Rheumatology Primer:  
What Labs and When

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Disclosures

• None
Objective

• Discuss principles of laboratory evaluation in diagnosing common rheumatologic conditions
• Cases of common rheumatologic conditions and evaluations
• Basics of treatment

Case #1

• A 55 year old female comes into your office complaining of joint pain.
• She reports pain and swelling in both wrists and in multiple knuckles of her hands for over 8 weeks. No fevers, chills. Has been taking NSAIDs with minimal relief of symptoms.

• On physical exam, she has bilateral 2\textsuperscript{nd} and 3\textsuperscript{rd} MCP and bilateral wrist synovitis (joint swelling/ inflammation). She has trouble gripping your hands and making a fist. No other joint tenderness or swelling.
• The rest of the physical exam is normal.
What is your diagnosis?

RHEUMATOID ARTHRITIS

• What tests to order?
Testing for Diagnosis of Rheumatoid Arthritis

<table>
<thead>
<tr>
<th>Rheumatoid factor</th>
<th>Anti-CCP</th>
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<tbody>
<tr>
<td>• 60% sensitivity, 79% specificity</td>
<td>• Cyclic citrullinated peptide antibody</td>
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<tr>
<td>• 45% positive in first 6 months</td>
<td>• 64% sensitivity; 94% specificity</td>
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<tr>
<td>• 75-85% positive with established disease</td>
<td>• Increased risk of progressive disease</td>
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<td>• High-titer poor prognostic indicator</td>
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**Anti-CCP**

- Has higher specificity for diagnosing rheumatoid arthritis than rheumatoid factor
- Useful in diagnosis of early RA
- Appears years before development of clinical rheumatoid arthritis
- Associated with high risk of erosive disease
- Approximately 10% of RA patients are RF+/CP- and RF-/CCP+
- Currently we test for both when suspecting rheumatoid arthritis
- Serial RF and anti-CCP have no clinical value
What about inflammatory markers?

- ESR/CRP – can be elevated in Rheumatoid arthritis
- Not specific for RA or other inflammatory conditions
- Not a good screening test for RA
- Can be elevated with infections, inflammatory conditions, malignancies, other chronic disease, age, obesity
- Abnormal inflammatory markers give us 1 point on ACR RA criteria
- In patients with established RA useful in monitoring of disease activity
Rheumatoid Arthritis

- Autoimmune systemic inflammatory disorder that affect approximately 1% of the world population
- Mean age of onset - 52 years (range 40-70 yo)
- Female: Male ratio - 3-5:1

Key Clinical Features

- Morning stiffness for at least one hour and present for at least six weeks
- Swelling of at least one small joint, with other diagnoses excluded
- Swelling of wrist, metacarpophalangeal, or proximal interphalangeal joints
- Symmetric joint swelling
- Hand x-ray changes typical of RA: erosions
- Rheumatoid subcutaneous nodules
- + RF and/or anti-CCP
Synovitis

Rheumatoid nodules
Radiographic Findings

Treatment Options

Non-biologic DMARDs
- Sulfasalazine
- Hydroxychloroquine
- Methotrexate
- Leflunomide
- Azathioprine
- NSAIDs
- Prednisone

Biologic DMARDs
- Anti-TNF inhibitors
  - Etanercept, Infliximab, Adalimumab, Certolizumab, Golimumab
- B cell depletion
  - Rituximab
- Disruption of T cell costimulation
  - Abatacept
- IL-6 Inhibition
  - Tocilizumab
- JAK kinase inhibitor
  - Tofacitinib
Non-biologic DMARDs monitoring

- Methotrexate, Leflunomide, Azathioprine, Sulfasalazine - CBC, LFTs
- Hydroxychloroquine – CBC, eye exam
- Prednisone – bone health

Considerations in use of biologic DMARDs

- Any biologics - higher risk for infections (viral/ bacterial)
- Any biologics - need for screening for latent TB (Quantiferon - TB Gold test)
- Rituximab - need to screen for hepatitis B
- TNF inhibitors - contraindicated in patients with CHF
- Abatacept – can worsen reactive airway
- Tocilizumab – close LFT monitoring, lipids monitoring
RA and Heart Disease

• Patients with Rheumatoid Arthritis - at increased risk of cardiovascular disease.

• Annual cardiovascular risk factor assessment including lipid and blood pressure is suggested.

• Patients should have at least annual visits with the primary care provider important evaluation and other health maintenance measures.

Case #2

• A 20 year old AA female comes in for evaluation of multiple complaints: facial rash, joint pain and swelling for the last 3-4 months, fatigue, hair loss, oral ulcers. Gets rash when in the sun

• Physical exam:
• Facial rash, 2 oral ulcers, synovitis affecting MCP’s and wrists bilaterally

• Labs: WBC count of 2.8 (with lymphopenia), Hb 7.8, Platelet count 86k
• UA: 2+ protein, 5-10 RBCs
• ANA 1:1,280, anti-Smith antibody +
What is your diagnosis?

SYSTEMIC LUPUS ERYTHEMATOSUS

• What tests to order?
ANA

- 5% of general population may have a positive ANA and have no symptoms
- Normal ANA titer ≤ 1:40 done by immunofluorescence
- ANA 1:40, 1:80 weakly positive - can be seen with aging
- Higher titer ANA >1:160 - more indicative of autoimmune disease
- >1:160 – SLE, Sjogren’s syndrome, Systemic sclerosis, Myositis
- + ANA can be seen in chronic liver disease, ILD, thyroid disease, RA.

ANA patterns

- Rim pattern: SLE
- Homogeneous pattern: SLE, RA
- Speckled: systemic sclerosis, Sjogren’s syndrome, SLE
- Nucleolar: diffuse cutaneous systemic sclerosis
- Anti-centromere: limited cutaneous systemic sclerosis
Immunofluorescent ANA Patterns

What other tests to order?

- ANA by ELISA is cheaper and faster.
- When ordering ANA ELISA in Wisconsin Diagnostic lab, order ANA with reflex to comprehensive profile

  ![ANA Reflex to Comprehensive Profile](image)

- If ANA is positive, the rest of the panel will be done (anti-smith, ds-DNA, SSA, SSB, RNP, anti-centromere, SCL 70).
- Order both ANA ELISA and ANA titer
- Serial ANAs have no clinical value
Other Antibodies

- **Anti-centromere**
  - Limited cutaneous systemic sclerosis (CREST)
- **Ant-SCL 70** (topoisomerase I)
  - Diffuse cutaneous systemic sclerosis
- **Anti-Jo1**
  - Anti-synthetase syndrome (myositis)
- **Anti-RNP**
  - Mixed Connective Tissue Disease
- **Anti-dsDNA**
  - SLE (97% specific)
- **Anti-smith**
  - SLE (97% specific, low sensitivity)
- **Anti-histone**
  - SLE and drug-induced SLE
- **Anti-SSA/SSB**
  - Sjogren’s, SLE, SCLE

Other labs to order when suspecting SLE and for disease monitoring

- **CBC** : anemia, leukopenia, thrombocytopenia
- **BMP** : creatinine
- **UA** : hematuria, proteinuria
- Urine protein/creatinine ratio
- Complement: C3, C4 low in patients with active SLE, can be monitored serially
- dsDNA: can be monitored serially, correlates with disease activity
SLE

• Chronic autoimmune disease affecting multiple organ systems
• 90% of patients with SLE - women
• Disease onset: 15-44 yo
• 3 x more common in AA women than white women
• More common in women of Hispanic, Asian, and Native American descent

SLE Criteria

• 1. Malar rash
• 2. Discoid rash
• 3. Photosensitivity
• 4. Oral ulcers
• 5. Arthritis
• 6. Serositis (pleuritis, pericarditis, peritonitis)
• 7. Hematological disorder (leukopenia, hemolytic anemia, thrombocytopenia)
• 8. Renal disorder
• 9. ANA positive (99% sensitive, 49% specific)
• 10. Immunologic disorder (+ds DNA, anti-smith, antiphospholipid ab)
• 11. Neurological disorder (seizure, psychosis)
Malar rash

Discoid Rash
Photosensitivity

Oral Ulcers
Treatment Options

- Corticosteroids
- Hydroxychloroquine
- Azathioprine
- Mycophenolate Mofetil
- Methotrexate
- Cyclophosphamide
- Rituximab
- Belimumab

FDA—approved Rx for SLE

- Hydroxychloroquine (Plaquenil) – 1955 FDA approved
- Corticosteroids – 1955 FDA approved
- Belimumab (Benlysta) – 2011-FDA approved to treat lupus
- Targets B-lymphocyte stimulator (BLYS) protein
- Reduces the number of abnormal B cells thought to be a problem in lupus
Cardiovascular Disease

- Major cause of illness and death in patients with SLE
- Women with SLE are 5-8 x more likely to develop CHD than women in the general population
- In younger women with SLE risk for CHD may be >50 x greater than that of their counterparts in general population
- Important to keep regular follow up with PCP for monitoring and Rx

Case #3

- 53 yo male with h/o chronic sinusitis admitted to hospital with 4 week history of fatigue, malaise, myalgias and arthralgias. 1 week PTA he developed productive cough with small amount of hemoptysis. 3 days ago noticed purple rash on bilateral legs and feet. In the morning of admission woke up with right wrist drop.
- One exam has palpable purpura, unable to extend right wrist
- Labs:
  - WBC 15.6, (neutrophil predominant differential), Hb 8.6, Plat 233k
  - Creatinine 3.4
  - UA: 2+ blood, 2+ protein, 10-20 RBCs
  - CXR: cavitary lesion right upper lobe
What is your diagnosis?

• Vasculitis - Granulomatosis with Polyangiitis (GPA)

• What tests to order?
When suspecting vasculitis:

- cANCA, pANCA - immunofluorescent tests
- Proteinase-3 (PR-3), Myeloperoxidase (MPO) - ELISA
- ANA, Cryoglobulins
- CBC (leukocytosis, anemia, thrombocytosis)
- BMP (renal insufficiency)
- UA (hematuria, proteinuria), urine protein/creatinine ratio
- Chest X-ray
- Tissue biopsy
ANCA associated vasculitis

- Granulomatosis with Polyangiitis – GPA (cANCA/PR-3)

- Microscopic Polyangiitis – MPA (pANCA/MPO)

- Eosinophilic Granulomatosis with Polyangiitis - EGPA (pANCA/MPO)
GPA

- Necrotizing granulomatous inflammation usually involves upper and lower respiratory tract

- Necrotizing vasculitis affects small to medium vessels (e.g., capillaries, venules, arterioles, arteries, and veins)

- Necrotizing glomerulonephritis is common.

GPA

- **Upper airway** - sinusitis, otitis, nasal ulcerations, septal perforations, saddle nose deformities
- **Lower airway** - cough, hemoptysis, infiltrates, nodules, cavities
- **Renal** involvement – GN, hematuria, casts, proteinuria, ARF, HTN
- **Musculoskeletal** - arthralgias, myalgias, weakness
- **Eye** - conjunctivitis, uveitis, episcleritis
- **Neurological symptoms** - mononeuritis multiplex
- **Cutaneous vasculitis/digital necrosis**
- C-ANCA
- PR3
Saddle nose deformity

Eye involvement
Mononeuritis

Pulmonary infiltrates
Pathology

Treatment

• Glucocorticoids and immunosuppressive therapy

• For induction – Rituximab (FDA approved Rx), Cyclophosphamide

• For maintenance - Azathioprine, Mycophenolate Mofetil, Methotrexate
Take Home Points

• Tests to order when suspecting RA: anti-CCP antibodies- more specific test than RF, but order both).
• Inflammatory markers useful in disease monitoring, but not diagnosis of RA
• Know what test to order when suspecting SLE: ANA titer, ANA ELISA with reflex to comprehensive profile, C3, C4, CBC, Creat, UA
• Patients with inflammatory arthritis and SLE are at higher risk for heart disease than general population
• Know when to suspect vasculitis and what tests to order

References

• Kelley and Firestein's Textbook of Rheumatology
• ACR image bank
• ACR/ EULAR classification criteria
• ACR/ EULAR guidelines
• Lexicomp
• Google images
• UpToDate