Rheumatologic Manifestations of Gastrointestinal Diseases

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Objectives

- To discuss a few common rheumatologic manifestations of GI diseases
- To discuss the work-up for diagnosis
- To discuss the potential treatment options

Disclosure

- I have received honorariums and have participated in advisory boards for Roche, UCB, Janssen, Sanofi Genzyme, Abbvie, Celgene, Merck and Pfizer
- I have received a research grant from Roche

Mitigating Potential Bias

- I will not be discussing specific treatment strategies with biologics during this talk.

What about GI manifestations of rheumatologic diseases?

- Vasculitis: Takayasu arteritis, PAN, ANCA-associated vasculitis, IgA vasculitis (HSP), Behcet's
- Ankylosing spondylitis: IBD in 5-10%. About 50% have histologic abnormalities
- Systemic sclerosis: Esophageal dysmotility → GERD, bacterial overgrowth, malabsorption, bloating, dysphagia, watermelon stomach
- SLE: Oral ulcers, hepatitis, pancreatitis, vasculitis
- Sjogren's: Dysphagia, Celiac disease, primary billiary cirrhosis, hepatitis
- Rheumatoid arthritis: Felty's (splenomegaly)
- Medication related: NSAIDs, methotrexate, sulfasalazine, azathioprine, hydroxychloroquine, etc

Shimoda S, et al. Hepatic and GI manifestations in Rheumatic and Connective Tissue Diseases. *Journal of General and Family Medicine*. 2016, vol 17, no. 2, p. 132-127.

Rheumatologic Manifestations of Gastrointestinal Diseases

Overview

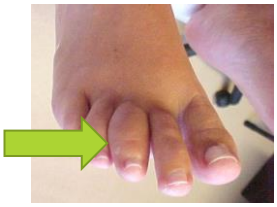
- Intestinal disorders:
  - Infections → reactive arthritis
  - IBD → sacroiliitis, peripheral arthritis, enthesitis, dactylitis, osteoporosis, hypertrophic osteoarthropathy, AVN, septic arthritis
  - Celiac disease → arthritis, osteoporosis
- Hepatobiliary disorders:
  - Hep C: cryoglobulinemia, Sjogren's, arthritis
  - Hep B: cryoglobulinemia, PAN (polyarteritis nodosa)
  - Hemochromatosis: chondrocalcinosis, pseudogout, chronic arthritis
  - PBC: Sjogren's, osteoporosis

Overview - continued

- Pancreatic:
  - Pancreatic panniculitis (subcutaneous fat necrosis associated with pancreatic disease)
  - Autoimmune pancreatitis and sclerosing cholangitis: IgG4-RD
  - Cystic fibrosis: osteoporosis from malabsorption, seronegative arthritis, hypertrophic osteoarthropathy
- Other:
  - FMF: arthritis
  - Medication related: anti-TNF agents

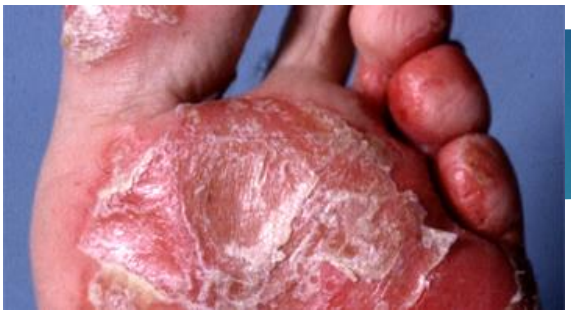
Case 1

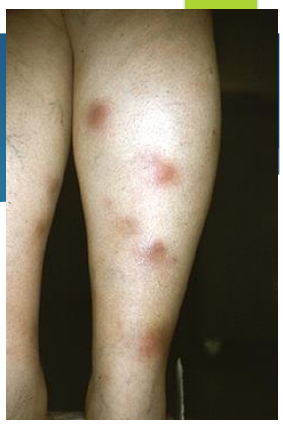
- 50M with a history of GERD presents to your office for the treatment of recurrent c. diff
  - He has had multiple courses of flagyl and oral vancomycin
  - On further questioning, he complains of pain and swelling in multiple joints
  - On exam, you find multiple swollen joints and what looks like dactylitis
  - Diagnosis?

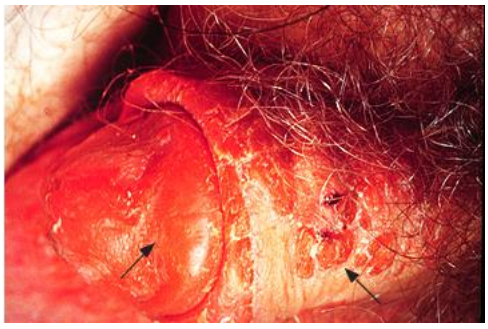


Reactive arthritis

- Etiology: enteric pathogens, chlamydia
- Presentation: Occurs days to weeks after infection
  - MSK:
    - Peripheral arthritis: asymmetric oligoarthritis, lower extremities > upper
    - Enthesitis (inflammation of the tendon insertion to the bone)
    - Dactylitis
    - Axial involvement less common
  - Conjunctivitis, iritis
  - Urethritis, cervicitis, prostatitis
  - Skin





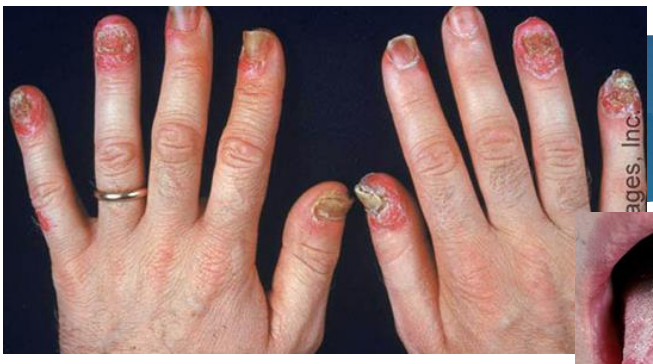


Keratoderma blennorhagica

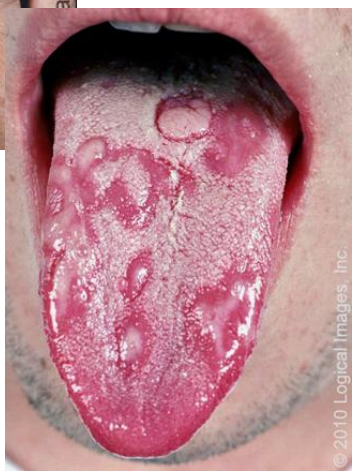
Erythema nodosum

Circinate balanitis

Images courtesy of UpToDate



Subungual hyperkeratosis, onycholysis, periungual erythematous plaques



Oral plaques

Images courtesy of UpToDate

Reactive arthritis

- Workup:
  - Stool culture (usually by the time arthritis develops, diarrhea has resolved)
  - Check urine for chlamydia
  - HLA B27 positive in 30-50%
  - If there is a joint effusion → ASPIRATE the joint and send for cell count, crystals and culture
  - Rule out other causes: could be RA, other forms of seronegative spondyloarthropathy, crystal arthropathy, etc

Pearl

- **Seronegative spondyloarthropathy (SpA)**
  - **Ankylosing spondylitis**
    - **Axial**
    - **Peripheral**
  - **IBD-associated arthritis**
  - **Psoriatic arthritis**
  - **Reactive arthritis**
- **All have features that overlap: arthritis, axial involvement, enthesitis, dactylitis, uveitis, GI and skin involvement**

Reactive arthritis

- Treatment:
  - If infection still present → treat with antibiotics
  - Acute arthritis:
    - NSAIDs → full dose regularly for 2 weeks
    - Steroids: intra-articular or oral
      - If oral, start at prednisone 20-30
  - Chronic or resistant arthritis:
    - DMARDs: Sulfasalazine up to 3g daily
      - If not responsive to SSZ, then methotrexate and ultimately anti-TNF agents
- Prognosis:
  - 50% resolve by 6 months and majority resolve by 1 year

Hochberg MC, et al. Reactive arthritis: clinical features and treatment. Rheumatology. Elsevier/Mosby, Philadelphia, PA 2011. p.1113.

Case 1

- Patient on po vanco
- Plan for fecal transplant
- Patient referred to me for management
  - Found to have a fused spine → underlying ankylosing spondylitis asymptomatic for > 20 years
  - Many swollen joints with enthesitis and dactylitis
  - Started on full dose NSAIDs
    - Too many joints to inject. Avoiding prednisone
    - Patient was started on methotrexate, SSZ and ultimately required an anti-TNF agent to control symptoms

Case 2

- 30F with known Crohn's on mesalamine complains of chronic migratory joint pain
- What questions do you need to ask?

Case 2

- History of Crohn's
  - Diagnosed 5 years ago
  - Large bowel involvement
  - Mild to moderate disease activity: initially required steroids but has been stable on mesalamine
  - No complications thus far
  - Has had no recent flares
- MSK history
  - Pain involving the MCPs, wrists and knees
  - No swelling but has morning stiffness for 2 hours
  - No axial symptoms
- Diagnosis?
- Workup?

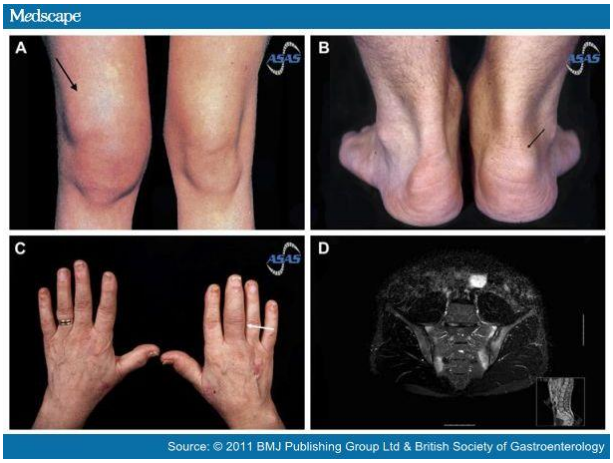
Case 2

- Workup
  - Examine the patient
  - Aspirate joints to rule out infection or crystal arthropathy in older patients
  - Consider x-rays

IBD-associated arthritis

- Occurs in 6-46% of patients
- More common in patients with large bowel disease and in those with prior complications (fistula, abscess)
- More common in patients who have had other extraintestinal manifestations such as pyoderma gangrenosum, uveitis and erythema nodosum

IBD-associated arthritis



IBD-associated arthritis

- Axial involvement:1-26%
  - Unrelated to IBD status
  - HLA B27 positive in 50-75%
    - In Crohn's, sacroiliitis associated with CARD15 gene polymorphisms

IBD-associated arthritis

- Peripheral arthritis: up to 20%
  - Type I: acute onset; occurs early in the disease course; correlates with disease activity; self-limiting; non-erosive
    - 90% resolve within 6 months
    - Responds to treatment of IBD
  - Type II: chronic with frequent relapses; migratory; polyarticular with MCP involvement; does not parallel disease activity
  - Rheumatologists rarely use this distinction in practice

Fornaciari G, et al. Muscoloskeletal manifestations in inflammatory bowel disease. Can J Gastroenterol. 2001;15(6):399.

Pearl

- **IBD-associated arthritis should be suspected whenever an IBD patient develops joint pain, stiffness, or symptoms of inflammatory back pain**

IBD-associated arthritis

- Workup
  - Axial
    - x-rays of the lumbar spine and SI joints
    - If patient has had a CT abdo/pelvis, review with radiology to look for sacroiliitis
    - If x-ray negative and no previous CT, may need MRI
  - Peripheral
    - Diagnosis based on history and exam findings
    - May have elevated CRP (can't interpret if IBD active)

Treatment: Pearl

- **Optimize therapy for IBD and exclude active IBD in asymptomatic patients**

IBD-associated arthritis

- Treatment
  - Axial
    - Physiotherapy
    - NSAIDs if ok by GI
    - Anti-TNF agents
    - Treatment of IBD with surgery has no impact on axial disease
  - Peripheral
    - NSAIDs if ok by GI
    - Local joint injections
    - Sulfasalazine
      - If not responding, can consider methotrexate, steroids or anti-TNF agents

Van Bodegraven AA, et al. Treatment of Extraintestinal Manifestations in Inflammatory Bowel Disease. Curr Treat Options Gastroenterol. 2003;6(3):201.

Van den Bosch F, et al. Crohn's disease associated with spondyloarthropathy: effect of TNF-alpha blockade with infliximab on articular symptoms.*Lancet*. 2000;356:1821-1822.

Case 2

- Patient diagnosed with IBD-associated arthritis (type 2)
  - Started on NSAIDs prn
  - Plan to change to sulfasalazine if symptoms worsen

Case 3

- 40M with Crohn's disease diagnosed in 1986 complicated by anal fistula and ischiorectal abscess. Currently on infliximab for 1 year and azathioprine for 11 years
- Also history of autoimmune hepatitis with compensated cirrhosis and esophageal varices, portal hypertension and possible PSC
- Flare of IBD 5 months ago requiring prednisone for 4 months and an increase in his infliximab dose
- Presents with diffuse arthralgias with no swelling and morning stiffness
- Diagnosis?

TNF-induced autoimmunity

- Infliximab: ANA 29-77%, dsDNA 10-29%
- Adalimumab: ANA 13%, dsDNA 5%
- Can get antiphospholipid antibodies with both but no clinical significance
- Can get lupus, lupus-like illness, psoriasis and vasculitis (mainly leukocytoclastic vasculitis)

Ramos-Casals M, et al. Autoimmune diseases induced by biological agents: a double-edged sword? Autoimmun Rev. 2010;9(3):188.

TNF-induced lupus

- Mainly presents with mucocutaneous symptoms, arthralgias, serositis
- Very rare to have organ-threatening involvement such as renal or neurological involvement

Williams EL, et al. Anti-TNF-induced lupus. Rheumatology (Oxford). 2009;48(7):716.

TNF-induced lupus

- Workup
  - ANA, dsDNA, anti-histone
    - Histone only positive in 17-57% of patients (most patients positive in other drug-induced lupus)
    - dsDNA usually negative in other drug-induced lupus
- Treatment
  - Discontinue medication
  - Can consider switching to a different anti-TNF or use a biologic with a different MOA
  - May need steroids to treat initially
  - Use of methotrexate to prevent anti-drug antibodies does not seem to decrease the risk of TNF-induced lupus

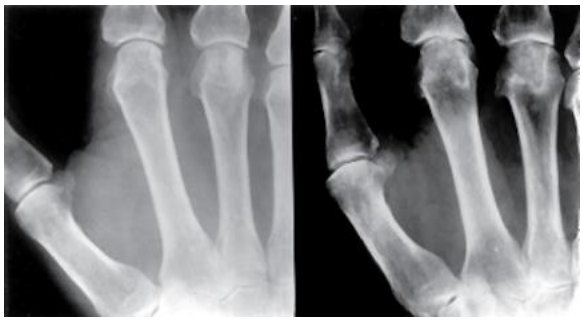
Case 3

- Patient started on NSAIDs (had recent bacteremia so avoided prednisone)
- Had an upper GI bleed 2 weeks later and NSAIDs discontinued
- Then developed chest pain, shortness of breath and was found to have a large pericardial effusion that required draining
- ANA and dsDNA positive. Anti-histone negative
- Patient switched to adalimumab and is doing well so far

Case 4

- 50M with diabetes and elevated transaminases presents to you for workup
- He complains of chronic pain in his MCPs, PIPs, wrists and knees
- GP has kindly forwarded you his hand x-rays

Case 4



Diagnosis?

Hemochromatosis

- C282Y mutation in the HFE gene
- Arthritis is the most common extra-hepatic manifestation
- Presents with polyarthropathy involving MCP joints, PIPs, knees, wrists, and vertebral joints
  - Asymptomatic osteophytes or chondrocalcinosis
  - Pseudogout (CPPD as a result of inhibition of pyrophosphatase by iron deposition in synovial cells)
  - Chronic arthritis
- X-rays show joint-space narrowing, hook osteophytes (at MCPs), squaring of the MCPs, subchondral cysts, erosions, chondrocalcinosis
- Phlebotomy or chelation therapy does not improve joint symptoms

Sinigaglia L, et al. Bone and joint involvement in genetic hemochromatosis: role of cirrhosis and iron overload. J Rheumatol. 1997;24(9):1809.

Summary/pearls

- Rheumatologic manifestations of GI diseases are common
- Reactive arthritis can occur days to weeks after a GI/GU infection
- IBD-associated arthritis is common and can occur even in patients who have no GI symptoms
- Optimize therapy for IBD and exclude active IBD in asymptomatic patients
- Patients with SpA have many overlapping features
- Anti-TNF agents can cause autoimmune diseases
- Arthritis is common in patients with hemochromatosis

Summary

- If a joint is swollen, always try to aspirate
- Consider referral to a rheumatologist for all of the above
  - Consider calling the RACE line if you are not sure how to proceed


Questions?