When is it Rheumatoid Arthritis
When to Refer

Learning objectives
- To review the definition and epidemiology of Rheumatoid Arthritis
- To become familiar with the ACR 2010 Classification of Rheumatoid Arthritis
- To be aware of the difference between classification and diagnosis
- To review the more systemic manifestations of Rheumatoid Arthritis
- To be aware of the common patterns of disease onset
- To be aware of the supportive role laboratory exams play in the diagnosis of Rheumatoid Arthritis

Rheumatoid Arthritis
Definition

- RA is an autoimmune disease
  - The immune system is triggered to attack the synovial lining of joints.
  - The cause of RA is not known but there does appear to be a genetic predisposition although it is not a truly inherited disease.
  - It is marked by a variable course, involving exacerbations and remissions of disease activity. Most cases are chronic and progressive.
Rheumatoid Arthritis Major Target

- Normal joint structure is on the left.
- On the right is a demonstration of synovitis.
- Synovitis results in destruction of cartilage and bony erosions.
- A major target of treatment is the control of synovitis.

Rheumatoid Arthritis Epidemiology

- RA is the most common form of autoimmune arthritis.
- It affects more than 1.3 million Americans.
  - 75% are women – 1-3% of women may get RA in their lifetimes.
  - Most often begins between the 4th and 6th decade of life, but can start at any age.
- Extra-articular features are common, numerous and sometimes serious. Most are due to serositis, nodule formation or vasculitis.

ACR 2010 Rheumatoid Arthritis Classification

- Target population (Who should be tested?): Patients who
  - 1. have at least one joint with definite clinical synovitis (swelling)
  - 2. with the synovitis not better explained by another disease.
2010 ACR Rheumatoid Arthritis Classification

• JOINT DISTRIBUTION (0-5)
  – 1 large joint = 0
  – 2-10 large joints = 1
  – 1-3 small joints (large joints not counted) = 2
  – 4-10 small joints (large joints not counted) = 3
  – >10 joints (at least 1 small joint) = 5

2010 ACR Rheumatoid Arthritis Classification

• SEROLOGY (0-3)
  – Negative RF and negative ACPA (CCP) = 0
  – Low-positive RF or low-positive ACPA (CCP) = 2
  – High-positive RF or high-positive ACPA (CCP) = 3

2010 ACR Rheumatoid Arthritis Classification

• ACUTE PHASE REACTANTS (0-1)
  – Normal CRP and normal ESR = 0
  – Abnormal CRP or abnormal ESR = 1
2010 ACR Rheumatoid Arthritis Classification

- **SYMPTOM DURATION (0-1)**
  - < 6 weeks - 0
  - > or = 6 weeks - 1

- **Joint Distribution (0-5)**
- **Serology (0-3)**
- **Acute Phase Reactants (0-1)**
- **Symptom Duration (0-1)**

- > or = 6 is 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

Helpful Definitions on Joints

- **SMALL JOINTS**
  - MCP, PIP, MTP 2-5, thumb IP, wrist
  - NOT: DIP, 1st CMC, 1st MTP
- **LARGE JOINTS**
  - Shoulder, elbow, hip, knee, ankles
- > 10 JOINTS
  - At least one small joint
  - Additional joint include: TMJ, sternoclavicular, acromioclavicular and others (reasonably expected in RA)
Classification vs Diagnosis

- We don’t have diagnostic criteria for RA
- Typically in rheumatic diseases, criteria are labeled as “classification” criteria
  - These are helpful in defining homogeneous treatment populations for study purposes
- A clinical “diagnosis” has to be established by the physician
  - It includes many more aspects than can be included in formal criteria
  - Formal classification criteria might be a guide to establish a clinical diagnosis

Diagnosis of Rheumatoid Arthritis

- The goal is diagnosis and treatment within three months of disease onset.
  - Primary goal of treatment is to prevent joint destruction.
  - Joint destruction can occur very early in the disease, especially in very aggressive RA.
- Relying solely on classification criteria will miss many patients with early RA, especially those with a less aggressive form of the disease.

Diagnosis of Rheumatoid Arthritis

What makes you think RA

- Various patterns of disease onset to be aware of.
  - Fulminate disease onset
  - Additive disease onset
  - Sudden change in severity in patient with osteoarthritis
  - Disease onset after pregnancy
  - Patient has a cold or flu and joints begin hurting during or after recovery
Diagnosis of Rheumatoid Arthritis
What makes you think RA

• Fulminant disease onset
  – Probably the easiest to diagnosis
  – The patient awakens one morning and is unable to get out of bed.
  – Multiple joints are red, hot and swollen.
  – Almost all ADL's are affected.
  – Often will also run a low-grade fever.

Diagnosis of Rheumatoid Arthritis
What makes you think RA

• Additive disease onset.
  – One joint swells and then gets better, although never totally goes back to normal.
  – Then another joint will swell and it will also get better.
  – Over time, multiple joints become involved and stay more consistently painful and swollen.

Diagnosis of Rheumatoid Arthritis
What makes you think RA

• Sudden change in severity in a patient with osteoarthritis.
  – This patient is most likely well known to you.
  – Joints have hurt for years from OA.
  – They present with sudden worsening of their joint pain.
  – This could be a new onset RA, often rather mild, on top of known OA.
Diagnosis of Rheumatoid Arthritis
What makes you think RA

- Disease onset after pregnancy.
  - Patient may or may not have been having some joint issues before pregnancy.
  - The joints all seem to get much better during pregnancy.
  - After pregnancy, the joint pain comes back and is usually much worse then before pregnancy and can even have a fulminate onset.

Diagnosis of Rheumatoid Arthritis
What makes you think RA

- Patient has a cold or flu and joints begin hurting during or after recovery.
  - RA is felt to have a genetic predisposition but is not truly inherited.
  - It is felt that there has to be a triggering event.
  - This even can be any kind of stressor, such as surgery, a viral illness, or even a significant emotional stress.

Diagnosis of Rheumatoid Arthritis
What makes you think it is RA

- The patient can give you many clues as to the diagnosis.
  - Profound morning stiffness that can last for several hours.
  - Often feeling better in the evenings vs the mornings due to being up and moving around.
  - When they step out of bed in the morning they will often say it feels like they are walking on marbles.
Diagnosis of Rheumatoid Arthritis
What makes you think RA

- Additional hallmarks of the disease
  - Marked fatigue
  - Unable to make a fist in the morning or pick up a cup of coffee with one hand
  - Difficulties with ADL such as dressing, particularly with buttons
  - Low grade fever
  - Unexplained weight loss
  - Malaise or depression

What to look for in the physical exam

- Total joint exam is very important — palpate the joints with special attention to the small joints of the hands and feet.
- You may often only find tenderness to palpation in early disease with only very subtle synovitis
- The patient may not report tenderness except with ROM
- RA tends to be a very symmetrical disease so be aware of that pattern

- Muscle atrophy can be present, especially on the dorsal surface of the hands
- Decreased grip strength
- Fallen arches of the feet
- Rheumatoid nodules
- Subluxation of fingers and toes
Diagnosis of Rheumatoid Arthritis
What makes you think RA

- Extra-articular involvement is seen in RA
- Usually in more long standing disease, but can be the presenting symptom.
- Most common
  - Vasculitis
  - Rheumatoid eye
  - Rheumatoid lung

Diagnosis of Rheumatoid Arthritis
What makes you think RA

- Laboratory exam in RA
  - Always remember in early RA lab can be totally normal
  - Lab can support the diagnosis of RA, it never makes the diagnosis
- What lab to order
  - Rheumatoid Factor and CCP
  - Sed rate and CRP
  - CBC and CMP

Diagnosis of Rheumatoid Arthritis
What makes you think RA

- Rheumatoid Factor and CCP
  - Rheumatoid Factor has been used as a marker for RA for more than half a century. IgM RF is the isotype most typically detected.
  - In earlier studies with CCP, the CCP1 assay was used; in more recent studies, the CCP2 assay is used (refers to the coating on the plates used for the study).
  - Sensitivity for the two tests is comparable. About 50-75%.
  - Specificity is higher for CCP (90-95%)
  - It appears that anti-CCP positive early RA patients may develop a more erosive disease.
Diagnosis of Rheumatoid Arthritis
What makes you think RA
• Sed rate and CRP
  – Very non-specific indicators of inflammation
  – They can be elevated for a variety of reasons
• Sed rate and CRP are both nonspecific and their clinical usefulness is therefore limited, especially in diagnosis.

Diagnosis of Rheumatoid Arthritis
What makes you think RA
• Erythrocyte sedimentation rate
  – Measures how fast red cells fall through a column of blood
  – It is an indirect index of acute-phase protein concentrations – particularly dependent on the concentration of fibrinogen
  – It is a sensitive but nonspecific index of plasma protein changes which result from inflammation or tissue damage
  – High ESR: any inflammatory disorder (i.e., infection, rheumatoid arthritis), tuberculosis, myocardial infarction (early response), anemia
  – Also affected by age, sex, menstrual cycle, pregnancy and drugs (steroids)

Diagnosis of Rheumatoid Arthritis
What makes you think RA
• C-reactive protein
  – Name derives from its ability to react with the C polysaccaride of Streptococcus pneumoniae, but it may also bind to chromatin in nuclear DNA-histone complexes. Once bound it activates the classical complement pathway.
  – An increased CRP may be due to :
    • Inflammatory disorders – inflammatory arthritis, Crohn's disease, vasculitis
    • Tissue injury or necrosis – burns, MI, PE
    • Infections, especially bacterial
Diagnosis of Rheumatoid Arthritis

What makes you think RA

- CBC and CMP
- Basic laboratory tests which can give some clues to the diagnosis of RA
- CBC
  - Look for slight leukocytosis, thrombocytosis, anemia
- CMP
  - Look for increased total protein, particularly globulins
  - on SPE usually a polyclonal response
  - Expect normal renal, hepatic and metabolic functions
  - if not normal, may need to reconsider diagnosis

Diagnosis of Rheumatoid Arthritis

The Stiff Man

- DJ is a 67 yr old male referred due to
  - + Rheumaoid factor of 44
  - Joint pain
  - Stiffness
  - Problems with joints over many years
  - Worked as a small engine mechanic most of his life
  - About a year ago, it seemed he could not continue to do much of anything with hurting
  - He reduced his activities a great deal and, upon finding a comfortable position, he would just stay that way to reduce his pain

- He has a high pain tolerance
  - Used to have Cluster Headaches and so compares any pain to that
  - His shoulders and neck hurt the most and his hands swell some
- He is stiff in the morning for about an hour – the stiffness is a very significant problem
- He does not sleep well due to pain, has a great deal of fatigue, has difficulty doing things anymore
Diagnosis of Rheumatoid Arthritis
The Stiff Man

- Joint exam reveals tenderness to palpation of
  - Right shoulder and ankle, both wrists
  - In the right hand, 1st MCP, 3rd and 5th PIP joints
  - In the left hand, only the 1st MCP joint is tender, but he has quite a bit of numbness in that hand
  - He does have Heberden and Bouchard nodes present

- Most striking things in his history were
  - Extreme level of stiffness
  - Significant fatigue
  - Difficult doing things anymore
- Lacking in the exam was significant synovitis
- Opted to try a therapeutic trial of prednisone, 10mg q am with food as osteoarthritis is not usually significantly affected by prednisone, but RA is

- Return visit in 2 weeks
  - Improved 60-75%
  - Morning stiffness decreased to 15-20 minutes
  - Much more mobility and able to do things better
- Continued the prednisone at 10mg and began methotrexate at 10mg weekly
  - Initially tolerated methotrexate well and felt the 10mg helped
  - As we increased methotrexate, he developed significant GI distress
  - Currently on 10mg prednisone and Imuran BID
  - If we don’t get adequate response to Imuran or he develops GI issues, he will be a good candidate for a biologic
- Over time he has developed more significant synovitis in the hands and wrist and pain in additional joints
Diagnosis of Rheumatoid Arthritis
Rheumatoid Eye without RA?

• LS is a 31 yr old female referred for scleritis/uveitis
  – In November of 2013, presented to ophthalmology with episcleritis – expected that this would resolve on its own and given steroid drops to use prn
  – 6 months later woke up one day with both eyes red and very painful with sensitivity to light
  – Diagnosis remained as episcleritis, but she continued to worsen

• She presented back to her ophthalmologist and was treated with prednisone drops every hour
• After two weeks of this therapy, she was much improved and was subsequently referred to rheumatology
• All lab including RF, ANA, ANCA, ESR, CBC and CMP with normal limits

Diagnosis of Rheumatoid Arthritis
Rheumatoid Eye without RA?

• Rheumatoid Eye
  – Can run the gamut from mild inflammation to full blown scleritis
  – With scleritis, the sclera becomes inflamed and weakened even to the point of perforation
• Simple visual inspection of the sclera in this patient revealed thinning of the sclera in the temporal portion of the eye bilaterally
• Currently methotrexate is being initiated as a steroid sparing agent and to get better control of this condition
• Interestingly, this patient presents with rheumatoid eye but without RA
• Only the future will tell if this patient does subsequently develop RA
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• References utilized in this CME presentation
  – The following articles can be found on the ACR website
    • ACR 2010 Rheumatoid Arthritis Classification
    • The use of Anti-cyclic Citrullinated Peptid (anti-CCP) Antibodies in RA
    • Rheumatoid Arthritis
    • 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis