EXTRAINTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

Epidemiology

- 21-36% of patients
- occurrence of first EIM predisposes to additional hits
- divided broadly into three groups
  - Disorders involving skin, eye, joints, mouth
    - mostly in patients with colonic disease
    - activity of colitis related manifestations parallel activity of underlying disease
  - Disorders secondary to complications of direct extention of bowel disease
    - usually in CD patients
    - kidney stones, obstructive uropathy, malabsorption, gallstones
  - Other
    - osteoporosis, hepatic diseases, amyloidosis
    - complications involving vascular, hematologic, pulmonary, cardiac, neurologic systems

Pathogenesis

- not well understood
- immunologic mechanisms most likely
  - mucosa from underlying IBD may provide associated immune system responses for the inflammatory process in extraintestinal sites
- role of bacteria
  - animal studies
- genetic factors
  - concordance in parent-child and sibling pairs

Musculoskeletal Manifestations

- most common EIM
- Rheumatologic Disorders
  - includes peripheral and axial arthropathy
    - peripheral arthropathy: 5-20% IBD patients, does not lead to joint deformity
      - risk of developing peripheral arthropathy increases with extent of colonic disease and with presence of complications (abscesses, perianal disease, erythema nodosum, stomatitis, uveitis, pyoderma gangrenosum)
      - Type I: pauciarticular, <5 joints, large joints (knees, elbows, ankles)
        - acute, self-limited, lasting ~5 weeks
        - parallels underlying disease activity and assoc with increased incidence of EN and uveitis
      - Type II: polyarticular, >5 joints, small joints
        - persistent symptoms, lasting ~ 3 yrs
        - independent of bowel activity and assoc with uveitis
      - usually responds to medical or surgical treatment of colitis
        - can also use rest, PT, intra-articular steroid injections
        - caution with NSAIDS : associated with exacerbation of IBD

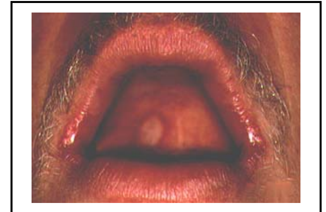
        - axial arthropathy: 3-5% IBD patients
            - does not parallel IBD activity
            - most are HLA-B27 positive
            - ankylosing spodylitis and isolated sacroiliitis
            - does NOT respond to med/surg therapy of underlying IBD
                - sulfasalazine, mesalamine, methotrexate, azathioprine, anti-TNF, thalidomide, infliximab

- Metabolic Bone Disorders
    - osteoporosis and osteopenia: 23-59% patients
        - bone loss in trabecular (primary supportive bone) and cortical bone
        - pathophysiology not well understood
        - contributing factors: steroids, low physical activity, inflammatory cytokines, small bowel resection, vitamin D deficiency
        - may occur without steroids in CD patients
            - should undergo baseline bone densitometry
        - UC patients without steroid use have similar risk to general population
    - osteomalacia
        - accumulation of bone matrix that fails to mineralize properly
        - 1-5% CD patients usually due to vitamin D deficiency (decreased dietary intake, lack of sun exposure, fat malabsorption, disruption of enterohepatic circulation)
    - osteonecrosis
        - due to steroid use, rare
        - bilateral, multifocal, hips most common > knees > shoulders
- Treatment: preventive measures
    - hormone replacement therapy in perimenopausal/ postmenopausal women
    - oral contraceptive use
    - calcium/ vitamin D supplementation

<u>Dermatologic Manifestations</u>

- 15% of patients
- erythema nodosum and pyoderma gangrenosum most common
- Erythema Nodosum: 10-20% IBD patients
    - red, tender nodules on extensor surfaces of lower extremities
    - correlates with bowel activity
    - often occurs in conjunction with peripheral arthritis
    - lesions respond to treatment of IBD, if not then systemic corticosteroids or immunosuppressive therapy
- Pyoderma Gangrenosum: 1-10% IBD patients (UC>CD)
    - erythematous pustule or nodule that spreads rapidly to adjacent skin, develops burrowing ulcer with irregular, violaceous edges
    - found on extensor surfaces of lower extremities

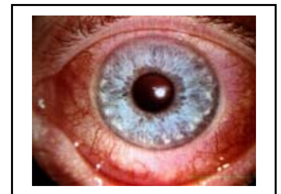
- may resolve with treatment of underlying IBD
  - mild cases: local and topical therapy including intralesional corticosteroid injections, topical cromolyn sodium, topical 5-ASA
  - systemic agents include: oral sulfasalazine, dapsone, corticosteroids, immunomodulators
- Sweet's Syndrome
  - acute febrile neutrophilic dermatosis
  - associated with CD and UC
  - tender, erythematous plaques or nodules involving arms, legs, trunk, hands or face
  - associated systemic manifestations: arthritis, fever, ocular symptoms
  - parallels IBD activity but may precede diagnosis of IBD
  - reponds to systemic corticosteroids



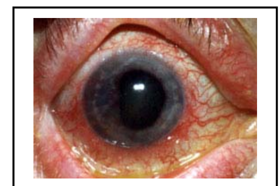
- Oral Lesions
  - most common lesions are apthous ulcers and angular stomatitis
  - other less common lesions: pyoderma vegetans, epidermolysis bullosa acquisita, erythema multiforme, psoriasis

Opthalmologic Manifestations

- 1.6-4.6% patients UC, 3.5-6.3% patients with CD
- some treatment related complications, not IBD-associated manifestations
- two most common manifestations: episcleritis and uveitis
- Episcleritis
  - painless hyperemia of sclera and conjunctiva without loss of vision
  - parallels IBD activity
  - reponds to anti-inflammatory therapy



- Uveitis
  - acute or subacute painful eye with visual blurring, photophobia, headache, iridospasm
  - diagnosed on slit-lamp exam
  - temporal correlation with IBD activity unpredictable, may precede diagnosis
  - need prompt treatment with systemic or topical steroids to prevent progression to blindness



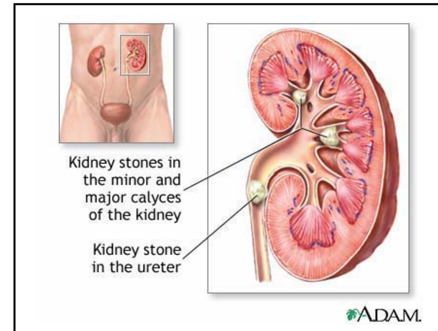
Hematologic Manifestations

- anemia most common
  - Fe/folate/B12 deficiency, chronic disease, autoimmune hemolysis, chronic GI blood loss
- thromboembolic events: 1.3-39% (various retrospective studies)
  - hypercoagulable states in IBD pts. Manifest mostly as PE and DVT

GU Manifestations

- 3 most common: nephrolithiasis, obstructive uropathy, fistulization to urinary tract
- 4-23% of patients

- Nepthrolithiasis
  - uric acid stones and calcium oxalate stones most common
  - calcium oxalate from hyperoxaluria associated with distal ileal CD or ileal resection, present only in patients with intact colon
  - uric acid stones found in patients with ileostomy due to frequent dehydration
- obstructive uropathy
  - extrinsic compression of the ureter by the intestinal inflammatory process
  - surgical treatment
- fistulous disease
  - may present with pneumaturia or recurrent UTIs
  - medical or surgical treatment



Miscellaneous

- Cardiovascular: pleuropericarditis, pathogenesis unknown, use NSAIDS judiciously
- Pulmonary: increase in FRC, decrease DLCO, fibrosing alveolitis, pulmonary vasculitis, apical fibrosis, bronchiectasis, bronchiolitis, bronchitis, granulomatous lung disease
- Neurologic: peripheral neuropathy, myopathy, vasculopathy, focal CNS defects, seizures, confusional episodes, meningitis, syncope
- Hepatobiliary
  - Primary Sclerosing Cholangitis: prevalence 2.4-7.5% in IBD patients
  - 75% PSC patients have IBD, most commonly UC
- Metastatic Crohn's Disease
  - rare, skin most common site
  - ulcerating nodules usually in skin folds, classically ant abdominal wall and submammary areas, but also upper and lower extremities
  - retroauricular skin fold, umbilicus, penis, malar area, vulva, ankles, knees, lungs, pancreas, bladder
  - responds to mesalamine or systemic corticsteroids, both

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