Evaluation and Management of Monoarticular Arthritis

Robert W. Janson, MD FACR FACP
Division of Rheumatology
Denver VA Medical Center; UCSOM

Learning Objectives

• Identify the causes of acute and chronic monoarticular arthritis
• List the tests which should be routinely performed on synovial fluid analysis
• Discuss the different types and significance of synovial effusions
• Develop an approach to the evaluation and treatment of monoarticular arthritis

Case Presentation

• A 52-year-old man is admitted with community–acquired pneumonia (CAP). On hospital day 3, the patient was awakened at 4:00 am by an aching pain in his right knee. Within a few hours, the joint was dusky red, hot, and exquisitely tender to the point that the patient was unable to actively move the joint or ambulate. There is no history of trauma to the joint.
Case Presentation

1. What procedure is critical to the diagnosis?
   a. Blood cultures
   b. CBC with differential
   c. Weight-bearing knee x-ray
   d. Arthrocentesis
   e. Serum uric acid level

2. Synovial fluid analysis should be sent for all of the following except:
   a. Cell count with differential
   b. LDH and total protein
   c. Crystal analysis by polarized microscopy
   d. Gram’s stain
   e. Synovial fluid culture

3. Inflammatory (Type II) synovial fluid has a cell count of:
   a. < 200 leukocytes/mm$^3$
   b. 200-2000 leukocytes/mm$^3$
   c. 200-2000 RBCs/mm$^3$
   d. 2000 or greater leukocytes/mm$^3$
   e. 2000 or greater RBCs/mm$^3$

4. Monosodium urate crystals are:
   a. Bipyramidal; positively birefringent
   b. Rhomboid; positively birefringent
   c. Needle-shaped; negatively birefringent
   d. Plate-like with a notched corner
   e. Needle-shaped; positively birefringent

---

**Monoarticular Pain: Clinical Features**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Tendinitis, Bursitis</th>
<th>Non-Inflammatory Joint Pain</th>
<th>Systemic Rheumatic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am stiffness</td>
<td>Localized, brief</td>
<td>Localized, brief</td>
<td>&gt; 30-60 min</td>
</tr>
<tr>
<td>Constitutional</td>
<td>None</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td>Peak period of discomfort</td>
<td>With use</td>
<td>After prolonged use</td>
<td>After prolonged inactivity</td>
</tr>
<tr>
<td>Locking or instability</td>
<td>Unusual, except with RTC tears and trigger fingers</td>
<td>Suggests internal derangement</td>
<td>None</td>
</tr>
</tbody>
</table>

_Arthritis Rheum 1996; 39:1-6._


**Monoarticular Pain: Clinical Features**

<table>
<thead>
<tr>
<th>Signs</th>
<th>Tendinitis, Bursitis</th>
<th>Non-Inflammatory Joint Pain</th>
<th>Systemic Rheumatic Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenderness</td>
<td>Localized, periarticular</td>
<td>Mild, over the joint line</td>
<td>Diffuse over exposed joint space</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Over tendon or bursa</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Instability</td>
<td>Uncommon</td>
<td>Occasional</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Multisystem disease</td>
<td>No; Occasionally with GC</td>
<td>No</td>
<td>Often</td>
</tr>
</tbody>
</table>

**Causes of Monoarticular Arthritis**

- **Septic:**
  - Bacterial
    - Septic joint
    - Osteomyelitis
  - Mycobacterial
  - Fungal
  - Lyme disease

- **Crystal disease:**
  - Gout
  - Calcium pyrophosphate dihydrate deposition disease (pseudogout)
  - Hydroxyapatite deposition disease
  - Calcium oxalate deposition

- **Traumatic:**
  - Fracture
  - Internal derangement
  - Hemarthrosis
  - Coagulopathy
  - Anticoagulation

- **Other:**
  - *Any polyarticular arthritis*
  - Osteoarthritis
  - Avascular necrosis
  - Foreign-body synovitis
  - Pigmented villonodular synovitis
  - Hemoglobinopathies
  - Palindromic rheumatism
  - Reflex sympathetic dystrophy
  - Paget’s disease of the joint
  - Pancreatic fat necrosis
  - Regional migratory osteoporosis
  - Synovial osteochondromatosis
  - Synovioma / sarcoma / mets
Approach to the Patient with Acute Inflammatory Monoarthritis

• Three most common etiologies:
  – Infection: assume present until proven otherwise
  – Crystal-induced
  – Chronic inflammatory arthropathy

• Diagnostic studies:
  – Synovial fluid analysis
  – Radiograph of the joint
  – CBC
  – In selected patients:
    • ESR; pan-cultures; PT, PTT; uric acid - not diagnostic as the level can be normal in up to 30% of patients experiencing an acute gouty attack

Synovial Fluid Analysis

The Big Three

1. Cell count with differential
2. Gram’s stain and culture
3. Crystal analysis by polarized microscopy

Synovial Effusions: Classification

<table>
<thead>
<tr>
<th>Type of Fluid</th>
<th>Special Features</th>
<th>Leukocytes/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Clear, Colorless, Viscous</td>
<td>&lt;200 (&lt;25% PMNs)</td>
</tr>
<tr>
<td>Noninflammatory (Type I)</td>
<td>Clear, Yellow, Viscous</td>
<td>200-2,000 (&lt;25% PMNs)</td>
</tr>
<tr>
<td>Inflammatory (Type II)</td>
<td>Cloudy, Yellow, Low viscosity</td>
<td>2,000 or greater (&gt;50% PMNs)</td>
</tr>
<tr>
<td>Septic (Type III)</td>
<td>Purulent</td>
<td>&gt;50,000 (&gt;75% PMNs)</td>
</tr>
</tbody>
</table>
Synovial Fluid Characteristics

- Cell count:
  - WBCs > 50,000: increase suspicion of infection;
  - WBCs < 25,000 (LR 0.32)
  - WBCs > 25,000 (LR 2.9)
  - WBCs > 50,000 (LR 7.7)
  - WBCs > 100,000 (LR 28)
- Not all counts > 50,000 are septic!
- WBCs > 100,000:
  - Infection
  - Reactive arthritis (Reiter’s): neg GS and culture
  - Crystal-induced: neg GS and culture
  - RA pseudosepsis syndrome: neg GS and culture

Types of Synovial Effusions
Noninflammatory (Type I)

- Osteoarthritis
- Early RA
- Trauma
- Internal derangement
- Osteochondritis dissecans
- Osteonecrosis
- Sickle cell disease
- Chronic/subsiding crystal synovitis
- Lupus
- Scleroderma
- Amyloidosis
- Hypothyroidism
- Milwaukee shoulder
### Types of Synovial Effusions

**Inflammatory Fluid (Type II)**
- Rheumatoid arthritis
- Acute crystal synovitis
- Reactive arthritis
- Psoriatic arthritis
- Arthritis of IBD
- Ankylosing spondylitis
- Viral Arthritis
- Rheumatic fever
- Juvenile chronic arthritis
- Behçet's syndrome
- Vasculitis
- Lyme disease
- Infection

**Septic Synovial Fluid (Type III)**
- Bacterial infection
- Fungal infection
- Mycobacterial infection

**Hemorrhagic Synovial Fluid (Type IV)**
- Trauma with or without fracture
- Bleeding disorders:
  - Anticoagulation, Hemophilia, von Willebrand’s, Scurvy, Thrombocytopenia
- Charcot's arthropathy
- Crystalline arthropathy
- Tumor, Villonodular Synovitis, Hemangioma
- Prosthetic joint, post-op aneurysms
- Sickle Cell Arthropathy
Synovial Fluid Characteristics

- Gram’s stain (sens 50-75%; spec 100%):
  - 60-75% positive in gram positive septic arthritis
  - < 50% positive in nongonococcal gram negative septic arthritis

- Culture:
  - Bacterial: nearly 95% positive with exception of gonococcus (25%)
  - AFB: 50-80% positive; may need synovial biopsy for culture, histology
  - Fungal: < 50% positive, candida higher yield; may need synovial biopsy for culture, histology

Septic Arthritis

- A true rheumatologic emergency!
- “If you don’t aspirate, prepare to litigate”
- A missed septic joint = irreversible cartilage loss within a few days particularly with gram-positive organisms
- Rule of thumb: assume that the joint is infected until proven otherwise
- If infection cannot be ruled out by initial diagnostic studies, treat presumptively for a septic joint until synovial culture results become available

Septic Arthritis
Pathophysiology

- Synovium is highly vascular and not lined by a limiting basement membrane
- Organisms infect the joint through:
  - Hematogenous spread from a remote infection (70%)
  - Direct inoculation (20%): surgery, penetrating wound, injection
  - Local invasion by contiguous infection
Septic Arthritis

Classification

- Multiplication of the organism within the joint space:
  - Bacteria
  - Mycobacteria
  - Fungi
  - Viruses
  - Parasites

- Reactive arthritis secondary to distant infections:
  - SBE
  - Hepatitis B & C
  - Post-chlamydia or GI tract pathogens
  - Rheumatic fever
  - (Disseminated GC)

Septic Arthritis

Predisposing Factors

- Systemic diseases: cancer, CKD, DM, cirrhosis, sickle cell, HIV, RA
- Abnormal joint: chronic arthritis or prosthetic joint
- Intravenous drug abuse
- Impaired host defense mechanisms: extremes of age (infants and elderly), complement deficiencies (C5-C9 deficiency and DGI), hypogammaglobulinemia, impaired chemotaxis, immunosuppressive agents

Septic Arthritis: Common Organisms

<table>
<thead>
<tr>
<th>AGE</th>
<th>ORGANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 months</td>
<td>Staph, Strep, gram neg</td>
</tr>
<tr>
<td>6 months – 2 years</td>
<td>H. influenzae, S. aureus</td>
</tr>
<tr>
<td>2-15 years</td>
<td>Staph, Strep pneumoniae</td>
</tr>
<tr>
<td>16-50 years</td>
<td>Neisseria gonorrhoeae, S. aureus</td>
</tr>
<tr>
<td>&gt; 50 years</td>
<td>Staph, Strep, gram neg</td>
</tr>
</tbody>
</table>

*S. aureus: most common due to a collagen adhesion factor (agr gene) and fibronectin binding proteins*
Septic Arthritis
Clinical Manifestations

- Abrupt onset of an acutely painful, swollen joint
- Joint effusion with painful decreased active and passive ROM
- Monoarticular presentation (80-90%)
- Joints affected: knees (55%) > hips > ankles > shoulder > wrist > elbow > other
- Fever: may be low-grade
- R rigors are unusual: more common if blood cultures positive

Bacterial Septic Arthritis

<table>
<thead>
<tr>
<th></th>
<th>GONOCOCCAL (DGI)</th>
<th>NON-GONOCOCCAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host</td>
<td>Young, healthy adults; immunocompromised</td>
<td>Extremes of age, immunocompromised</td>
</tr>
<tr>
<td>Pattern</td>
<td>Migratory polyarthralgias / arthritis</td>
<td>Monoarthritis</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>+ Synovial cult</td>
<td>&lt; 25%</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>+ Blood cult</td>
<td>Rare (10%)</td>
<td>50%</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Hypersensitivity or immune-mediated</td>
<td>Bacteremic seeding of the joint</td>
</tr>
</tbody>
</table>

DGI: extensor tenosynovitis / dactylitis
Septic Arthritis
Intravenous Drug Abuse

- Joints affected: axial skeleton – lumbar vertebral, sacroiliac, acromioclavicular, sternoclavicular; lower extremity joints
- Organisms:
  - S. aureus most common; concern for MRSA
  - Higher incidence of gram-negatives:
    - Pseudomonas
    - Serratia
    - Enterobacter
- Course: insidious with longer duration of symptoms; rule out HIV

Septic Arthritis
Diagnosis and Treatment

- Non-gonococcal bacterial arthritis:
  - Dx: arthrocentesis and synovial fluid culture
  - Rx: joint drainage and parenteral abs; typical course 4-6 weeks or longer
- Disseminated gonococcal infection (DGI):
  - Occurs in 1%-3% of patients infected with GC
  - Dx: arthrocentesis often low yield; culture GU tract, pharynx, and rectum
  - Rx: ceftriaxone 1-2 gm iv daily until improved, then complete 7-10 day course with ciprofloxacin 500 mg bid or cefixime 400 mg po bid; rx chlamydia with doxycycline 100 mg bid x 7 days
Synovial Fluid Examination
Crystals / Refractile Material

- Monosodium urate (MSU): needle-shaped; yellow-parallel; negative birefringence
- Calcium pyrophosphate dihydrate (CPPD): rhomboid-shaped; blue-parallel; positive birefringence; ABC: Align, Blue, Calcium
- Hydroxyapatite: “stacks of shiny coins” by EM

Gout
- Predilection for cool, peripheral joints
- Onset in men:
  - 40 to 50 years of age
  - Onset before the age of 30: inherited enzyme defect in the purine degradation pathway, alcoholism, renal insufficiency
- Onset in women:
  - Postmenopausal: hypertension, renal insufficiency, diuretic usage
  - Can form tophi in OA joints of the hands

Synovial Fluid Examination
Crystals / Refractile Material

- Oxalate: bipyramidal; positive birefringence; rarely intracellular
- Cholesterol: large, stacked, plate-like with a notched corner (RA, chronic inflammatory effusions)
- Talc (gloves): Maltese cross
**Podagra**: gout of the 1st MTP joint

---

**Diagnosis of Gout**
- Requires aspiration of synovial fluid or a tophus for polarized microscopy evaluation
- Synovial fluid analysis:
  - Cell count with differential: 20,000-100,000 cells/mm³
  - Crystal analysis: + MSU crystals
  - Gram staining with culture: negative
- Septic synovial fluids may contain MSU crystals
- Elderly patients may have gout and pseudogout crystals in the same joint

---

**Treatment of Acute Gouty Arthritis**
- Comorbid medical illnesses, status of GI, hepatobiliary, cardiac, hematopoietic, and renal function guide the safest options:
  - NSAIDs
  - Colchicine: IV usage prohibited due to the potential for excessive dosing in high-risk patients resulting in death
  - Corticosteroids
  - Analgesics with observation
Oral Colchicine

- Most effective within 24 hr of an attack
- Dosing (normal renal and hepatic function): 0.6 mg orally every hour until:
  - Joint symptoms ease
  - GI toxicity occurs: nausea, vomiting, diarrhea (N/V/D)
  - Maximum dose of 6.0 mg (10 tabs)
- 80% of patients develop increased peristalsis, abdominal pain, or N/V/D before pain relief occurs!

Prophylactic Colchicine

- Prophylactic colchicine is used to prevent recurrent attacks of gout or when starting urate-lowering therapy (24% risk of precipitating an acute gouty attack)
- Dosage:
  - Normal renal and hepatic function: 0.6 mg po bid
  - Elderly or CrCl 30-50: 0.6 mg po qd or qod
  - CrCl < 30: avoid acute or prophylactic therapy

Gout: Systemic Corticosteroids

- Indications: contraindications to other acute therapies, acute gout refractory to other therapies
- Widely used: PO, IM, IV routes
- Prednisone: 30-50 mg daily with taper over 7-10 days (rare CNS effects; cautious use in diabetics, concurrent infection)
- Triamcinolone acetonide: 60 mg IM - can repeat x 1 the next day if necessary
- Rebound arthropathy: rare

钙化磷灰石沉着病（CPDD）

- **命名**:
  - CPPD: 钙磷灰石二水合物晶体
  - 假性痛风: 急性炎性关节炎，伴有CPPD晶体的释放进入关节腔
  - 钙化软骨病: 纤维或透明软骨钙化 [CPPD, 二水合磷酸钙二水合物 (刷牙), 钙石酸]

钙化磷灰石沉着病（CPDD）

- 发病率：
  - 青少年罕见，50岁以下15%，75岁以上65-75%，80岁以上30-60%
  - 男性与女性比例：2-7:1
  - 病情发作：50-70岁

CPDD: 钙化软骨病

- 关节部位：
  - 膝关节：半月板和关节软骨
  - 腕关节：三角纤维软骨复合体
  - 髋骨关节：纤维软骨

- X线影像学特征：
  - 骨关节炎样改变："OA在所有错误的地方"
  - "包绕"髌骨
  - 软骨和滑膜钙化
Chondrocalcinosis

of the triangular
fibrocartilage
complex (TFCC)

Normal

Chondrocalcinosis

Pseudogout

- Acute or subacute arthritis attacks which last several days if untreated; clusters of attacks may last several weeks to months
- Typically involves a large joint: knee, wrist, ankles, shoulders; successive polyarticular involvement with a migratory pattern can occur
- In the elderly, attacks may be associated with high and prolonged fever, confusional state
Pseudogout: Precipitating Events

- Trauma
- Surgery (especially parathyroidectomy)
- Serious medical illnesses: MI, CVA, pneumonia
- Arthroscopy
- Pamidronate therapy
- GCSF therapy
- Intra-articular injections of sodium hyaluronate
- Initiation of levothyroxine therapy

Pseudogout: Laboratory Findings

- Diagnosis is confirmed by the demonstration of rhomboid-shaped, positively-birefringent crystals in synovial fluid or articular tissues
- Synovial fluid cell counts range from 2,000 to 80,000/mm³ or greater with 80% PMNs
- Elevated ESR
- WBC and/or platelets may be increased

CPDD: Classification

- Sporadic (idiopathic): 90% cases
- Hereditary: autosomal dominant, familial case series, early onset (3rd-4th decade)
- Secondary associations:
  - Hyperparathyroidism
  - Hemochromatosis
  - Hypophosphatasia (low alk phosphatase)
  - Hypomagnesemia (idiopathic or Bartter’s)
  - Possibly hypothyroidism
CPDD: Screening for Secondary Associations

• Indications for screening:
  – Early onset arthritis (< 55 years of age)
  – Polyarticular disease
  – Recurrent acute attacks > chronic arthropathy
  – Clinical clues suggestive of a metabolic disease
• Screening tests: Ca, Phos, Alk phos, Mg, Fe/TIBC, Ferritin, and +/- TSH

CPDD: Management

• Acute attacks (pseudogout):
  – NSAIDs
  – Aspiration and injection of steroids
  – Prednisone 30-50 mg daily with taper over 7-10 days
  – Triamcinolone acetonide 60 mg IM, can repeat x 1
• Recurrent attacks:
  – Prophylactic oral colchicine (requires renal dosing, do not use if CrCl < 30)

Chronic Monoarticular Arthritis
(symptoms within a single joint for > 6 wks)

• Inflammatory:
  – Mycobacterial
  – Fungal
  – Lyme arthritis
  – RA – monoarticular
  – Seronegative spondyloarthropathy
  – Sarcoid
  – Foreign-body synovitis
• Non-inflammatory:
  – Osteoarthritis
  – Knee internal derangement
  – Avascular necrosis
  – Pigmented villonodular synovitis (PVNS)
  – Synovial chondromatosis
  – Synovioma
Approach to the Patient with Chronic Monoarticular Arthritis

- Radiograph of the joint; may need an MRI (AVN, osteo, PVNS, internal derangement)
- Synovial fluid analysis: non-inflammatory vs inflammatory vs bloody; cultures for routine and atypical infections
- CXR: mycobacterial disease, sarcoidosis
- AP pelvis film to r/o sacroiliitis
- PPD
- Selected serologies: ANA, RF, anti-CCP, Lyme disease
- Arthroscopy / synovial biopsy with cultures

The Case of the Acutely Swollen Knee

1. What procedure is critical to the diagnosis?
   a. Blood cultures
   b. CBC with differential
   c. Weight-bearing knee x-ray
   d. Arthrocentesis
   e. Serum uric acid level

2. Synovial fluid analysis should be sent for all of the following except:
   a. Cell count with differential
   b. LDH and total protein
   c. Crystal analysis by polarized microscopy
   d. Gram’s stain
   e. Synovial fluid culture

The Case of the Acutely Swollen Knee

3. Inflammatory (Type II) synovial fluid has a cell count of:
   a. < 200 leukocytes/mm²
   b. 200-2000 leukocytes/mm²
   c. 200-2000 RBCs/mm²
   d. 2000 or greater leukocytes/mm²
   e. 2000 or greater RBCs/mm²

4. Monosodium urate crystals are:
   a. Bipyramidal; positively birefringent
   b. Rhomboid; positively birefringent
   c. Needle-shaped; negatively birefringent
   d. Plate-like with a notched corner
   e. Needle-shaped; positively birefringent

Answers: 1-d; 2-b; 3-d; 4-c.
Key Concepts / Summary

- Arthrocentesis should be performed on any new synovial fluid collection:
  - Cell count with differential
  - Crystal analysis
  - Gram’s stain and culture
- Most common etiologies of an acute inflammatory monoarticular arthritis:
  - Infection
  - Crystal-induced
  - Chronic inflammatory arthropathy
- If infection cannot be ruled out by initial diagnostic studies, treat presumptively for a septic joint until synovial fluid culture results become available

Selected References