Suspecting and treating inflammatory polyarthritis

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Disclosures

• None
Evaluation of Early Inflammatory Arthritis

• Why is this important?
  • Early RA and PMR syndromes present to primary care and generalists first.
  • Appropriate diagnosis, initiation of treatment and referral is paramount in early effective control of RA
Learning objectives

• Understand the initial evaluation of a patient with new onset polyarthritis
• Learn the differential diagnosis of patterns of disease presentation
• Understand the initial treatment of newly diagnosed RA and PMR
Identification of Early Synovitis

- History is the first clue
  - Morning time symptoms in the hands and forefeet
  - AM stiffness for > 30 minutes
  - Symptoms respond to NSAIDs
- Subtle exam findings
Inflammatory Arthritis vs DJD

Inflammatory

- Sudden onset
- Bilateral symmetric symptoms
- Constitutional symptoms
- Constitutional symptoms
- Elevated inflammatory markers
- Morning stiffness > 30 minutes
- MCP/ MTP squeeze tenderness

Degenerative

- Gradual onset of scattered symptoms in joints of fingers, knees, spine
- No constitutional symptoms
- No constitutional symptoms
- Use related pain with minimal stiffness
- Heberden nodes (DIP), Bouchard nodes (PIP)

Can be erosive
Marginal erosions (RA)

Can be erosive!
Central erosions
Case 1

• 32 year old housewife, mother of three school aged children.

• Referred by her family doctor for an acute inflammatory polyarthritis involving the hands, feet and knees.

• ESR is 87 mm/Hr, RF 389 IU/ML, anti-CCP antibody negative, ANA is positive at 6.3 U with a positive ENA panel to SSA, SSB, RNP, Sm, Jo-1 and Scl-70.

• She has been ill for 3 weeks and now is getting better with naproxen 375 mg twice daily
Which of the following will most likely confirm the diagnosis?

- A) HLA-B27
- B) Parvovirus B19 antibodies
- C) Serum urate
- D) HIV testing
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• A) HLA-B27
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Case 2

• 30-year old man is evaluated for arthritis.
• 3 weeks ago he noticed dysuria without discharge and right eye redness.
• 2 weeks later developed warmth, pain and swelling in the left knee, then right knee, then left heel, then right wrist.
• Dysuria and eye redness have resolved.
• Physical exam: vital signs normal; moderate effusion of the affected joints with tenderness and pain on ROM. Tenderness of Achilles tendon. No rash.
Case 2, continued

• Knee x-ray: joint effusion, no bony abnormalities, normal joint space
• Left knee aspiration: synovial fluid leukocyte count 5,000/µL, 65% Neutrophils and 35% mononuclear cells, Gram stain negative, cultures negative, no crystals.
Which of the following is the most appropriate diagnostic test to perform next?

• A) Chlamydia nucleic acid amplification urine testing
• B) C-reactive protein
• C) HLA-B27
• D) Interferon gamma release assay
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Rheumatoid Mimics Early Synovitis Patients

- **Viral Arthritis**
  - Rubella
  - Parvovirus B19

- **Reactive Arthritis Syndromes** *(Chlamydia trachomatis – most commonly involved)*

- **Seronegative Arthritis Syndromes/PMR in the Elderly**

- **Systemic Lupus Erythematosus**

- **Atypical crystalline arthritis** – CPPD, gout
Early Arthritis Syndromes
If not RA, what is it?

Early Inflammatory Arthritis

- RA 21%
  - Seropositive 55%
  - Seronegative 45%
- Post Infectious ReA 24%
- Undifferentiated Arthritis 36%
  - Self Limited
  - Early RA
  - Unrecognized ReA
  - PMR
  - Early AnkSpond
- PsA 7%
- Lyme Disease 2%
- Sarcoid 2%

Parvovirus B19 Arthropathy

Epidemiology

- Single strand DNA virus
- Winter-Spring outbreaks
- Adult risk groups: daycare workers, parents
- Respiratory secretion or pooled blood product transmission
  - Infection most common in young school children
  - 60% of adult blood donors are seropositive (IgG)
Acute Parvovirus Arthritis

- Females : Males 3:2
- Synovitis in hands, feet, knees, elbows
- 7% of “acute RA” in primary care
  - Always check IgM Parvovirus serology
- Serologically confused as RA or SLE: transient RF and ANAs
- 20% of cases may persist for > 2 months
- Symptomatic management

Illness Course in Adult Volunteers (Intranasal Inoculation)
Case 3

- A 36 year old woman presents with a 2-month history of morning stiffness in her hands, wrists, knees, feet for 1.5 hours. Her only medication is ibuprofen which is helpful.

- Physical exam: normal vital signs. Tenderness and swelling of the 2nd, 3rd and 5th MCPs bilaterally, 2-4th PIPs bilaterally, right wrist, left knee and 2-5th MTPs.
What is the most appropriate diagnostic test to perform next?

- A) Anti-cyclic citrullinated peptide antibodies
- B) HLA-B27
- C) Parvovirus IgG antibodies
- D) Serum urate
- E) TSH
What is the most appropriate diagnostic test to perform next?

- A) Anti-cyclic citrullinated peptide antibodies
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**Rheumatoid arthritis**

**Risk factors**

- Genetic (60%): HLA-DRB1 and other HLA and non-HLA susceptibility genes
- Environmental (40%): smoking, air pollution
- Other: periodontitis (Porphyromonas gingivalis), hormonal (?)

*Viatte S et al. Arthritis Rheumatol 2016*
*van Beers-Tas MH et al. Best Pract Clin Rheumatol 2015*
## RA laboratory panel

<table>
<thead>
<tr>
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<th>Anti-CCP</th>
<th>RF</th>
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<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>70%</td>
<td>72%</td>
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<tr>
<td><strong>Specificity</strong></td>
<td>95%</td>
<td>80%</td>
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| **Utility**       | - Identifying early inflammatory arthritis patients at risk for erosive disease  
                    - Evaluating RF negative inflammatory arthritis patients  
                    - Evaluating a positive RF in a person who doesn’t seem to have RA  
                    - In high titers uniquely specific for potentially erosive rheumatoid arthritis  
                    - Higher likelihood of detection and higher titers in established disease  
                    - High titers correlate with more severe disease |                  |
| **Impact of other factors** | Smoking                        | Smoking, age     |
### 2010 ACR/EULAR Classification Criteria for RA

<table>
<thead>
<tr>
<th>JOINT DISTRIBUTION (0-5)</th>
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<tr>
<td>1 large joint</td>
<td>0</td>
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<tr>
<td>2-10 large joints</td>
<td>1</td>
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<tr>
<td>1-3 small joints (large joints not counted)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (large joints not counted)</td>
<td>3</td>
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<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
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<table>
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<tr>
<th>SEROLOGY (0-3)</th>
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<tr>
<td>Negative RF AND negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF OR low positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF OR high positive ACPA</td>
<td>3</td>
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<tr>
<th>SYMPTOM DURATION (0-1)</th>
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<tr>
<td>&lt;6 weeks</td>
<td>0</td>
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<tr>
<td>≥6 weeks</td>
<td>1</td>
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<tr>
<th>ACUTE PHASE REACTANTS (0-1)</th>
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<tr>
<td>Normal CRP AND normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP OR abnormal ESR</td>
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≥6 = definite RA

What if the score is <6?

Patient might fulfill the criteria...

→ **Prospectively** over time (cumulatively)

→ **Retrospectively** if data on all four domains have been adequately recorded in the past

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Making a Diagnosis of Early RA

• Synovitis of at least 3 joints
  • Symmetric, small joint polyarthritis is strongly suggestive

• Positive RF or CCP antibody

• Elevated ESR or CRP

• Exclude other possible mimics

• Persistence > 6 weeks

This is a practical approach that reflects the new ACR/EULAR classification criteria
Case 3, continued

- Patient returns with the following results of additional work-up:
  - CRP 36.0 mg/dl
  - Positive CCP antibody >250 U
  - Positive Rheumatoid factor 120 IU
  - Hand x-rays reveal periarticular osteopenia

Magnified view of the left 5th MTP
Which of the following is the most appropriate treatment at this time?

- A) Continue ibuprofen
- B) Initiate mycophenolate mofetil
- C) Initiate methotrexate
- D) Initiate monotherapy with prednisone
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RA management: Methotrexate

- Methotrexate is the anchor DMARD
- Prevents radiologic progression (disease-modifying!)
- Weekly PO or SQ dosing
- Potential up-titration to max 25 mg/week
- Folic acid supplementation 1 mg/day
- Safety monitoring: CBC, Creatinine, AST, ALT

Adenosine pathway is the likely primary down-regulator of RA inflammation
Methotrexate Toxicity

- One of the mechanisms: folate depletion

- Minor: Nausea, stomatitis, hair loss, headache, fatigue

- Serious but rare:
  - Megaloblastic anemia and pancytopenia
    - Increased risk with folate deficiency or azotemia
  - Liver fibrosis
    - Increased risk in NAFL/NASH patients
  - Hypersensitivity pneumonitis

- Teratogenic effect
RA treatments

- **Treatment goal:** Remission or low disease activity
- **Synthetic DMARDs:** Methotrexate, Sulfasalazine*, Hydroxychloroquine*, Leflunomide
- **Biologic DMARDs:**
  - TNF inhibitors (Infliximab, Adalimumab, Etanercept, Golimumab, Certolizumab*)
  - IL6-receptor antagonists (Tocilizumab, Sarilumab)
  - T-cell co-stimulator blocker (Abatacept)
  - JAK kinase inhibitor (Tofacitinib, Baricitinib, Upadacitinib)
- **Rituximab** - antibody against CD20 on B-lymphocytes

* safe in pregnancy and breastfeeding

RA treatment strategies

- Glucocorticoids: bridge-therapy, management of flares, low-moderate doses, limited duration.

Case 4

- A 30-year-old man is evaluated for a 7-year history of intermittent pain and swelling in multiple fingers and toes; 1 hour morning stiffness. Treated with multiple NSAIDs, Ibuprofen most efficacious.

- Physical exam: normal vital signs. Tenderness and swelling of the 4th and 5th PIPs and DIPs bilaterally, swollen right second toe.

- Labs: Uric acid 6.7 mg/dL, RF and CCP-antibody negative.
Which of the following is the most likely diagnosis?

- A) Gouty arthritis
- B) Psoriatic arthritis
- C) Reactive arthritis
- D) Rheumatoid arthritis
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- B) Psoriatic arthritis
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CASPAR – classification criteria for PsA

<table>
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<tr>
<th></th>
<th>Evidence of current psoriasis, a personal or family history of psoriasis (in 1&lt;sup&gt;st&lt;/sup&gt; or 2&lt;sup&gt;nd&lt;/sup&gt; degree relative) – score of 1; evidence of current psoriasis – 2 points</th>
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<tbody>
<tr>
<td>2</td>
<td>Typical psoriatic nail dystrophy on current physical exam – 1 point</td>
</tr>
<tr>
<td>3</td>
<td>Negative RF – 1 point</td>
</tr>
<tr>
<td>4</td>
<td>Dactylitis, either current or in a history recorded by a rheumatologist – 1 point</td>
</tr>
<tr>
<td>5</td>
<td>Radiographic evidence of juxta-articular new bone formation, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on radiographs of the hand or foot – 1 point</td>
</tr>
</tbody>
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Diagnosis of PsA requires ≥ 3 points

Psoriatic arthritis – Clinical Features

- Oligo/polyarthritis (symmetric or asymmetric); DIP joints
- Arthritis mutilans: deforming and destructive (X-ray: “Pencil-in-cup”)
- Spondyloarthritis: sacroiliitis and spondylitis
- Enthesitis
- Dactylitis: "sausage digit"
- Skin and nail disease
- Lab: elevated uric acid
Traditional Classification of the Spondyloarthropathies

- Ankylosing spondylitis
- Psoriatic arthritis
- Reactive arthritis
- Arthritis associated with IBD
Clinical characteristics of spondyloarthropathy

- Inflammatory back pain 69%
- Peripheral arthritis 29%
- Enthesitis 29%
- Uveitis 2.5%
- Dactylitis 3.3%
- Positive FHx 32.1%

Rudwaleit M et al. A&R 2004. 50(suppl):S617
Patterns are Important

RA   PsA   Ank Spond   OA
Polymyalgia Rheumatica

At Initial Presentation Think of PMR as a Syndrome

- Review for symptoms of GCA
- Elderly onset RA or a spondyloarthropathy
- Malignancy
  - Paraneoplastic syndrome
  - Myeloma or bone metastases
- Infectious endocarditis
Diagnosis of PMR

- > Age 50 years (reality >> 60 years)
- Bilateral shoulder pain
- Morning stiffness > 45 minutes
- Elevated C-reactive protein and/or ESR
  - A small number of patients may have normal acute phase response
- New hip pain
- Negative RF or CCP antibody

Some pearls about PMR

• A disease of Vikings
  • Don’t consider it in one of your clinic patients from Somalia

• If a patient is < 60 years old, think of an alternative diagnosis
  • Late onset spondyloarthropathy is the closest mimic

• If patient’s feet and ankles are involved, it’s another condition, likely RA
Case 5

• A 75 year old woman presents with 2-week history of worsening shoulder and hip pain.

• No headache, jaw claudication, or vision changes.

• Dx of PMR 3 months ago, Rx Prednisone 15 mg/day down taper with substantial improvement. Was asymptomatic on 10 mg/day. Current dose 8 mg/day (started 1 month ago).

• Physical exam: normal vital signs. BP identical on both arms. No TA tenderness/induration. Painful ROM in shoulder and hips.
Which of the following is the most appropriate management?

• A) Prednisone, 10 mg/d
• B) Prednisone, 30 mg/d
• C) Prednisone, 60 mg/d
• D) Prednisone, 20 mg/d, and methotrexate
Which of the following is the most appropriate management?

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- B) Prednisone, 30 mg/d
- C) Prednisone, 60 mg/d
- D) Prednisone, 20 mg/d, and methotrexate
Prednisone Dosing in PMR

• Excessive dosing will obscure your assessment of treatment response
  • Polymyalgia is a syndrome
    • Malignancy, endocarditis, systemic vasculitis
    • Many fatal diseases feel better on steroids for a while

• Treatment response to prednisone 15 mg daily should be rapid – a day or two
  • Persons > 75 Kg may require 20 mg daily
  • CRP should be normal within days

Prednisone Dosing in PMR relapse

• Increase prednisone to the last pre-relapse dose, at which patient was doing well
• Gradual reduction within 4-8 weeks back to the relapse dose
• Taper below 10 mg/day by 1 mg every 4 weeks
• Methotrexate can be added if recurrent relapses/ significant glucocorticoid toxicity

Case 6

- A 78 year old man presents with 2-week history of pain and swelling in his left knee.
- He had 2 similar episodes over the past 6 months in his knees, ankles and wrists, each resolving after 3 weeks.
- Physical exam: normal vital signs. Swollen left knee, left ankle and wrists, with tenderness and decreased ROM.
- Labs: ESR 53 mm/h, uric acid 3.8 mg/dL.
- Knee radiograph:
Which of the following is the most likely diagnosis?

- A) Gout
- B) Acute CPPD arthritis
- C) Infectious arthritis
- D) Palindromic rheumatism
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Acute CPPD arthritis (Pseudogout)

- Most common form of calcium pyrophosphate disease
- Mono-oligoarticular, most commonly in the elderly
  - DDx acute gout versus septic arthritis
  - Fever and delirium in the elderly
  - Slower resolution than acute gout
- Knee > Wrist > MCP>>>1\textsuperscript{st} MTP
Acute Pseudogout, treatment

- Treat like acute gout but modify for the elderly
  - Intra-articular steroid, short course prednisone, short dosing colchicine, preferable to NSAIDs
- No way to remove CPPD from the joints, unlike intra-articular urate
  - Screen all patients for hyperparathyroidism and hypomagnesaemia
Take home points

- Arthritis: Inflammatory or degenerative?
- Remember patterns of joint involvement
- Understand the approach to identification of poor prognosis polyarthritis
- Know the serious complications of MTX therapy
- Recognize PMR but always think of it as an inflammatory syndrome first
- Do not over treat PMR
Helpful resources

• https://www.acponline.org/featured-products/mksap-18

• https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines

• https://www.rheumatology.org/Learning-Center/Medication-Guides

• https://www.uptodate.com/contents/search
Questions & Discussion