with visual blurring
  - photophobia, headache, and eye pain
- Frequently present with other EIM’s like arthritis
- “ciliary flush”-redness most intense in center and diminishes outwards
- Needs immediate evaluation and systemic or topical steroids
Hypercoagulability

Coagulation abnormalities in IBD:

• Thrombocytosis
• qualitative platelet abnormalities
• increased levels of fibrinogen, coagulation factors V and VIII
• decreased antithrombin III, protein C and S, factor V Leiden, and tissue plasminogen activator

• Manifests predominantly as DVT or PE
• Incidence ranges from 1.3% to 25%
• Anticoagulation is the mainstay of therapy
Renal

• Nephrolithiasis
• Obstructive uropathy
• Fistulization of bladder
• Secondary Amyloidosis leading to renal failure
Nephrolithiasis

Calcium Oxalate Stones
- Result from fatty acid malabsorption
- Decreased calcium/oxalate binding leads to increased oxalate absorption

Hyperoxaluria
- Formation of calcium oxalate stones
- Increase significantly after more than 100 cm of ileum have been resected
- Entails intact colon for absorption of sodium-bound oxalate

Oral calcium supplementation for prophylaxis (binds to oxalate)
Nephrolithiasis

Uric Acid Stones

• Chronic dehydration and loss of alkaline intestinal fluid
• Urine becomes highly concentrated and acidic, enhancing uric acid stone formation
• Predisposed by ileostomy
• Hydration, Alkalization, dietary control, allopurinol and avoid high-protein diet
Summary

• EIM’s are common in IBD patients and underdiagnosed

• Most common are peripheral arthritis, osteoporosis, erythema nodosum

• Recognition important as need to involve other subspecialists