Rheumatoid Arthritis

Shawn Macalester, DO
August 15, 2014
OPSO
Disclosures

• Speaker for Abbvie
• Advisory board for Crescendo Bioscience
Objectives

• 2010 ACR/EULAR classification criteria
• Discuss new developments in imaging and disease activity evaluation
• Highlight new understanding of management issues
Pattern Matching
Pattern Matching
Pattern Matching

Images from the ACR and mensweardog.tumblr.com
Pattern

- Monoarthritis
  - Crystal
  - Infectious
  - Traumatic
  - OA
  - Tumor
Pattern

• Oligoarthritis
  – Crystal
  – Sepsis
  – Rheumatoid
  – Spondyloarthropathy
Pattern

• Polyarticular
  – Rheumatoid arthritis
  – SLE/DIL
  – Viral/infectious
  – Spondyloarthropathy
Summary

- Polyarticular symmetric inflammatory arthritis
- Greater than 6 weeks
- Small joints
Summary

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- Greater than 6 weeks
- Small joints
- A complex systemic illness with lab and imaging features
Summary

• Polyarticular symmetric inflammatory arthritis
• Greater than 6 weeks
• Small joints
• A complex systemic illness with lab and imaging features
• Risk to multiple organ systems
• RA described in anthropology
• First clinical description in 1800 by a student
  – At least very uncommon prior to 18th century
• Etiology?
  – Industrial revolution
  – Infection
  – Sugar
    • “white gold” of the upper class
    • By 1815 tea with sugar for all

*The Rheumatologist*, September 2012
Etiology/Pathogenesis

• Most common inflammatory arthritis
  – 0.5-1% worldwide
  – China ~0.3%
  – Pima Indians of N America ~5%
• Primarily joints
  – Extra-articular manifestations
  – Unique properties of synovium
• Environmental and genetic risk factors
Etiology/Pathogenesis

• Initiation of RA probably begins years ahead
  – MHC class II molecule (e.g. HLA-DR4)
• Specific genes can break tolerance
  – Abnormal T cell selection
  – May happen in normal individuals
  – Susceptible people develop RF and CCP
• Cigarette smoke, bacterial products, viral components, environmental stimuli
Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over forty-years
Specific autoantibodies precede the symptoms of rheumatoid arthritis: A study of serial measurements in blood donors
Synovium

Synoviocytes
- Diarthrodial joints
- Macrophages & fibroblasts
- Unique low-friction environment
**Synovium**

**Synoviocytes**
- Diarthrodial joints
- Macrophages & fibroblasts
- Unique low-friction environment
- Potential for destruction
- Cartilage loss
- Erosions
- Ligamentous laxity
Clinical presentations of RA

<table>
<thead>
<tr>
<th>Joint Involvement</th>
<th>% Patients (Mean)</th>
<th>% Patients (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCP, PIP</td>
<td>91</td>
<td>74-100</td>
</tr>
<tr>
<td>Wrists</td>
<td>78</td>
<td>54-82</td>
</tr>
<tr>
<td>Knees</td>
<td>64</td>
<td>41-94</td>
</tr>
<tr>
<td>Shoulders</td>
<td>65</td>
<td>33-75</td>
</tr>
<tr>
<td>Ankles</td>
<td>50</td>
<td>10-67</td>
</tr>
<tr>
<td>Feet</td>
<td>43</td>
<td>15-73</td>
</tr>
<tr>
<td>Elbows</td>
<td>38</td>
<td>13-60</td>
</tr>
<tr>
<td>Hips</td>
<td>17</td>
<td>0-40</td>
</tr>
<tr>
<td>TMJ &amp; Cricoarytenoid</td>
<td>8</td>
<td>0-28</td>
</tr>
<tr>
<td>Cervical spine</td>
<td>4</td>
<td>0-11</td>
</tr>
<tr>
<td>Sternoclavicular</td>
<td>2</td>
<td>0-6</td>
</tr>
<tr>
<td>Peri-articular sites</td>
<td>27</td>
<td>20-29</td>
</tr>
</tbody>
</table>

Early Synovitis

- Inflammatory polyarthropathy NOS
  - Up to 40% spontaneous remission
  - Those with autoimmune abs more likely to prog
  - Only 20% initially met diagnostic criteria

- Palindromic pattern

- Insidious onset in older individuals (>64)

- Arthritis Robustus

- Rheumatoid nodulosis

Extra-articular Complications

• Linked to RF on foci of immune response
Extra-articular Complications

• Linked to RF on foci of immune response
• Rheumatoid nodules
  – Palisading fibroblasts with central necrosis
  – Clinically similar to tophi, xanthomas, yaws, BCC
  – Histologically similar to granuloma annulare
  – Can be found in heart, lungs, CNS, vertebral bodies, skin, sclera
Extra-articular Complications

• Linked to RF on foci of immune response
• Rheumatoid nodules
• Bone density
  – Generalized osteopenia
  – Periarticular demineralization
  – Nuclear factor κβ ligand (RANKL)-induced
Extra-articular Complications

- Linked to RF on foci of immune response
- Rheumatoid nodules
- Bone density
- Eye
  - Keratoconjunctivitis sicca (Sjogren syndrome)
  - Scleritis and episcleritis
  - Scleromalacia
Extra-articular Complications

• Linked to RF on foci of immune response
• Rheumatoid nodules
• Bone density
• Eye
• Vasculitis
  – Distal arteritis
  – Peripheral neuropathy
  – Palpable purpura
Extra-articular Complications

• Linked to RF on foci of immune response
• Rheumatoid nodules
• Bone density
• Eye
• Vasculitis
• Hematologic abnormalities
  – Anemia chronic disease
  – Folate of vitamin B12 deficiency
Extra-articular Complications

- Linked to RF on foci of immune response
- Rheumatoid nodules
- Bone density
- Eye
- Vasculitis
- Hematologic abnormalities
- Renal Disease
  - May be ANCA associated
Extra-articular Complications

- Linked to RF on foci of immune response
- Rheumatoid nodules
- Bone density
- Eye
- Vasculitis
- Hematologic abnormalities
- Renal Disease

- Pulmonary disease
  - Pleuritis ~20%
  - Exudative effusions (very low glucose)
  - ILD pneumonitis and fibrosis
  - Bronchiolitis
  - Treatment-related pulmonary toxicity
Extra-articular Complications

- Linked to RF on foci of immune response
- Rheumatoid nodules
- Bone density
- Eye
- Vasculitis
- Hematologic abnormalities
- Renal Disease
- Pulmonary disease

- Cardiovascular disease
  - Atherosclerosis
  - Congestive heart failure
  - Pericarditis
  - Myocarditis
  - Endocardial inflammation
  - Conduction defects
  - Granulomatous aortitis or valvular disease
<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Joint Involvement</strong></td>
<td>(0-5)</td>
</tr>
<tr>
<td>1 medium to large joint</td>
<td>0</td>
</tr>
<tr>
<td>2-10 medium to large joints</td>
<td>1</td>
</tr>
<tr>
<td>1-3 small joints (with or without large joints)</td>
<td>2</td>
</tr>
<tr>
<td>4-10 small joints (with or without large joints)</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td>5</td>
</tr>
<tr>
<td><strong>Serology</strong></td>
<td>(0-3)</td>
</tr>
<tr>
<td>Negative RF AND negative CCP</td>
<td>0</td>
</tr>
<tr>
<td>Low positive RF OR low positive CCP</td>
<td>2</td>
</tr>
<tr>
<td>High positive RF OR high positive CCP</td>
<td>3</td>
</tr>
<tr>
<td><strong>Acute Phase Reactants</strong></td>
<td>(1)</td>
</tr>
<tr>
<td>Normal CRP AND normal ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal CRP OR abnormal ESR</td>
<td>1</td>
</tr>
<tr>
<td><strong>Duration of Symptoms</strong></td>
<td>(0-1)</td>
</tr>
<tr>
<td>&lt; 6 weeks</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 6 weeks</td>
<td>1</td>
</tr>
</tbody>
</table>

*Ann Rheum Dis 69:1580-1588, 2010*
The Rheumatoid Factor

- Rheumatoid arthritis
- Viral arthritis
- Tuberculous arthritis
- Bacterial endocarditis
- SLE
- Sarcoidosis
- Systemic vasculitis
- Normal aging
CCP antibody

- Anticitrullinated protein antibodies (ACPAs)
- Present in smokers
- 80% to 90% of RA patients
- Specificity approaching 90%
- May be present for years prior to RA onset
ANA

- Tangential to RA
- Sjogren syndrome
ANA

- Tangential to RA
- Sjogren syndrome
- Much too sensitive
- Not at all specific
- Recent study showed 90% false positivity
- No one with titer <1:160 associated with dz
- Positive predictive power was 11%
- Negative predictive value around 95%

*Am J Med* 2013 Apr;126(4)342-8
Quick Case

- 26-year-old female with one year of activity related hip and shoulder pain
- Intermittently has finger pain and stiffness
- Artist, but insured after starting at HD
- RF 13, CCP 85 (<20 normal)
- ESR, CRP, TSH, other labs negative
- Physical exam equivocal
- She had a 1-2 cm gap in R 3rd finger fist closure
Quick Case

- 26-year-old female with one year of hip and shoulder pain with activity
- IF you give her 4 medium to large joints = 1
Quick Case

• 26-year-old female with one year of hip and shoulder pain with activity
• IF you give her 4 medium to large joints = 1
• THEN high-positive ACPA = 3
Quick Case

• 26-year-old female with one year of hip and shoulder pain with activity
• IF you give her 4 medium to large joints = 1
• THEN high-positive ACPA = 3
• ≥ 6 weeks = 1
Quick Case

• 26-year-old female with one year of hip and shoulder pain with activity
• IF you give her 4 medium to large joints = 1
• THEN high-positive ACPA = 3
• ≥ 6 weeks = 1

• Total = 5/10
Quick Case

- 26-year-old female with one year of hip and shoulder pain with activity
- IF you give her 4 medium to large joints = 1
- THEN high-positive ACPA = 3
- ≥ 6 weeks = 1

- Total = 5/10
- Why couldn’t I just have liked cardiology?
Quick Case

26-year-old female with one year of hips and shoulder pain with activity
Intermittently has finger pain and stiffness
Artist, but insurance after starting at HD
RF 30, CCP 85 (<20 normal)
ESR, CRP, TSH, other labs negative
Okay another case

- 50-year-old female with widespread pain for 2 years
Okay another case

- 50-year-old female with widespread pain for 2 years
- Has a walker, moved from SoCal, pack a day
Okay another case

- 50-year-old female with widespread pain for 2 years
- Has a walker, moved from SoCal, pack a day
- Got started on Vicodin
Okay another case

- 50-year-old female with widespread pain for 2 years
- Has a walker, moved from SoCal, pack a day
- Got started on Vicodin
- Got referred to rheumatology
Okay another case

- 50-year-old female with widespread pain for 2 years
- Has a walker, moved from SoCal, pack a day
- Got started on Vicodin
- Got referred to rheumatology
- Labs negative physical exam equivocal
Okay another case

- 50-year-old female with widespread pain for 2 years
- Has a walker, moved from SoCal, pack a day
- Got started on Vicodin
- Got referred to rheumatology
- Labs negative physical exam equivocal
- Returns 4 months later diagnosed with OSA on CPAP and starts with pain management
Okay another case

• 50-year-old female with widespread pain for 2 years
• Comes back to rheumatology 7 months later
Okay another case

• 50-year-old female with widespread pain for 2 years
• Comes back to rheumatology 7 months later
• Repeat the work up
Okay another case

- 50-year-old female with widespread pain for 2 years
- Comes back to rheumatology 7 months later
- Repeat the work up
- RF 43, ESR 59, other tests negative
Okay another case

- 50-year-old female with widespread pain for 2 years
- Comes back to rheumatology 7 months later
- Repeat the work up
- RF 43, ESR 59, other tests negative
- Vectra DA 55
Okay another case

- 50-year-old female with widespread pain for 2 years
- Comes back to rheumatology 7 months later
- Repeat the work up
- RF 43, ESR 59, other tests negative
- Vectra DA 55
- Started DMARDs and symptoms melted away
Tree algorithm to classify definite rheumatoid arthritis (RA) (green circles) or to exclude its current presence (red circles) among those who are eligible to be assessed by the new criteria.

MRI

- Visualizes inflammatory and destructive changes in RA with high sensitivity
- Differential diagnostic value
- Has strong prognostic value in early RA
- Allows more sensitive monitoring
- Shows inflammation in some patients in clinical remission

### MRI vs US

<table>
<thead>
<tr>
<th></th>
<th>MRI</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synovitis</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Bone edema</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Bone erosions</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

MRI

- X-ray shows (part of) what has happened
- MRI and ultrasound show us what has happened and *what is happening*
- MRI now essential in clinical trials
MRI

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MRI

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- MRI is currently available
- Ultrasound:

MRI

• X-ray shows (part of) what has happened
• MRI and ultrasound show us what has happened and what is happening
• MRI now essential in clinical trials
• MRI is currently available
• Ultrasound: it’s complicated

Vectra DA

Biomarker screening

Feasibility

Development

396 candidate biomarkers

130 candidate biomarkers

25 candidate biomarkers

12 final biomarkers

Adapted from B Bakker MF et al. Ann Rheum Dis 2012 Ocr;71(10) 1692-7
Curtis JC, et al. AC&R 2012; 64(12):1794-1803
DMARDs

• Triple therapy
  – Methotrexate
  – Sulfasalazine
  – Hydroxychloroquine

• Leflunomide

• Azathioprine

• Corticosteroids
Biologics

- **Anti-IL1**
  - Anakinra (Kineret)
- **TNF antagonists**
  - Etanercept (Enbrel), adalimumab (Humira), golimumab (Simponi), infliximab (Remicade), certolizumab (Cimzia)
- **Anti-IL6**
  - Tocilizumab (Actemra)
- **CTLA4 blocker**
  - Abatacept (Orencia)
- **B cell depletion**
  - Rituximab (Rituxan)
Biologics

• Small molecule
  – Tofacitinimab (Xeljanz)
The earlier the better

• Prevention would be ideal
  – Understanding of cause lacking
• Early diagnosis and treatment
  – All medicines work better the earlier started
  – Hope to minimize harm
• RA affects 1.3 million Americans
  – Pain and impaired quality of life
  – 10 year shortened life span
  – Twofold increase for cancer
  – Up to threefold increase of cardiovascular disease
  – Up to ninefold increase in serious infections

The cost of delays

• High risk patients can be identified
• Delays beyond 3 months common
• Less than 15% seen within 6 months
  – 38 work days average wait
  – 27% seen in less than 2 weeks
  – 40% wait 6 weeks to 6 months

## Poor prognostic predictors

### Early RA

<table>
<thead>
<tr>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High disease score</td>
</tr>
<tr>
<td>• Extra-articular manifestations: nodules, Sjogren’s, Felty’s, neuropathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HAQ showing progressive impairment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High titer RF or CCP antibodies</td>
</tr>
<tr>
<td>• High inflammatory markers</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Erosions on joint x-ray, ultrasound, or MRI</td>
</tr>
</tbody>
</table>

Needle in the haystack

- Vast majority start with visit to PCP
- RA makes up 1-2% of new PCP visits
- Gradual onset & equivocal exam common
- Test results often negative for first 6 months
Needle in the haystack

- Vast majority start with visit to PCP
- RA makes up 1-2% of new PCP visits
- Gradual onset & equivocal exam common
- Test results often negative for first 6 months
- British rheumatologist Paul Emery
  - 30 minutes AM stiffness
  - Pain with squeezing mid-hand and/or forefoot
  - Refer to rheumatology
How do we capture early RA?

• Free Arthritis Screening Clinic
  – Advertisements to the public
  – Tuesday afternoon for 4 months
  – Two rheumatologists and a NP
  – Patients filled out a form and were triaged
  – Result: very few early RA patients identified
How do we capture early RA?

• Free Arthritis Screening Clinic
• Early Arthritis Screening Clinic
  – 200 primary care providers received a letter
  – All referrals seen within 2 weeks
  – Result: 4-5 new referrals/week ~10% with IA with symptoms ranging from 16-52 weeks
How do we capture early RA?

- Free Arthritis Screening Clinic
- Early Arthritis Screening Clinic
- Network-wide Early Arthritis Clinic
  - Result: complete failure indicating that it requires complete system involvement with ongoing education
How do we capture early RA?

• Free Arthritis Screening Clinic
• Early Arthritis Screening Clinic
• Network-wide Early Arthritis Clinic
• Also tried:
  – Physician-to-physician requests
How do we capture early RA?

• Free Arthritis Screening Clinic
• Early Arthritis Screening Clinic
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• Also tried:
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  – Prescreening chart review
How do we capture early RA?

• Free Arthritis Screening Clinic
• Early Arthritis Screening Clinic
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• Also tried:
  – Physician-to-physician requests
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  – Screening algorithms or surveys
How do we capture early RA?

• Free Arthritis Screening Clinic
• Early Arthritis Screening Clinic
• Network-wide Early Arthritis Clinic
• Also tried:
  – Physician-to-physician requests
  – Prescreening chart review
  – Screening algorithms or surveys
  – Physician extenders to screen new patients
Conclusions

• To diagnose aggressively
  – Patients with new-onset arthritis want prompt consultation, diagnosis and relief
  – Preference to refer
  – Unfortunately there are numerous impediments

• 75,000 new RA patients this year, but rheumatologists will need to see many more
Treat to Target

• TICORA and BeST trial demonstrate reduced joint damage

• Yet to see if short term gains will translate into
  – Longer term cost reductions
  – Less disability
  – Survival advantages
## Priorities in RA care

<table>
<thead>
<tr>
<th>New RA treatment rules</th>
<th>“The bottom line”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnose and treat early</td>
<td>Reduce wait times and create access by improving practice processes</td>
</tr>
<tr>
<td>Measure disease activity</td>
<td>Routinely use composite disease activity measures</td>
</tr>
<tr>
<td>Treat to target with drug combinations and biologics</td>
<td>Based on disease activity and prognostic factors</td>
</tr>
<tr>
<td>Avoid toxicity</td>
<td>Careful patient selection, tailored screening, monitoring individually</td>
</tr>
<tr>
<td>Identify and treat comorbid conditions</td>
<td>Manage “whole patient” cooperatively with PCP and specialists</td>
</tr>
</tbody>
</table>
Summary

• 2010 ACR/EULAR classification criteria intended to speed evaluation
• Early management hopefully will reduce the long-term burden
• Newer diagnostic and management tools helping us reach those goals
Thank you

• Shawn Macalester
• 503-754-3676