Differential Diagnosis of Polyarthritis/Polyarthralgia

Robert P. Friday, M.D., Ph.D.

Newton-Wellesley Hospital Rheumatology
Mass General Hospital Rheumatology
Disclosures

None.
Polyarthritis – Outline

1. DDx: broad array of choices
   - History narrows the field
   - Physical exam confirms suspicion
   - Labs and x-rays – not to be used as screening tools since results can be misleading in the absence of a good history and exam.

2. Common arthritides – a few key points.

Rheumatology Consult for Joint Pain: Common Chief Complaints

“Doc, my body is full of arthritis.”

“My bones hurt!”

“My joints hurt, but my arthritis test was negative.”

“I have pain all over and tested positive for lupus.”

“I don’t know why I’m here.”
### Joints (or not…)

- Osteoarthritis
- Erosive Osteoarthritis
- Rheumatoid arthritis
- Gout
- CPPD arthropathy
- Psoriatic arthritis
- Ankylosing spondylitis
- Reactive arthritis
- Palindromic rheumatism
- Undifferentiated polyarthritis
- Polymyalgia rheumatica
- Fibromyalgia
- “Poly-bursitis”
- Peripheral neuropathy

### Joints PLUS

- SLE
- Sjögren’s syndrome
- Systemic sclerosis
- Inflammatory myopathy
- Adult-onset Still’s disease
- Sarcoidosis
- Relapsing polychondritis
- Behçet’s disease
- Systemic vasculitis
- Parvovirus B19 infection
- Hepatitis C > B
- Acute rheumatic fever
- *Early* Lyme disease
- Chikungunya virus
- Zika virus
A more basic view of the DDx for polyarticular pain

1. Osteoarthritis
2. Inflammatory arthritis (has its own DDx)
3. Arthralgia (pain without joint abnormality)
4. Bursitis or Tendinitis
5. Myofascial pain / Fibromyalgia

When it is early in the course of symptoms, differentiating among these causes is often difficult for anyone. Embrace the challenge!
Diagnostic Evaluation of Joint Pain

1. A thorough HISTORY and EXAM are critical for differentiating causes of joint pain.
   - Pain localized to joints or more diffuse?
   - Laboratory studies and radiographs provide supportive diagnostic and prognostic information.

2. Joint pain is like a heart murmur.
   - Significance is determined by the company it keeps.

3. Read a joint exam like an EKG.
   - Pattern recognition may point you to the diagnosis.
Normal Joint Homunculus
Rheumatoid Arthritis
Case 1 – Slam dunk

18yF w/ 1 year of joint pain, previously healthy.

- Progressively: hands (MCPs and PIPs), elbows, shoulders, ankles, feet, jaw. Knees swollen more recently.
- Pain 8-9/10, with naproxen 5-6/10.
- In college, going to the gym regularly. +Fatigued.
- AM stiffness lasts 4 hours.
- Can’t walk up stairs easily.
- No rashes, no fevers, no weight loss, no alopecia.
- Saw PCP (after a year), ESR 11→25, CRP 11.7 mg/L, RF positive (x2), ANA neg, TSH normal, vit D low (17 ng/mL).
- Tearful in office – swollen joints = 34, tender joints = 36

MEDS: naproxen, vitamin D.
LABS: ESR 70, CRP 65 mg/L, RF 565, CCP 261, ANA 1:40.
Osteoarthritis
RA, PsA, SLE, other CTD, CPPD, Gout
Historical Clues

Duration - when did it start?
Location - which joints? (if joints at all…)
Character - pain, swelling, stiffness?
Onset - acute or insidious?
Timing - AM? eve? night? with rest or activity?
Treatment - what have you tried?
Other - symptoms of connective tissue disease?
Family History - Gout, OA, RA, psoriasis or PsA especially.
Duration of Polyarticular Complaints

**Acute (days)**
→ Typically inflammatory
- Infection
  - Viral
  - Bacterial (usu. monoarth)
  - *Early* Lyme disease
- Crystal
  - Often have est. diagnosis of Gout or CPPD
- Reactive
- Early chronic cause

**Chronic (wks to yrs)**
→ Is it inflammatory or not?
- Rheumatoid
- Psoriatic
- Crystal
- Connective tissue dz
- Vasculitis
- Myositis
- Adult Still’s disease
- Osteoarthritis
- Fibromyalgia
### Inflammatory vs. Non-inflammatory Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Inflammatory</th>
<th>Non-inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>++ / +++</td>
<td>+ / ++</td>
</tr>
<tr>
<td>Stiffness</td>
<td>++ / +++</td>
<td>+ / ++</td>
</tr>
<tr>
<td>Swelling</td>
<td>+++</td>
<td>+ / -</td>
</tr>
<tr>
<td>Nighttime Pain</td>
<td>++</td>
<td>+ / -</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>&gt; 60 min</td>
<td>&lt; 30 min</td>
</tr>
</tbody>
</table>
Useful questions to ask

**Morning Stiffness:** How long until you feel the best you are going to feel for the day?
- “Stiffness” has various meanings for patients.

**Activity Limitations / Disruptions:**
- Do you have difficulty with ADLs? (offer examples)
- What would you like to be doing that you can no longer do?
- How well do you sleep? Does pain wake you from sleep?
Physical Exam

Look for signs of CTD, psoriasis, vasculitis:

- **Skin rash**
  - Sun exposed (SLE, Dermatomyositis, other CTD)
  - Extensor surfaces, umbilicus, gluteal cleft, scalp (Psoriasis)
  - Palpable purpura (Vasculitis)
- **Skin thickening or morphea** (Systemic sclerosis)
- **Hair loss** – thinning, patchy alopecia (SLE)
- **Nails** – pitting/onycholysis (Psoriasis), abnormal nailfold capillaries (CTD)
- **HEENT**
  - dry eye and dry mouth (Sjogren’s)
  - oral ulcers/lesions (SLE, Behçet’s)
  - ocular inflammation (Spondyloarthritis, RA, Behçet’s)
  - abnormal temporal arteries (GCA/PMR)
  - nasal crusts or blood; nose or ear cartilage inflammation (ANCA vasculitis, Relapsing polychondritis)
Photodistribution of SLE Rashes

Most common  common  uncommon  rare
Distribution of Psoriasis

http://www.moondragon.org/health/disorders/psoriasis.html
DIP-limited Psoriatic Arthritis
Joint exam – synovitis (soft tissue swelling +/- effusion) is the hallmark of inflammatory arthritis:

- **Inspection, Palpation, ROM, Strength, DTRs.**
  - Erythema, warmth, tenderness, effusion – EASIER to detect
  - Soft tissue swelling (may be subtle) – HARDER to detect
  - Neuro exam goes along with MSK exam.
  - If only one or a few joints hurt, examine *every* joint.
### Joint Exam Elements

<table>
<thead>
<tr>
<th>Element</th>
<th>OA</th>
<th>Inflammatory</th>
<th>Arthralgia</th>
<th>Bursitis or Tendinitis</th>
<th>Myofascial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inspection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>varies</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Erythema</td>
<td>no</td>
<td>varies</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td><strong>Palpation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warmth</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Tenderness</td>
<td>along joint line</td>
<td>varies</td>
<td>varies</td>
<td>peri-articular</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Movement</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROM</td>
<td>limited</td>
<td>limited</td>
<td>full or limited</td>
<td>full, pain often limits</td>
<td>full</td>
</tr>
<tr>
<td>Pain w/active or passive</td>
<td>both</td>
<td>both</td>
<td>usually both</td>
<td>active &gt; passive</td>
<td>usually both</td>
</tr>
</tbody>
</table>
Some Non-inflammatory / Non-arthritic causes of musculoskeletal pain

Thyroid disease
Fibromyalgia syndrome
Medications (temporally associated with use)
  – Cholesterol-lowering agents; SERMs & aromatase inhibitors; anti-thyroid drugs (methimazole, PTU)
Primary sleep disorders
  – Obstructive sleep apnea
  – Restless legs syndrome
Joint hypermobility / hyperextensibility
  – Ehlers-Danlos syndrome
Malignancy
Diagnostically Helpful:

Creatinine and liver enzymes – assess for renal and hepatic dysfunction as signs of systemic illness; baseline for therapy.

CBC – anemia due to chronic inflammation, cytopenias in SLE/CTD, heme malignancy (rare).

Urinalysis – Renal disease is often asymptomatic in SLE and vasculitis.

ESR and CRP – non-specific, often helpful, but often normal in patients with active inflammatory disease. **NOTE:** a ‘high normal’ CRP of 7-8 mg/L may be elevated for a given patient.
Laboratory Testing

Not usually helpful diagnostically:

**Uric Acid** – this is **not** a diagnostic test for gouty arthritis. Hyperuricemia is a **risk factor** for gout, so when gout is a possible cause of joint pain it is appropriate to assess the level (i.e., typically NOT in a 30yo woman!).

**Lyme serology** – only helpful if early Lyme disease is suspected to be the cause of polyarthralgia. *Lyme arthritis* is **NOT** polyarticular – it is a late manifestation of infection with *B. burgdorferi* presenting with **inflammatory** monoarticular (or oligoarticular) joint disease.
Serological Testing

Serologies support the clinical impression – they are not diagnostic as isolated positive test results.

**Anti-CCP Ab**  (CCP = cyclic citrullinated peptide)
- Highly specific for RA (low titers seen in other dz), a/w extra-articular manifestations and high risk for joint damage.

**Rheumatoid factor** (RF)
- A reliable marker of RA only in a patient with polyarticular synovitis, otherwise it is non-specific.

**Anti-nuclear antibody** (ANA)
- Not specific for SLE – positive in other CTDs, RA, autoimmune liver and thyroid disease, healthy individuals.
Additional Testing

**HLA-B27** – only helpful if suspecting spondyloarthritis, which is not typically polyarticular (usually presents as inflammatory back pain +/- mono- or oligoarticular peripheral arthritis).

**Calcium axis evaluation** – if CPPD arthropathy confirmed or suspected, assess Ca, Mg, Phos, PTH and 25-OHD. Additional studies to assess for hemochromatosis may also be appropriate if otherwise suspected clinically.

**Serum Ferritin** – if considering Adult Onset Still’s Disease or CPPD arthropathy related to hemochromatosis.
Case 2 – Not So Crystal Clear

65yM w/ CAD s/p stenting 4 years ago p/w bilateral shoulder pain and stiffness and bilateral knee pain and swelling x3 weeks.

• Feels his symptoms are muscle and joint related.
• Cramping sensation behind both knees.
• Difficulty getting up from low seats (e.g., toilet).
• Nocturnal pain, hard to sleep, AM stiffness lasts hours.
• Advil 400mg 5x/day and Aleve 440mg BID only slight relief.
• Stopped rosuvastatin for 3 days, no improvement in symptoms.
• Avid golfer, no tick bites but worried about Lyme.
• No FH of arthritis or autoimmune disease.
Case 2 (continued)

ROS: No rash, headache, eye/vision symptoms, jaw claudication, fever, chills, sweats, unexplained weight loss.
Meds: ASA, lisinopril, rosuvastatin, metoprolol, clopidogrel.

Exam: Looks well, discomfort when moving (shoulders and knees). No ocular inflammation. No lymphadenopathy. Lungs clear. Heart regular, no murmur. No peripheral edema. No rash. No neuro deficits, but strength exam limited by pain. Unable to abduct right shoulder beyond 90 degrees, pain on the left with better ROM. Bilateral knee effusions L > R, with warmth, tenderness and pain upon flexion. Hip ROM is stiff with only mild discomfort. No abnormalities of hands, wrists, ankles or feet.

Labs: Mild anemia, otherwise CBC and CMP unremarkable. ESR 54, CRP 91 mg/L, ANA negative, RF negative, anti-CCP negative, uric acid 5.4 mg/dL, CPK 35, parvovirus negative, Lyme negative.
Case 2 (continued)

IMAGING: None obtained.

PROCEDURE: Bilateral knee arthrocentesis

- 10mL from L knee and 35mL from R knee, yellow fluid with moderate turbidity. Both joints injected with depomedrol.
- Fluid WBC counts: L knee = 4084, R knee = 2729.
- Crystal analysis: L knee = no crystals, R knee = +CPPD crystals inside WBCs.

DDx: Polymyalgia rheumatica (no sx of temporal arteritis)
      Rheumatoid arthritis, seronegative
      Polyarticular CPPD arthropathy ("pseudogout")
      Other inflammatory arthritis

Rx: Prednisone 15mg daily (cures all ills … at least initially!)
Radiographs (usually normal at first)

**RA** = soft tissue swelling, **periarticular osteopenia**, joint space narrowing, **marginal erosions**.

**OA** = **osteoophytes**, narrowing, central erosion, **subchondral sclerosis** and **subchondral cysts**.

**Gout** = calcified tophi, **overhanging edges** ("rat bite" erosions).

**CPPD** = chondrocalcinosis (wrist, knee, hips/pelvis).

**PsA** = **periostitis**, erosion, narrowing, fusion, **pencil-in-cup deformity**.

**SLE** = **non-erosive**, reducible ulnar deviation.

**SSc** = calcinosis (in soft tissue), distal tuft resorption.
Osteoarthritis

Epidemiology
• Rare <35yo, incidence and prevalence increase with age (>80% of population >55yo).
• Numerous risk factors, both environmental and genetic.

Diagnostic considerations
• Joints most affected: hand IP joints, feet, knees, hips, spine.
• Distinguishing between Inflammatory vs. Non-inflammatory OA may affect therapy.
• May be associated with CPPD crystal deposition (with evident chondrocalcinosis on radiographs).
• Typical radiographic changes develop over years.
Osteoarthritis (and osteopenia)
Erosive osteoarthritis
CPPD Arthropathy
Rheumatoid Arthritis

**Epidemiology**
- 1% of Caucasian population, up to 5% of women >65yo.
- Women affected 2-3x > Men.
- Occurs at any age, peak incidence 50-75yo.
- Genetics and smoking identified as risk factors.

**Diagnostic considerations**
- Constitutional symptoms: fatigue, weight loss, occ. fever.
- Numerous extra-articular organs can be involved (40% of pts over lifetime): skin, bone, muscle, eye, heart, lung, CNS, PNS.
- Recent guidelines devised to promote EARLY diagnosis.
- Radiographs normal in early disease, and we like to keep them that way!
- RA and fibromyalgia are often co-morbid, sometimes leading to diagnostic confusion or a delay in the diagnosis of seronegative RA.
Rheumatoid arthritis (early)
Case 3 – A Cautionary Tale

68yoM with alcohol use disorder (sober 2 years), h/o Lyme arthritis (knee), polyarticular synovitis with effusions and bursitis.

**Labs:**
- ESR 54 mm/hr
- CRP 68.9 mg/L
- HCT 34.5 %
- Plts 633,000
- RF 537
- Anti-CCP 237
Psoriatic Arthritis

**Epidemiology**
- Male:Female equally affected
- Age of onset 30s and 40s
- Psoriasis - up to 30% have arthritis
  - 20-40% involves spine or SI joints
  - Arthritis may precede skin disease

**Extra-articular Features**
- Psoriatic skin lesions - typically thick scale on erythematous base, but some variability
- Fingernails: pitting, onycholysis, transverse depressions
- Eye inflammation (30%) - conjunctivitis, iritis
- Dactylitis, tendinitis

**5 subtypes:** Spondyloarthritis, Mono/oligoarthritis, Polyarthritis, DIP-limited arthritis, Arthritis mutilans.
Psoriatic Arthritis, Mutilans type

Dactyliitis
“sausage digits”
Psoriatic arthritis AND Osteoarthritis
SLE Arthropathy

- Joint pain and fatigue are the most common presenting symptoms of SLE.
- Up to 95% of SLE patients have arthritis.
- Symmetrical, polyarticular usu. involves knees, wrists, PIP joints.
- Non-erosive, migratory, may resolve in a given joint in <24h.
- Lax joint capsules, tendons, ligaments = reducible deformity.
- Often pain >> physical findings.
Lupus arthropathy
Case

75yF with recent onset of headache, proximal MSK aching (neck/shoulders > hips), decline in vision and elevated inflammatory markers.

2mo proximal pains ("all her bones hurt"), assoc with:

- temporal headaches and scalp tenderness.
- decline in vision starting after 3 weeks of symptoms.
- appetite off, has lost ~15-20 lbs.
- Feels "numbness" along the left side of her face and jaw, as well as a feeling of swelling in this area and over the forehead.
- Notes from recent EW visit, "She describes her jaw pain as "an electric shock" which is worse with chewing."
- ESR 91 and CRP 126 mg/L. ANA, RF, anti-CCP negative.

ANY THOUGHTS ON A DIAGNOSIS?
Case (cont’d)

Started on prednisone 80mg daily (worrisome story).
- Temporal artery biopsy (performed 3 days later).
- Ophthalmology evaluation.

RESULTS:
- TA biopsy = negative for arteritis.
- Eye exam = cataracts.
- Feels much better on prednisone.
- Tapered dose to 20mg/day since TA biopsy negative.
1 month later:

- Proximal aching has recurred on 20mg/day, just as severe.
- Vision stable, some headaches, not as bad.
- She reports increasing her prednisone to 80mg/day (on her own) to control symptoms, now at 40mg/day, a little better.
- ESR 83 and CRP 125 mg/L.

NOW WHAT?!?

- Advised to continue prednisone 40mg/day → ? Biopsy neg GCA
- Time to think…

Presents to EW the following week with temp 103, left sided neck swelling and pain. CT with 1.3cm hypodensity in the left neck with surrounding inflammation. ? Abscess, ? Lymph node.
Lymphoma, not PMR/GCA
Summary

1. The DDx for polyarthritis is large, though a patient’s history and demographics quickly narrow the field.

2. Identifying the pattern of joints involved and identifying active synovitis (or not) very often yields the correct diagnosis.

3. Recognizing non-articular signs and symptoms are critical for identifying patients with complex systemic inflammatory disease.
Summary

4. Laboratory tests merely support or confirm the clinical impression – they are not useful as diagnostic screening tools.

5. Radiographs are very often normal in the early stages of joint disease, but aggressive joint disease can cause rapid damage, so early diagnosis and treatment are critical.

Thank you for your attention!