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**Objectives 1, 2, 3, 5 and 6 will be covered with a case**

**OBJECTIVE 1**

**In a patient presenting with joint pain, distinguish benign from serious pathology (e.g., sarcoma, septic joint):**

**a) By taking pertinent history**
**b) By investigating in a timely and appropriate manner (e.g., aspirate, blood work, an X-ray examination).**

**OBJECTIVE 2**

**In a patient presenting with non-specific musculoskeletal pain, make a specific rheumatologic diagnosis when one is evident through history, physical examination, and investigations. (e.g., gout, fibromyalgia, monoarthropathy vs. polyarthropathy).**

**OBJECTIVE 3**

**In a patient presenting with monoarthropathy, rule out infectious causes. (e.g., sexually transmitted diseases).**

**OBJECTIVE 5**

**Clinically diagnose ligamentous injuries. Do NOT do an X-ray examination.**

**OBJECTIVE 6**

**In a patient presenting with joint pain, include systemic conditions in the differential diagnosis (e.g., Wegener's granulomatosis, lupus, ulcerative colitis).**

**Case:**

Nicole is a 25 year-old female who presents to your office with a seven-week history of pain and swelling in her knees.

Excluding red flags can quickly help narrow your differential and rule out any pathology warranting urgent or emergent investigations. The main serious joint pathology to exclude would be a septic joint and fracture. Asking about a history of trauma is a quick screen to rule out any concern for a fracture causing joint pain. In this case, a septic joint would be unlikely due to the length of the presentation and the fact it's a bilateral presentation. Some key questions to ask regarding infection are:

- Fever and other constitutional symptoms
- Complete inability to bear weight
- Rapid progression or onset of symptoms
- Immunocompromised
- History of IV drug use
- Prosthetic joint
- Risk of sexually transmitted infections (gonorrhea)
- Tick bites (exposure to Lyme disease)

Red flags on history in the context of a red, hot, swollen joint raises suspicion for a septic joint. Septic joints have significant morbidity and mortality, and permanent joint destruction can occur within 24 to 48 hours of symptom onset. Joint aspiration is indicated if there is suspicion of a septic joint.

- Visually inspecting the fluid can provide some initial clues. Normal joint fluid is typically clear or straw colored and viscous. Infectious fluid is typically cloudy, with a low viscosity (low viscosity = more white blood cells or bacteria)
- The joint fluid should be sent for cell count with differential, gram stain, culture and crystal analysis
- Try to avoid starting antibiotics before joint aspiration
- Imaging Studies may not be helpful in diagnosing an acute septic joint, but are important to do as certain joints such as the hip, sacroiliac and spinal joints will require diagnostic imaging for diagnosis and guiding aspiration studies.
- Check with the lab to know which containers/tubes are needed for joint fluid analysis. The last thing you want is a rejected sample!
- Check out the references for a great article from the American Academy of Family Physicians, Approach to Septic Arthritis, which has a great table with differential diagnoses based on fluid analysis

So, for our case, let's assume there are no red flags in history. Where do we go from here?

Clarifying the duration of joint pain and the number and location of joints involved can further narrow your differential diagnosis.

Acute joint pain lasts less than 6 weeks, chronic joint pain lasts longer than 6 months:

- Septic arthritis and crystalline arthropathies, such as gout, are common causes of acute joint pain
- Insidious onset is often associated with degenerative joint disease, such as osteoarthritis
- Periods of exacerbations and remissions can occur with inflammatory pathologies
- Onset within one to four weeks after GI or GU infection is suspicious for reactive arthritis

Monoarticular refers to one joint, oligoarticular is greater than one joint but less than five, and polyarticular refers to greater than or equal to five. It's probably worth your while to remember what joints are commonly affected with specific inflammatory arthropathy, as this will help narrow your differential considerably.

- Osteoarthritis is a non-inflammatory arthropathy and is often asymmetrical and polyarticular but may present initially as monoarticular. It commonly affects the knees, DIP, PIP, 1st CMC, 1st MTP, hip, and the lumbar and cervical spine
- Rheumatoid arthritis is symmetric and polyarticular, commonly involving the PIP, MCP (aka the knuckle joint), and knees.
- Ankylosing spondylitis affects the spine and large joints such as the hips, shoulders, and SI asymmetrically.
- Psoriatic arthritis and reactive arthritis often present as asymmetric oligoarthritis.
- Gout commonly affects the first MTP, midfoot, ankle, and knee

In addition to symptom duration and number of affected joints, there are some other key questions to ask on history for a patient presenting with joint pain. These include:

- Location of pain: tenderness along the joint line suggests articular pathology. Pain in the muscle or around the joint suggests an extra-articular cause such as tendinopathy, ligament injury, bursitis, or muscle injury
- Stiffness: > 1 hr is suspicious for an inflammatory process. Patients with degenerative joint disorders can have stiffness, but it generally does not last more than 30 minutes
- Presence of pain at rest: degenerative joint disease is generally better with rest, compared to worsening pain in inflammatory joint disease
- History of injury or surgery increases the risk of degenerative joint changes
- Extra-articular involvement
    - A quick review of systems for rashes, skin changes, oral or nasal ulcers, respiratory issues, and ocular involvement should heighten your suspicion of inflammatory pathology
    - Discoid rash, malar rash, photosensitivity, oral ulcerations, and pleuritis are part of the diagnostic criteria for SLE
    - Dactylitis, psoriasis, and nail involvement can indicate psoriatic arthritis
    - Sinusitis and pulmonary involvement can also be seen in granulomatosis with polyangiitis, formerly known as Wegner's Granulomatosis
    - Fever, weight loss, or general malaise are non-specific but warrant further investigation

- If the patient has a history of inflammatory bowel disease or psoriasis, determining if the pain is associated with a flare of those symptoms is also important
- In the show notes, you can find information regarding specific extra-articular findings for various presentations.

Let's revisit our case.

- Nicole has had progressive worsening pain and swelling in both knees for seven weeks
- She has noticed sore wrists, hands, and fingers, especially in the morning. Nicole cannot hold her coffee until about an hour after she wakes up because her hands are so stiff
- Her pain improves throughout the day, and worsens when she is less active in the evenings
- She tore her right meniscus two years ago and had an arthroscopic repair but has had no further issues
- A review of systems is positive for a recent eye infection, fatigue and a 10lb weight loss over the past two months
- She has no other medical conditions, does not take any medications, and she has no known allergies
- She has not recently had any infections
- She thinks she may have an aunt who has arthritis, but she is unsure what kind

Based on her history, Nicole has a symmetrical polyarthritis with > 1hr morning stiffness, constitutional symptoms, and possible extra-articular ocular involvement. Our differential right now includes several inflammatory arthropathies and systemic illnesses.

- Because Nicole is female and has no axial involvement, ankylosing spondylitis is not in our differential
- She has no other medical conditions and has not had any recent infections, ruling out enteropathic or reactive arthritis, respectively.
- Nicole does not have a history of psoriasis, but up to 10% of individuals show arthritis as their first presentation.
- She did have an injury to her knee, which puts her at higher risk of osteoarthritis. However, she is young, and her surgery was only a short time ago, making it less likely.
- Gout may be polyarticular but would be unusual in a 25-year-old female. Gout occurs very rarely in pre-menopausal females.

Physical exam is a valuable tool when differentiating arthropathies. The acronym SEADS is helpful to remember what to look for when inspecting a joint; swelling, erythema, atrophy, deformity, and skin changes. Palpate joints for crepitus, tenderness, effusions, nodules, and warmth. A complete musculoskeletal exam also includes active and passive range of motion, strength and special tests.

As we have already discussed, an inflammatory joint will generally be red, hot, swollen, and tender. Do not be fooled though. Individuals with OA can have flares with joint swelling. Some

specific exam findings for common rheumatologic diseases are:

- OA - crepitus, tenderness along the joint line, bony prominences such as thumb squaring, Heberden's nodes at the DIP, and Bouchard's nodes at the PIP, and limited ROM of the affected joint
- Gout - severe pain with palpation, limited joint mobility, and evidence of tophi
- Reactive arthritis - enthesitis (plantar fasciitis and achilles tendonitis), a rash called ketoderma blennorrhagicum (hyperkeratotic skin on palms and soles of feet ), Circinate balanitis (a painless rash around the Glans Penis), cervicitis, prostatitis, and conjunctivitis
- Rheumatoid arthritis
    - Nodules
    - Swan neck deformity (hyperextension of the PIP and flexion of the DIP)
    - Boutonniere deformity (flexion of the PIP with extension of DIP)
    - Ulnar deviation at MCP and radial deviation at wrist
- Ankylosing spondylitis - mid and lower back pain and stiffness, decrease spine ROM on Schober test, decrease chest wall expansion, exaggerated lumbar lordosis and thoracic kyphosis, increased occiput to wall distance indicating increased c-spine flexion, enthesitis of achilles and plantar fascia, and uveitis.
- SLE - malar "butterfly" rash of the nose and cheeks sparing the nasolabial folds, discoid rash, painless oral or nasal ulcers, and alopecia
- Psoriatic arthritis - evidence of psoriasis, dactylitis, nail pitting, onycholysis, and sacroiliitis

Nicole's physical exam shows the following:

- She is alert and oriented, but appears pale and tired
- She has lost 6 kg 12 lbs since her last visit 4 months ago
- Bilateral swollen knees which are warm and tender to touch
- Swelling and tenderness to the 2nd-5th MCPs bilaterally and the wrists, with decreased active and passive range of motion
- Scarring to the right knee, consistent with her previous surgery
- No obvious deformities
- Right eye conjunctivitis, no discharge. She pulls away when you try to examine her eye with your light
- Cardiovascular, abdomen, respiratory, and gross sensory neurologic exam are all normal

So, where do we go from here?

Diagnostic imaging and blood work will provide additional information to further guide our differential diagnosis.

As we are suspicious of inflammatory pathology, an x-ray will help distinguish between degenerative and destructive joint changes and will provide a baseline going forward. As a general rule, x-rays are not always necessary for a soft tissue type injury.

The inflammatory markers ESR and CRP are sensitive, meaning they are good indicators of inflammation, but they are not specific to the cause of inflammation. About one third of the time, the ESR and CRP are discordant. Most labs will allow you to use only CRP's, as ESR's are more labour intensive.

Rheumatoid Arthritis may be Sero Positive - 80% - or Sero Negative – 20 %. What we formerly called the Sero Negative Spondyloarthropathies (SNSA) are now called the Spondylo Arthropathies - SpA. It includes Peripheral and Axial SpA's. SpA's include:

- Reactive Arthritis
- Idiopathic Ankylosing Spondylitis
- Psoriatic Arthritis
- Enteropathic Arthritis (aka arthritis associated with inflammatory bowel disease).

Each of the four SpA'a may have Axial or Peripheral Components or both Components at once.

The term Peripheral Spondyloarthopathy is an oxymoron as you are describing a "Peripheral Axial Disease" and the term Axial Spondyloarthropathy is redundant as you're describing an "Axial Axial Disease".

Ordering rheumatologic laboratory investigations can be overwhelming, so we will review some key points for each test.

- Rheumatoid Factor has a sensitivity of about 60 – 90% and a Specificity of about 85%
- Anti-CCP has a specificity of about 95% for RA and can be used to predict disease severity
- ANA is 95% sensitive for systemic lupus erythematosus, but is not specific
- Anti-dsDNA is a specific test for systemic lupus erythematosus in the range of 60-70%
- Anti-histone antibody is highly specific for drug-induced systemic lupus erythematosus
- If back pain is present and there are other signs of systemic inflammation such as uveitis, enthesitis, inflammatory bowel disease, or family history of ankylosing spondylitis, HLA-B27 testing can be considered to evaluate for ankylosing spondylitis. It is important to remember that not everyone with back pain requires this test, and a negative test does not rule out ankylosing spondylitis
- ~~p~~c-ANCA is both specific and sensitive for granulomatosis with polyangiitis.
- Elevated serum uric acid levels may help support a diagnosis of gout, however it does not need to be elevated to diagnose a gout flare. It is ~~best used~~ helpful when ~~to~~ assessing response to urate lowering therapy, such as allopurinol
- Check out the show notes for further explanation of the lab tests and their sensitivities and specificity. The Cleveland Clinic Journal of Medicine also has a great article on rheumatologic blood work, which is included in the reference list for this episode

So, what investigations should we order for Nicole based on our differential diagnosis?

- Routine CBC, renal function and liver transaminases are indicated
- CRP, RF, Anti-CCP, and ANA
- X-Rays of the hands, knees, and chest, (The Chest is done because diseases like RA and SLE may have sub-clinical findings such as a small pleural effusion)
- We are not suspicious for drug induced systemic lupus erythematosus, so anti-histone antibody testing is not indicated
- Ankylosing spondylitis is not on our differential, so HLA-B27 testing is not indicated
- Her clinical presentation does not fit with a diagnosis of gout, so uric acid testing is not indicated

Her blood work results show:

- Elevated CRP
- Highly positive RF
- Positive anti-CCP
- Her ANA is negative which essentially rules out SLE
- CBC, renal function, and liver transaminases are all within normal limits
- Her Diagnostic Imaging Tests are all normal

So, do we have enough information to make a diagnosis?

A score greater than 6 in the American College of Rheumatology criteria is diagnostic for rheumatoid arthritis. Points are assigned based on joint involvement, serology, acute phase reactants, and symptom duration.

Based on your thorough history, physical exam and laboratory investigations, Nicole's score based on the American College of Rheumatology criteria is 7, indicating a diagnosis of rheumatoid arthritis.

We don't have enough time to go through the diagnostic criteria for all rheumatic diseases, so it is important to know where to look for them! The American College of Rheumatology has published diagnostic criteria for rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, polymyalgia rheumatica, and many more, so be sure to have this resource saved. We will cover treatment for Nicole and her new diagnosis of rheumatoid arthritis later in this episode.

One other rheumatologic condition which we did not cover in this case, but is worth mentioning, is polymyalgia rheumatica, PMR. PMR is a non-articular rheumatic disease which causes pain

and stiffness. It affects women twice as much as men and is associated with Giant Cell Arteritis in about 15% of cases. It is generally seen in patients over 50 years of age and therefore would not be part of the differential diagnosis in our case. Patients will describe symmetrical morning stiffness, and pain in proximal muscle groups, including the shoulders, neck, hips, and thighs. They may present with constitutional symptoms. Blood work demonstrates an elevated CRP with a negative RF and anti-CCP. On exam, patients will have tenderness over the area but no true weakness or muscle atrophy.

We've covered a lot of information in our case! Let's move on to our other objectives.

END OF PART ONE

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| System | Clinical Findings |
|---|---|
| Cardiovascular | • Pericarditis<br>• Myocarditis — SLE, RA<br>• Aortic regurgitation - Ankylosing spondylitis<br>• CV risk comparable to DM - RA |
| Pulmonary | • Pleuritis - SLE<br>• Interstital lung disease - RA |
| Gastrointestinal | • IBD related symptoms such as + FOBT, diarrhea – enteropathy arthropathy, ankylosing spondylitis |
| HEENT | • Uveitis- Ankylosing spondylitis<br>• Scleritis/episcleritis - RA<br>• Oral ulcers — SLE<br>• Nasal ulcers<br>• Sinusitis - GPA |
| Neuro | • Seizures<br>• Psychosis<br>• Cerebritis — SLE<br>• Peripheral neuropathy<br>• Mononeuritis Multiplex — RA<br>• Carpal tunnel<br>• Facial palsy – Lyme disease |
| MSK | • Dactylitis – Psoriasis<br>• Boutonnière and swan-neck deformities – SLE, RA<br>• Enthesitis – Ankylosing spondylitis<br>• Heberden's nodes (DIP joints)<br>• Bouchard's nodes (PIP joints) — Osteoarthritis |
| Skin | • Discoid rash<br>• Photosensitivity<br>• Malar rash — SLE<br>• Alopecia<br>• Skin tightening - systemic sclerosis<br>• Psoriasis<br>• Erythema chronicum migrans – Lyme Disease<br>• Erythema nodosum – Crohn's Disease |

| | |
|---|---|
| | • Pyoderma gangrenosum - IBD, RA, SLE, ankylosing spondylitis, sarcoidosis, Wegener's granulomatosis<br>• Tophi – Gout<br>• Nail pitting<br>• Onycholysis } Psoriasis |
| Genitourinary | • Hematuria<br>• Proteinuria<br>• Glomerulonephritis } SLE<br>• Urethritis or cervicitis – Gonorrhea<br>• Prostatitis – Ankylosing Spondylitis |
| Hematologic | • Lymphoma – RA |
| Psychological | • Depression - all |

**Table 1. Extra-Articular Manifestations of Rheumatic Diseases**

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| Test | Disease | Sensitivity | Specificity | Prevalence |
|---|---|---|---|---|
| Rheumatoid Factor (RF) | **Rheumatoid Arthritis (RA)** | **80%** | **Non-specific** | **50-90%** |
| | Systemic Lupus Erythematosus (SLE) | | | 15-35% |
| | Sjögren's syndrome | | | 75-95% |
| | Systemic Sclerosis | | | 20-30% |
| Anti-CCP | **RA** | **74%** | **94-98%** | **80%** |
| ANA | **SLE** | **98%** | **Non-specific** | **99%** |
| | Antiphospholipid Antibody Syndrome (APLS) | 98% | | |
| | Drug Induced SLE | | | 100% |
| | Scleroderma | 97% | | 60-80% |
| | Sjögren's syndrome | | | 96% |
| | RA | | | 40% |
| Anti-dsDNA | SLE | | 95-99% | 60% |

| | | | | |
|---|---|---|---|---|
| Anti-Sm | SLE | Not sensitive | 95-99% | 20 to 30% |
| Anti-histone | **Drug Induced SLE** | | **Highly specific** | **95%** |
| | SLE | | | 30-80% |
| c-ANCA | Granulomatosis with Polyangiitis – GPA | Highly specific | Highly sensitive | 90% |
| Anti-Ro | Sjögren's syndrome | | | 75% |
| | SLE | | | 40% |
| Anti-La | Sjögren's syndrome | | Specific when Anti-Ro also positive | 40% |
| | SLE | | Specific when Anti-Ro also positive | 10-15% |

**Table 2. Laboratory Testing in Rheumatology**

**References:**


- Mirali, S., & Seneviratne, A. (2020). *Toronto Notes - Medicine*. Toronto Notes for Medical Students, Inc.
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