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 2nd and 3rd 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

Rheumatoid factor

- 60% sensitivity, 79% specificity
- 45% positive in first 6 months
- 75-85% positive with established disease

Anti-CCP

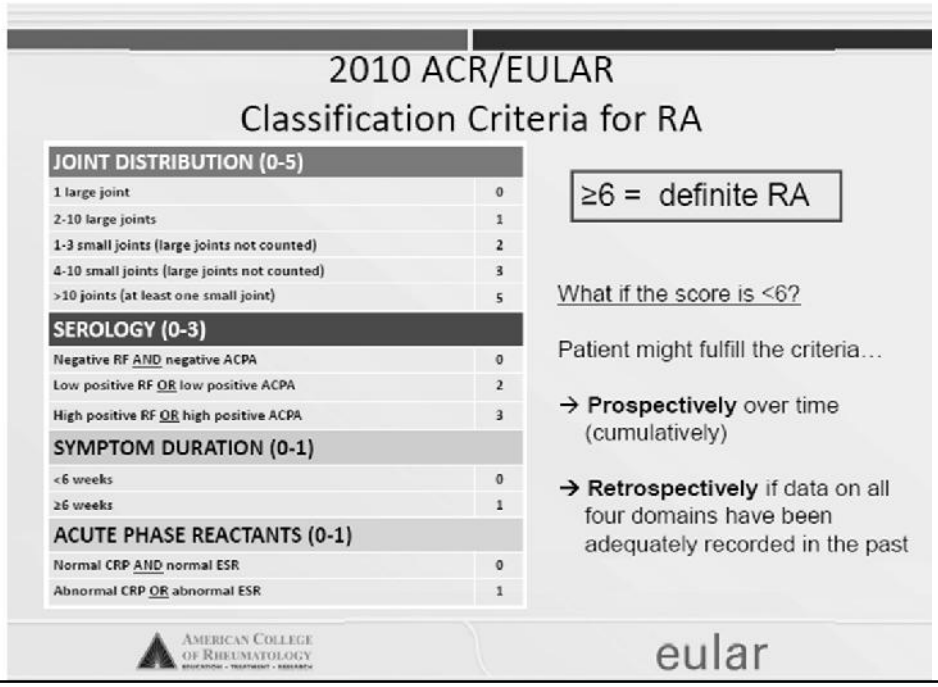
- Cyclic citrullinated peptide antibody
- 64 % sensitivity; 94% specificity
- Increased risk of progressive disease
- High-titer- poor prognostic indicator

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



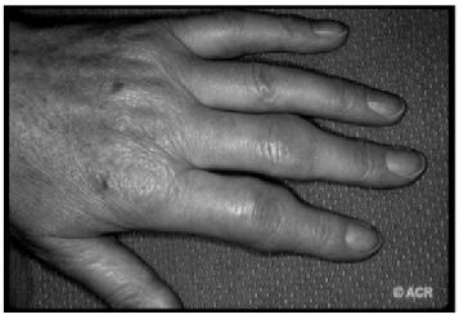
Rheumatoid Arthritis

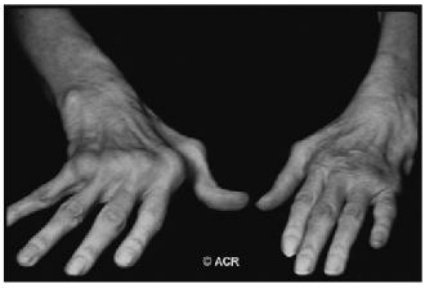
- Autoimmune systemic inflammatory disorder that affect approximately 1% of the world population
- Mean age of onset - 52 years (range 40-70 yo)
- Female: Male ratio - 3-5:1

Key Clinical Features

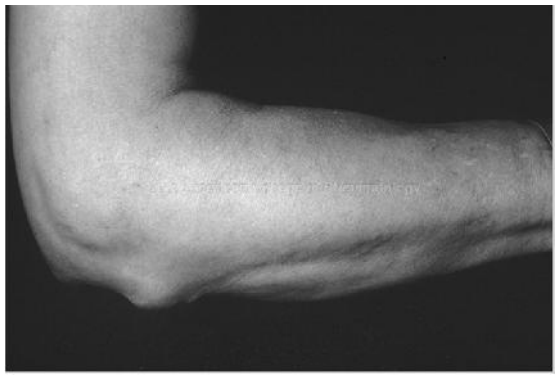
- Morning stiffness for at least one hour and present for at least six weeks
- Swelling of at least one small joint, with other diagnoses excluded
- Swelling of wrist, metacarpophalangeal, or proximal interphalangeal joints
- Symmetric joint swelling
- Hand x-ray changes typical of RA: erosions
- Rheumatoid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

Synovitis

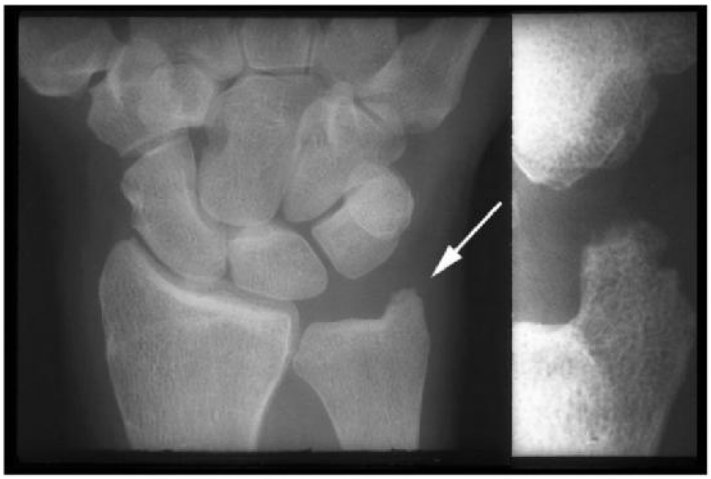




Rheumatoid nodules



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?**

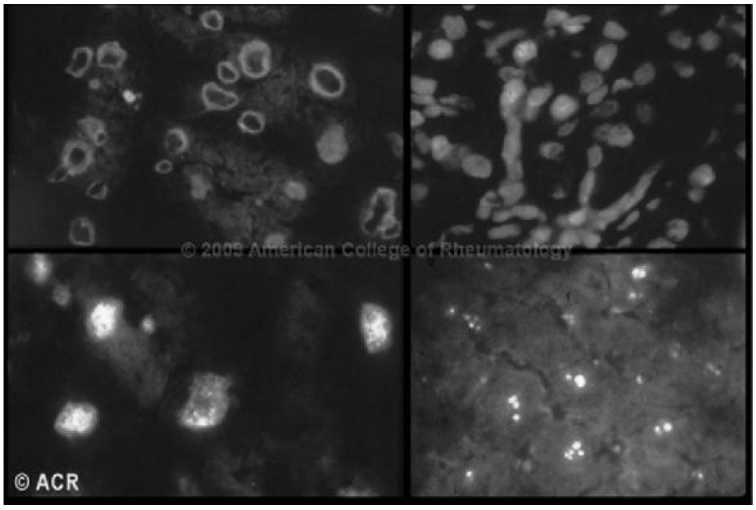
ANA

- 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

- 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/creatine ratio
- Complement: C3, C4 low in patients with active SLE, can be monitored serially
- dsDNA: can be monitored serially, correlates with disease activity

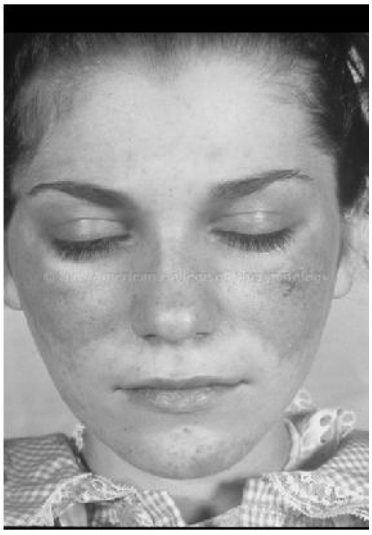
SLE

- 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

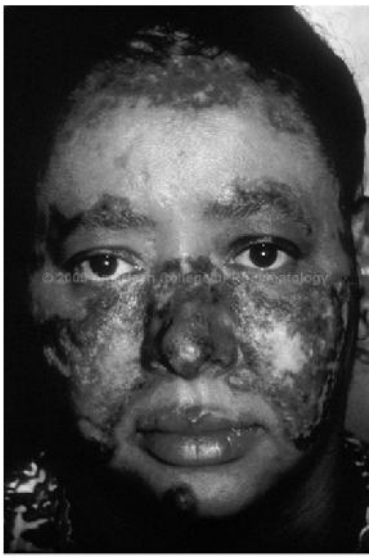
SLE Criteria

- 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)

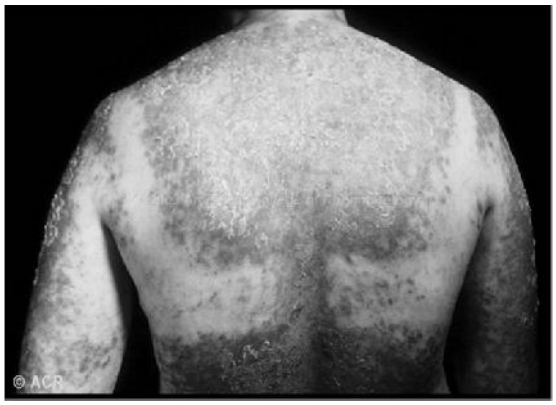
Malar rash



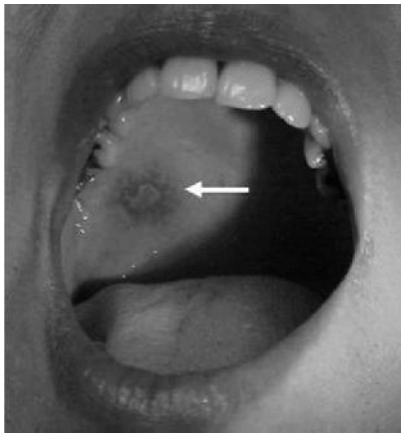
Discoid Rash



Photosensitivity



Oral Ulcers



Treatment Options

- Corticosteroids
- Hydroxychloroquine
- Azathioprine
- Mycophenolate Mofetil
- Methotrexate
- Cylcophoshamide
- 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

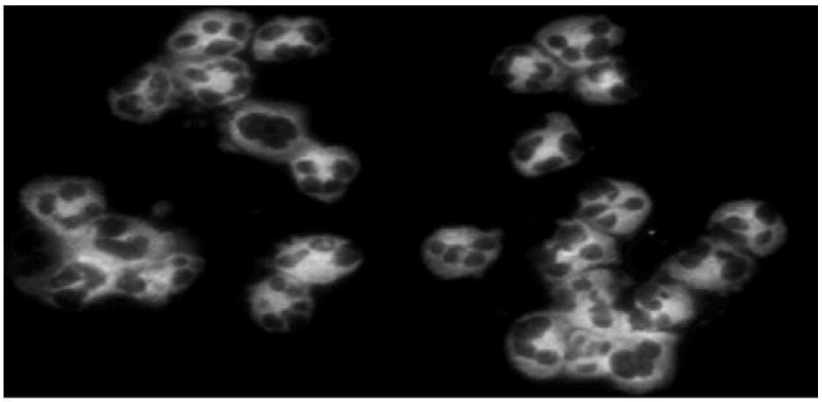
What is your diagnosis?

- **Vasculitis - Granulomatosis with Polyangiitis (GPA)**

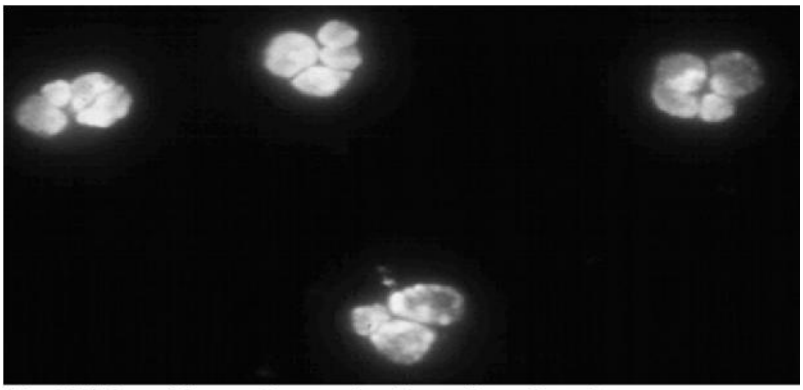
•What tests to order?

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/ creatine ratio
- Chest X-ray
- Tissue biopsy



C-ANCA pattern Demonstration of **cytoplasmic** antineutrophil cytoplasmic antibodies (C-ANCA) by indirect immunofluorescence with normal neutrophils. There is heavy staining in the cytoplasm while the multilobulated nuclei (clear zones) are nonreactive. These antibodies are usually directed against proteinase 3 and most patients have Wegener's granulomatosis. Courtesy of Helmut Rennke, MD.



P-ANCA pattern Demonstration of **perinuclear** antineutrophil cytoplasmic antibodies (P-ANCA) by indirect immunofluorescence with normal neutrophils. Staining is limited to the perinuclear region and the cytoplasm is nonreactive. Among patients with vasculitis, the antibodies are usually directed against myeloperoxidase. However, a P-ANCA pattern can also be seen with autoantibodies against a number of other antigens including lactoferrin and elastase. Non-MPO P-ANCA can be seen in a variety of nonvasculitic disorders. Courtesy of Helmut Rennke, MD.

ANCA associated vascultis

- Granulomatosis with Polyangiitis – GPA (cANCA/PR-3)
- Microscopic Polyangiitis – MPA (pANCA/MPO)
- Eosinophilic Granulomatosis with Polyangiitis - EGPA (pANCA/MPO)

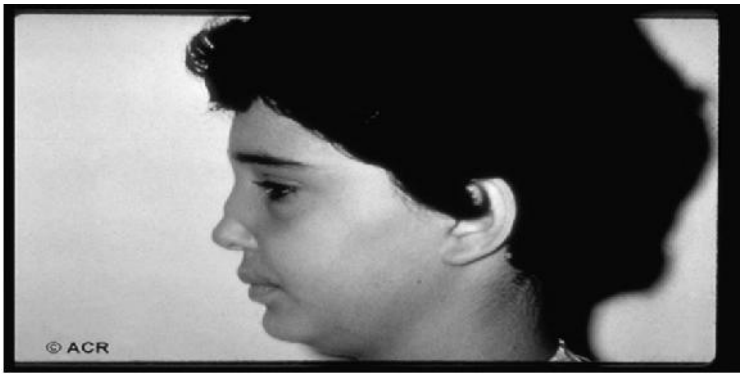
GPA

- 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.

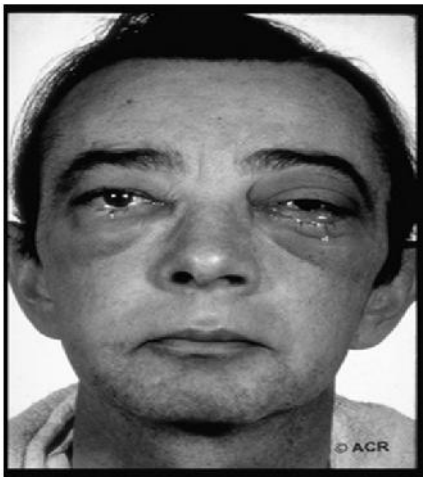
GPA

- **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** - conjuctivitis, uveitis, episcleritis
- **Neurological symptoms** - mononeuritis multiplex
- **Cutaneous vasculitis/ digital nevcrosis**
- C-ANCA
- PR3

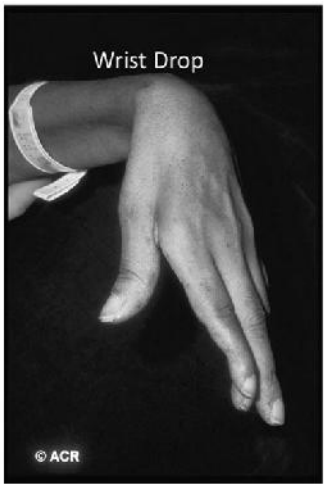
Saddle nose deformity



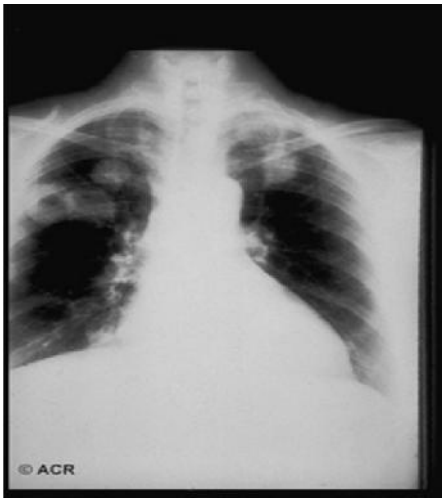
Eye involvement

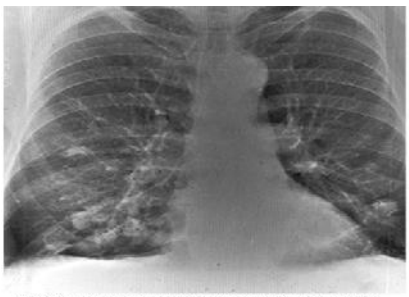


Mononeuritis

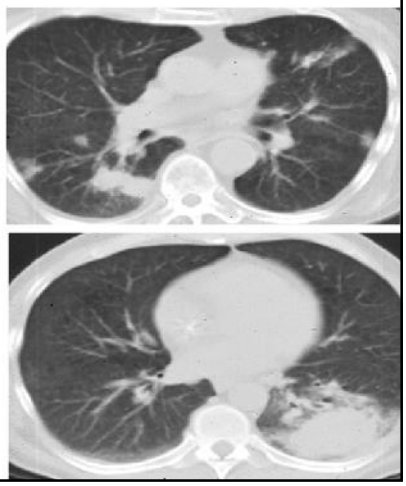


Pulmonary infiltrates

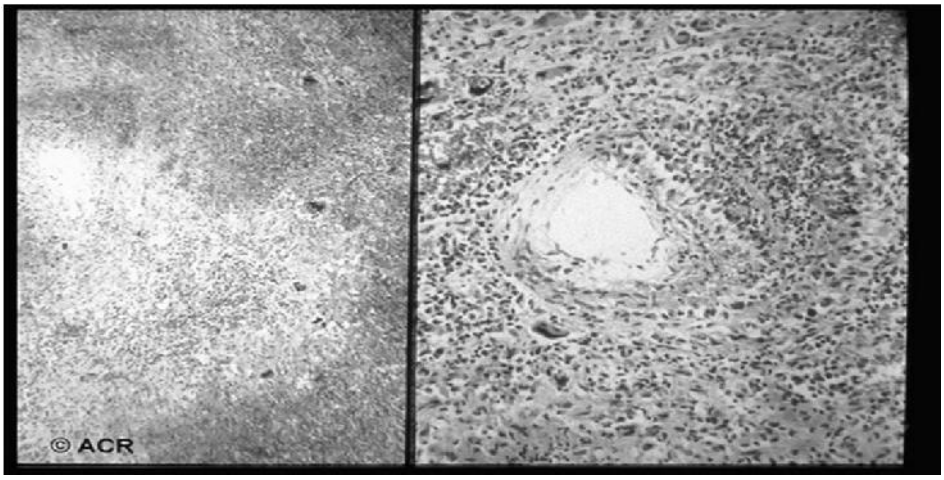




Wegener's granulomatosis. Chest radiograph and CT scans demonstrate bilateral nodules and masses, most prominent at the bases. (Courtesy of Paul Stark, MD).



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