INFLAMMATORY ARTHRITIS WITH FOCUS ON RHEUMATOID ARTHRITIS

Catalina Orozco, MD
Rheumatology Associates
October 1st 2016
OUTLINE

• Case presentations
• Overview of rheumatoid arthritis
• Pathophysiology of rheumatoid arthritis
• Diagnosis of rheumatoid arthritis
• Treatment of rheumatoid arthritis
• Take home messages
CASES

CC: Arthralgia
DIFFERENTIAL DIAGNOSIS

• Psoriatic arthritis
• Rheumatoid arthritis
• Spondyloarthritis

• Undifferentiated arthritis
• Crystal arthritis
• Other connective tissue diseases
• Erosive osteoarthritis
• Septic arthritis
RHEUMATOID ARTHRITIS

- Definition
- RA is the most common inflammatory arthritis
- Affects 0.5-1% of the general population
- Twice as common in women
- Costly

Alamanos Y, Semin Arthritis Rheum 2006; 36: pp. 182-188

RHEUMATOID ARTHRITIS

The hallmark of the disease is synovitis
RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a systemic disease

Crycoarytenoid
Lungs
Hepatic
Skin
Eye
Mouth
Blood
Cardiac
GI
Felty’s syndrome
Neurological

Kelley's Textbook of Rheumatology 2009
Kitas GD Ann Rheum Dis 2011; 70: pp. 8-1
Rheumatoid arthritis

- There are no diagnostic criteria

- The typical patient will present with tender and swollen joints, morning stiffness, abnormal markers of inflammation

- This presentation is non-specific and other causes must be considered and ruled out
What other tools are available to help making an accurate diagnosis?
1987 ARA RA CLASSIFICATION CRITERIA

<table>
<thead>
<tr>
<th>RA 4/7 of the following criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Morning stiffness</td>
</tr>
<tr>
<td>2. Arthritis of 3 or more joint areas</td>
</tr>
<tr>
<td>3. Arthritis of hand joints</td>
</tr>
<tr>
<td>4. Symmetric arthritis</td>
</tr>
<tr>
<td>5. Rheumatoid nodules</td>
</tr>
<tr>
<td>6. Serum rheumatoid factor</td>
</tr>
<tr>
<td>7. Radiographic changes</td>
</tr>
</tbody>
</table>

USEFULNESS AND PITFALLS:

- Discriminates RA from other rheumatologic diseases
- Exemplifies long standing, erosive disease
- Does not readily identify patients with early disease
Performance in early arthritis (EA)

• Meta-analysis of 138 publications yielded 19 that were analyzable

• Established arthritis sensitivity and specificity 79% and 90%

• EA sensitivity and specificity 77% and 77%

Banal F, Ann Rheum Dis 2009 68: 1184-1191
CYCLIC CITRULLINATED PEPTIDE AB

• Assay evaluates the presence of antibodies against modified peptides (fillagrin, vimentin, fibrin)

• Positive in 40% of RF negative RA

• Predicts RA and erosive disease

CYCLIC CITRULLINATED PEPTIDE AB

- **Sensitivity**
  - Rheumatoid factor: [Value]
  - CCP antibodies: [Value]

- **Specificity**
  - Rheumatoid factor: [Value]
  - CCP antibodies: [Value]
CCP is far more specific for RA than RF is, but a negative result does not exclude the diagnosis of RA
OBJECTIVES:

• Discriminate patients with early synovitis who are at risk for developing persistent or erosive disease

• Be used as a basis to start DMARD therapy

• Also able to capture patients later in the disease course
### 2010 ACR/EULAR CLASSIFICATION CRITERIA

<table>
<thead>
<tr>
<th>JOINT INVOLVEMENT (0-5)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 medium-large joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 medium-large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (with or without involvement of large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (with or without involvement of large joints)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEROLOGY (0-3)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF AND negative CCP ab</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF OR low positive CCP ab</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF OR high positive CCP ab</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACUTE PHASE REACTANTS (0-1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP AND normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP OR abnormal ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DURATION OF SYMPTOMS (0-1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>
2010 ACR/EULAR CLASSIFICATION CRITERIA

DEFINITE RA:

• Synovitis in one joint that is otherwise unexplained

• Score ≥6/10

Aletaha D, Arthritis Rheum September 2010, pp 2569–2581
Performance of the classification criteria

- 17 studies and 17 abstracts were included
- Sensitivity: 80-88%, Specificity 48-65%
WHY TO DIAGNOSE RA EARLY?

Early treatment of RA preserves function

WHY TO DIAGNOSE RA EARLY?

Early treatment limits joint damage and improves long term function

Korpela M, Arthritis and Rheum 2004, Jul;50(7):2072-81

Rantalaiho V. Arthritis Rheum. 2009 May;60(5):1222-31
WHY TO DIAGNOSE RA EARLY?

Increased mortality in RA is attributed to CVD

• Independent of traditional risk factors

• Hyperhomocysteinemia

• Disease-related dyslipidemia

• Vascular inflammation

• Morbidity related to high levels of cytokines (e.g. TNF)

• RA medications (e.g. NSAIDs, steroids)

Atzeni F, Autoimmun Rev. 2010 Jul 30
A WORD OF CAUTION

• Classification criteria is NOT synonymous with diagnostic criteria

• No single diagnostic criteria Classification criteria used as surrogate

Aletaha D, Arthritis Rheum September 2010, pp 2569–2581
MY MOTHER'S BEEN DROPPING THINGS AND JUST FOUND OUT IT'S BECAUSE OF ARTHRITIS...

PLEASE BE HEREDITARY...
WHEN ONE ENCOUNTERS A PATIENT WITH ACTIVE SYNOVITIS IN AT LEAST ONE JOINT, RA IS CONSIDERED. HOWEVER, OTHER FORMS OF INFLAMMATORY ARTHRITIS MUST BE EXCLUDED.
CASE #1

CC: Arthralgia in hands and feet

HPI: 50 y.o. WW presents with 6 weeks of arthralgia in hands and feet. Swelling over MCP’s, PIP’s. Has tried naproxen with partial relief

ROS, PMH, PSH, Social HX: Smokes 0.5 ppd

FH: mother with rheumatoid arthritis

PE: Tenderness & synovitis of wrists, R MCP 2-4 and B PIP 3

Labs: CRP: 1.3 mg/dl, RF - , CCP 25 (nl < 20 u/ml), normal Xray
## CASE #1

<table>
<thead>
<tr>
<th>JOINT INvolVEMENT (0-5)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 medium-large joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 medium-large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (with or without involvement of large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (with or without involvement of large joints)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SEROLOGY (0-3)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF AND negative CCP ab</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF OR low positive CCP ab</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF OR high positive CCP ab</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACUTE PHASE REACTANTS (0-1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP AND normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP OR abnormal ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DURATION OF SYMPTOMS (0-1)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>≥6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total Score:** 7/10
CASE #2

CC: Arthralgia in hands and knees

HPI: 45 y.o. WW presents with 8 weeks of arthralgia in hands and knees. Swelling on the left PIP’s 2-4, and right knee. Swelling on the right fourth finger 2 weeks ago that resolved within 1 week. Ibuprofen has not been helping

ROS, PMH, PSH, Social HX: Negative

FH: Father with history of psoriasis

PE: Tenderness & synovitis of left PIP 2-4, R knee

Labs: CRP: 1.3 mg/dl, RF -, CCP 15 (nl < 20 u/ml), normal Xrays
Psoriatic arthritis

- Can present with or without psoriasis
- 6-39% of patients with psoriasis will develop psoriatic arthritis
- Five different presentations

DIFFERENTIAL DIAGNOSIS

Psoriatic arthritis

Polyarticular arthritis

Oligoarticular arthritis

DIP arthritis
DIFFERENTIAL DIAGNOSIS

Arthritis mutilans  Psoriatic arthritis  Spondyloarthritis
DIFFERENTIAL DIAGNOSIS

Psoriatic arthritis

• Other associated features: Tenosynovitis, enthesitis, dactylitis, asymmetric distribution
CASE #3

CC: Arthralgia and low back pain

HPI: 30 y.o. WM presents with 12 weeks of arthralgia in right hip, bilateral knees and low back pain. He is worse in the morning and better with activity. AM stiffness 1.5 hrs

ROS, PMH, PSH, Social HX: Single episode of unilateral iritis in 2010

FH: Non contributory

PE: Tenderness bilateral SI joints, swelling on the right knee

Labs: ESR/CRP normal, RF -, CCP -, HLA B27 +, SI joint X ray: irregularity of synovial portion of SI joints
DIFFERENTIAL DIAGNOSIS

Spondyloarthritis

- Prevalence 0.9-1.4%
- Male predominance
- Umbrella for some specific conditions
- Inflammatory back pain is key to the diagnosis
- HLA-B27
- Associated features: anterior uveitis, peripheral arthritis, osteoporosis

DIFFERENTIAL DIAGNOSIS

Progressive deformity due to AS over a period of 36 years
TREATMENT OF RA

• ACR/EULAR: Treat to target approach

• Disease modifying agents reduce structural damage progression

• A better understanding of the pathophysiology of the disease has led to extensive, fruitful research
TREATMENT OF RA

- SSZ, Gold
- Glucocorticoids
- MTX
- Leflunomide, Etanercept
- Infliximab, Anakinra
- Adalimumab
- Abatacept
- Rituximab
- Certolizumab, Golimumab
- Tocilizumab
- Tofacitinib

- 1930s
- 1950
- 1988
- 1998
- '01 '02
- '05 '06
- '09
- '10 '12
TREATMENT OF RA

- Conventional synthetic disease modifying agents
  
  Methotrexate
  Leflunomide
  Sulfasalazine
  Hydroxychloroquine
Methotrexate

• Antimetabolite

• First developed to treat cancer in the 1950’s

• In 1988 methotrexate was approved for the treatment of RA

• Cornerstone of RA treatment and the comparator in most clinical trials
## TREATMENT OF RA

Table 2. Clinical and Laboratory Variables in Patients Completing Period 1 of the Study.*

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>TREATMENT †</th>
<th>VALUE AT ENTRY VISIT</th>
<th>DIFFERENCE AT CROSSOVER VISIT ‡</th>
<th>P VALUE $</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methotrexate (15)</td>
<td>34±3</td>
<td>14±2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Placebo (16)</td>
<td>28±2</td>
<td>5±2</td>
<td></td>
</tr>
<tr>
<td>No. of joints swollen</td>
<td>Methotrexate (15)</td>
<td>37±4</td>
<td>26±4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Placebo (16)</td>
<td>36±3</td>
<td>4±4</td>
<td></td>
</tr>
<tr>
<td>No. of joints tender to pressure or painful on passive motion</td>
<td>Methotrexate (15)</td>
<td>51±5</td>
<td>30±3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Placebo (16)</td>
<td>40±4</td>
<td>10±3</td>
<td></td>
</tr>
<tr>
<td>Joint-swelling index</td>
<td>Methotrexate (15)</td>
<td>58±8</td>
<td>46±7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Placebo (16)</td>
<td>52±4</td>
<td>6±6</td>
<td></td>
</tr>
<tr>
<td>Joint-tenderness/pain index</td>
<td>Methotrexate (15)</td>
<td>58±8</td>
<td>46±7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Placebo (16)</td>
<td>52±4</td>
<td>6±6</td>
<td></td>
</tr>
</tbody>
</table>

TREATMENT OF RA

Biologic DMARD

- TNF inhibitors: Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
- T cell co-stimulator inhibitor: Abatacept
- IL-6 receptor antagonist: Tocilizumab
- B cell depletion therapy: Rituximab
- IL-1 receptor antagonist: Anakinra

TREATMENT OF RA

A

[Graph showing ACR70 responses (%)]

- Methotrexate monotherapy
- Abatacept (~10 mg/kg) + methotrexate
- Golimumab (50 mg) + methotrexate

20% 32%

MTX-naive MTX-naive

AGREE

B

[Graph showing GO-BEFORE responses (%)]

16% 24%

MTX-naive MTX-naive

GO-BEFORE

Smolen JS. Lancet. 2016 May 3. pii: S0140-6736(16)30173-8
TREATMENT OF RA

C

- Methotrexate monotherapy
- Tocilizumab (8 mg/kg) + methotrexate
- Rituximab (1000 mg) + methotrexate

ACR70 responders (%)

MTX-naïve
MTX-naïve

FUNCTION

25%
39%

D

MTX-naïve
MTX-naïve

IMAGE

25%
47%
TREATMENT OF RA

Targeted synthetic DMARD: Tofacitinib

• Non selective JAK inhibitor

• It has been approved for use alone or in combination with methotrexate
TREATMENT OF RA

E

- Methotrexate monotherapy
- Tofacitinib (5 mg/kg twice a day)
- Baricitinib (4 mg/day)

F

- 42% RA-BEGIN
- 21% RA-BEGIN

Smolen JS. Lancet. 2016 May 3. pii: S0140-6736(16)30173-8
"Listen, when the side effects of this medication kick in, you'll forget what was wrong in the first place!"
TREATMENT OF RA

Complications from RA treatment: Infections

Serious and non serious infections
Mycobacterial infections
Fungal & opportunistic infections
Herpes Zoster
PML
WHAT TO KEEP IN MIND AS A PCP

• Low suspicion for infections

• Do not under estimate the immunosuppression from steroids

• Intra-cellular organisms

• Be aware of atypical or disseminated presentations

• Hold the immunosuppressant(s) during illness

• Communicate with Rheumatology
Complications from RA treatment: Malignancy

- RA increases the risk for lymphomas, skin and lung cancer
- Alterations on the immune system by biologic agents may increase the risk of malignancies
- Some data supports an increased risk of melanoma and non melanoma skin cancer and periodic skin exams should be considered
TREATMENT OF RA

Complications from RA treatment: Miscellaneous

- Cardiovascular considerations: CHF and hypercholesterolemia
- GI perforation
- Demyelinating conditions

References:

Wolf F. Arthritis Rheum 1994. 37, 481-494
Chung ES. Circulation. 2003 107(25):3133-40
TAKE HOME MESSAGES

• Full history, physical exam and labs differentiate various inflammatory arthritides

• The revised classification criteria for RA allow earlier diagnosis and institution of treatment, in turn improving disease outcomes

• Multiple treatment options are available for RA including synthetic and targeted DMARD’s and biologic agents

• Complications from RA and its treatment include infections, malignancy, hyperlipidemia