Take Home Messages:

Hint: Use all the Q and A’s
My view of what is board and clinically relevant

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Systemic Lupus Erythematosus Summary

SLE is a multi-system autoimmune disorder
SLE can look like many different disease entities
To diagnose SLE the ANA should be positive
A positive ANA does not the diagnosis make
Direct the treatment towards the underlying sxs
Everyone should be on hydroxychloroquine
Can use steroids and other immunosuppressive
Watch out –new therapies (e.g., belimumab) are on their way– full use to be determined.

What is the Association of DLE and SLE?

- Patients have defined plaques that become thickened over time. Can scar and leave hypopigmented lesions and telangectasia
- 5-10% of patients develop systemic lupus.
- Lesions occur in 10-15% of patients with SLE
- ANA + in 55%
- Treatment the same as SCLE

Pulmonary SLE

- Pleuritis
- Lupus Pneumonitis
- Chronic Interstitial Lung Disease
- Pulmonary Hemorrhage – morbidity approaches 50% Best test is....?
- BOOP
- Shrinking Lung Disease – secondary to diaphragmatic paralysis Best test is....?

Cardiovascular

- Pericarditis
- Valvular heart disease – most often seen in conjunction with the Anti-phospholipid Syndrome
- Accelerated atherosclerosis – major issue
- Coronary Vasculitis – rare
- Myocarditis – rare

Musculoskeletal

- 95% of patients will have musculoskeletal complaints
- Arthralgias and Arthritis – tends to be nonerosive and no nodules although both reported
- Septic Arthritis
- Osteonecrosis – risk increases with steroid use greater than 20 mg a day
Hematologic

- Anemia—usually Coomb’s positive
- Leukopenia—WBC less than 4000
- Lymphopenia—lymphocytes less than 1500
- Thrombocytopenia—Platelet count less than 100,000

WHO Classification

- Class I: Normal or Minimal Change
- Class II: Mesangial glomerulonephritis
- Class III: Focal proliferative glomerulonephritis
- Class IV: Diffuse proliferative glomerulonephritis
- Class V: Membranous glomerulonephritis

What are the lab findings of each???

Autoantibodies

- ANA—found in 95% of patients
- Anti-ds-DNA—40% -80% of patients
- Anti-Sm—25% of patients
- Anti-histone—seen in drug induced SLE
- Anti-Ro, Anti-La - Sjogren’s, SCLE
- Anti-RNP- Mixed Connective Tissue Disease
- False positive VDRL— an anti-phospholipid antibody

Diagnostic Criteria: 4 Necessary

- Malar Rash
- Discoid Rash
- Photosensitivity
- Aphthous ulcers
- Arthritis
- Serositis (pericarditis or pleuritis)
- Renal proteinuria or casts
- Neurologic: Seizures or Psychosis
- Hematologic: anemia, leuko(<4000) or lymphopenia(<1500), thrombocytopenia(<100,000)
- Immunologic: Anti-DNA, Anti-Sm, and/or antiphospholipid
- ANA

Drug Induced SLE

- Patients present with lupus like illness
- Usually arthritis, rash and serositis
- Positive ANA and anti–histone antibody
- Rare to have renal, neuropsychiatric, or vasculitic disease
- Often responds to drug withdrawal, NSAIDS or low dose prednisone

Drugs Involved

- Common
  - Procainamide
  - Hydralazine
  - Minocycline
  - methyldopa
- Rare
  - Beta blockers
  - D-Penicillamine
  - INH
  - Quinidine
  - PTU
  - Hydroxychloroquine
  - Trimethadione
  - Chlorpromazine
  - Anti-TNF
Antiphospholipid Syndrome (APS) is defined as:
1) arterial clots, venous clots or obstetrical complications in the context of 2) an antiphospholipid antibody (either anticardiolipin antibody or lupus anticoagulant) positive on two separate occasions 12 weeks apart.

- Treatment for arterial or venous complications is life-long anti-coagulation.
- Treatment of obstetrical complications is unfractionated or low molecular weight (LMW) heparin.

**Antiphospholipid Antibody Syndrome: Major Criteria**

- The presence of an anticardiolipin antibody (IgG or IgM) and/or lupus anticoagulant plus one of the following clinical events:
  - Arterial thrombotic events
  - Venous thrombotic events
  - Recurrent pregnancy losses:
    - 3 or more first trimester losses
    - A second trimester loss or severe intrauterine growth retardation

**Associated Medical Conditions**

- Sneddon’s syndrome: Strokes and livedo in young women.
- Evan’s syndrome: Thrombocytopenia and Coomb’s positive hemolytic anemia.
- CVAs and Myocardial Infarctions in individuals under 40.
- Sudden multisystem occlusive disease.

**Patients Who Should be Evaluated for Antiphospholipid Antibodies**

- All SLE patients
- Patients under age 40 with CVA, MI no obvious risk factors
- Recurrent venous or arterial clots
- Women with recurrent first trimester pregnancy losses, or second trimester loss

**ACL Antibodies in Various Patient Populations**

- Healthy controls: 1-2%
- Recurrent miscarriage population: 5-10%
- SLE: 20-40%
- SLE with livedo or Raynaud’s: 80%
- Stroke, MI under age 40: 20%
- HIV infected: IgM 50-60%

**Differential Diagnosis of Polyarthritis**

- Rheumatoid Arthritis
- PMR/GCA
- Psoriatic Arthritis
- Crystal – Gout, Pseudogout
- SLE/Vasculitis
- Sjogren’s and variants
**ACR Criteria for Diagnosis**

Four or more of the following criteria must be present:
- Morning stiffness > 1 hour
- Arthritis of ≥ 3 joint areas
- Arthritis of hand joints (MCPs, PIPs, wrists)
- Symmetric swelling
- Serum rheumatoid factor
- Radiographic changes

First 4 must be present for > 6 weeks.

**New 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis**

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who should be tested? Patients with definite clinical synovitis of at least one joint not better explained by another disease process. Score-based algorithm: add scores of A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA.</td>
<td></td>
</tr>
</tbody>
</table>

**A. Joint involvement (use highest applicable category)**

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

**B. Serology (high-positive: ≥ 3x upper limit normal for the test)**

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative RF and negative ACPA</td>
<td>0</td>
</tr>
<tr>
<td>Low-positive RF or low-positive ACPA</td>
<td>2</td>
</tr>
<tr>
<td>High-positive RF or high-positive ACPA</td>
<td>3</td>
</tr>
</tbody>
</table>

**C. Acute phase reactants**

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal CRP and ESR</td>
<td>0</td>
</tr>
<tr>
<td>Abnormally elevated CRP or ESR</td>
<td>1</td>
</tr>
</tbody>
</table>

**D. Duration of symptoms**

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</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>

ACPA: anti-citrullinated peptide antibodies; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; RA: rheumatoid arthritis.

**Rheumatoid Arthritis**

**Laboratory Abnormalities**

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Occasional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Leukocytosis/leukopenia</td>
</tr>
<tr>
<td>ESR</td>
<td>Platelets</td>
</tr>
<tr>
<td>Latex (+)</td>
<td>CCP+</td>
</tr>
<tr>
<td></td>
<td>ANA+</td>
</tr>
</tbody>
</table>

Hyper (γ) Globulinemia

N.B. Inflammatory Synovial Fluid with CH50

**Pulmonary Manifestations**

**Pleural Effusions**
- Exudates > Transudates
- Can have low pH
- Hallmark is low glucose – Often < 30

**Rheumatoid nodules**
Cardiac Manifestations

- Increased risk of virtually all cardiac manifestations in RA
- Monitor lipids and aggressive treatment
- Early interventions with DMARDs modify cardiac risk as well as changes natural history of RA

Dosing - MTX

Weekly
- Oral/SC – One Dose
  - Cycled
Initial Dose
- 7.5 mg/wk with folic/folinic acid
Therapeutic
- Most patients need 20 – 25mg/week (0.3mg/kg)
Maximum
- 25 mg/wk
Maintenance
- Lowest dose possible
- Steroid reduction

Methotrexate: Toxicity

- Gastrointestinal
- Stomatitis
- Hematologic
- Pulmonary
- Liver
- Infection–zoster
- Renal
- Rash/Headache
- Reproductive

Tb screening for Anti-tnf-and MTX

- 5mm positive, not 10
- If pos CXR to r/o active infection
- What if negative, but radiographic stigmata of prior Tb, including calcified granuloma?
- INH 300mg qd 9 months or alternative regimens if from country with drug resistant Tb
- I’ve had BCG – what to do?
- How long to wait before initiate anti-tnf?

Anti-TNF Therapies

Adverse Events

- Sepsis, Septic Joints, Pneumococci (Pneumovax)
- Tuberculosis (PPD and treat prior)
- Injection site reactions/diffuse rashes
- Pulmonary symptoms
- ? Increased risk lymphoma/solid tumors
- Increased risk Class III-IV CHF
- Neurologic-demyelination
- Hematologic-pancytopenia
- Autoimmune diseases SLE
- ?LFT abnormalities

Absolute Contraindications to TNF-Blockers

- CHF III/IV
- Active/latent Tb
- Active infection
- Active or recent h/o malignancy (solid tumors)
- MS/optic neuritis
- h/o lymphoma
- Live vaccines
- Anaphylaxis

Adapted Semin A&R 2005;34
### Newer Biologics in RA
- Abatacept—costimulatory blockade
- Rituximab—B cell depleted—unique AE=PML
- Tocilizumab—IL6 R antagonist—unique AE=colonic perforation

### Take Home Points: Scleroderma
- Complications associated with scleroderma are better managed, esp pulmonary hypertension and renal crisis, though there is no single effective treatment for the disorder
- ILD is most responsible for morbidity and mortality in Scl
- Raynaud's that develops in pts over 35 raises the suspicion of an underlying autoimmune disease

### Treatment in Scleroderma: There Has Been Progress!
- Interstitial lung disease (minimal improvement in lung function and skin scores with cyclophosphamide)
- Renal: ACE inhibitors
- Pulmonary hypertension: prostacyclin, endothelin antagonists (maybe), sildenafil
- Reflux: PPI high dose, anti reflux—surgery
- Stem cell transplant (ongoing trials)

### Take Home Points: Myositis
- Inflammatory myositis can have skin, lung and arthritis as complicating features outside of muscle weakness
- Steroids are still the mainstay of treatment
- DMARDs are often needed and useful to limit the side effects of steroids
- Interstitial lung disease can have a variable course, though often treatable, can rapidly accelerate to respiratory failure.

### Take Home Points Giant Cell Arteritis/PMR
- New onset headache in the elderly should always prompt suspicion of GCA
- Unusual symptoms = cough, weight loss, fever, anemia
- Never delay initiation of steroids in a patient with visual symptoms where GCA is suspected.
- Visual loss in GCA once it develops is often irreversible, though once appropriate treatment is given, the chance of developing visual loss is rare.
- Patients with a normal ESR or CRP can develop GCA and PMR —7Bx both sides
- Long term risk of thoracic aortic aneurysms

### PMR Pearls
- Synovitis of the hands can occur in PMR—subset evolves into RA
- A normal ESR does not exclude the diagnosis
- 15–20% of patients with PMR will develop GCA
- Consider a temporal artery biopsy where response is suboptimal to low dose steroids, or persistent constitutional symptoms or inflammatory markers remain high.
Giant Cell Arteritis: Diagnosis

Three of the following five criteria was associated with a 94% sensitivity and 91% specificity.

- Age greater than or equal to 50 years at time of disease onset
- Localized headache of new onset
- Tenderness or decreased pulse of the temporal artery
- Erythrocyte sedimentation rate greater than 50 mm/h (Westergren)
- Biopsy which includes an artery, and reveals a necrotizing arteritis with a predominance of mononuclear cells or a granulomatous process with multinucleated giant cells

Vasculitis

- Treatment for ANCA associated vasculitis is undergoing a paradigm shift with the use of B cell deleting agents like rituximab
- Patients treated with prolonged courses of high dose steroids especially in combination with other immunosuppressive agents should receive prophylaxis against Pneumocystis pneumonia and pneumococcal vaccination.
- Patients with Hepatitis C may develop a systemic vasculitis associated with cryoglobulinemia which ultimately requires treatment with antiviral therapy to control the vasculitis.
- The type of vasculitis is determined by vessel size involved, blood tests (ANCA, Complement among others) and pathology

Behcet’s Disease

- Aphthous Stomatitis
- Genital Ulcers
- Uveitis
- Arthritis
- Cutaneous and systemic vasculitis
- Meningoencephalitis
- Other: Phlebitis, Arteritis

What Are The Commonest Diagnoses for Monarthritis?

- Infection – usually the key diagnosis that needs to be ruled out (Include Lyme)
- Crystalline disorders – gout, pseudogout
- Spondyloarthritis (reactive arthritis, IBD, spA, AS)
  - Trauma – bleeding, hemophilia, coagulopathies
  - Less common – the monoarthritis evolves into a polyarticular presentation (eg RA, gout)

Clinical Aspects Of Gout

- Serum Urate > 7
- But diagnostic proof remains crystal dx
- Intracellular urate
- Mono or oligoarticular
- Podagra
- Review diet, ETOH (beer>liquor>wine)
- Diuretic use
- Family hx

- Diff dx of Podagra:
  - Gout/OA/SpA
  - Infection uncommon
  - Upper extremity involvement implies greater urate load

Systemic Disorders Presenting as Monoarthritis

- SPONDOLOARTHROPATHIES
  - IBD, AS, Psoriasis
  - Reactive (salmonella, shigella, yersinia)

- SARCOID
  - Penarthritis with swelling
  - Associated with E. nodosum

- RHEUMATOID ARTHRITIS
  - Rarely presents with monoarticular presentation

- OSTEOARTHRITIS
  - Inflammatory features affecting single joint
Gout [cont.]

- Rare in premenopausal women
- In men: highest incidence age 30-45
- In women: highest incidence age 55-70
- Drugs have changed the landscape for gout—especially cyclosporine, diuretics and the bimodal effect of asa—do you know?
- DX and natural history

Conclusion

- Febuxostat, at a daily dose of 80 mg or 120 mg, was more effective than allopurinol at the commonly used fixed daily dose of 300 mg in lowering serum urate—but is that the correct dose??
- Similar reductions in gout flares and tophus area occurred in all treatment groups
- Newer agents—Uricase iv

Synovial Fluid Analysis: What to Send-Make Every Attempt to Obtain!

- 1. Gram stain, C&S
- 2. Cell count and differential (anticoagulated tube)
- 3. Analysis for crystals by compensated polarized microscopy (anticoagulated tube; crystals will "keep" for hours)

**Synovial Fluid Analysis: Interpretation of Cell Count/Diff**

- <1-2,000 wbc/cc: noninflammatory fluid
- 2,000 wbc/cc: inflammatory fluid
- >2,000 wbc/cc: inflamatory fluid
- DDx is extensive; basically includes all the systemic rheumatic diseases

**Synovial Fluid Analysis: Interpretation of Cell Count/Diff [cont.]**

- >50-100,000 wbc/cc: suggestive of septic arthritis
- But may also be seen with gout and pseudogout
- And occasionally with R.A. and so-called "reactive arthritis"

Uricases

- Raspuricase—uricase from apergillus. High incidence of infusion reactions—anaphylaxis One time use.
- Uricase—pegylated urate oxidase. Mammalian. Breaks down uric acid to soluble allantoin.
- Phase III trial completed. Results positive
- FDA approved -IV infusions every two weeks

Synovial Fluid Analysis: Interpretation of Cell Count/Diff [cont.]

- Rare in premenopausal women
- In men: highest incidence age 30-45
- In women: highest incidence age 55-70
- Drugs have changed the landscape for gout—especially cyclosporine, diuretics and the bimodal effect of asa—do you know?
A Word on Hemarthrosis

- Hemarthrosis: in the context of acute trauma, consider subchondral fx; consider further imaging procedures.
- Other causes of hemarthrosis:
  - Some hemoglobinopathies (S-S disease, etc.)
  - Caisson’s/pseudogout
  - Concurrent anticoagulation with coumadin
    - OK to tap in this situation
    - Hemarthrosis rare with thrombocytopenia

Lyme Disease: Clinical Presentation

- Often chronic and/or recurring, but can be acute.
- Most common by far at the knee.
- Seen in late Lyme disease.
- Serologic tests for Lyme disease nearly always + in this setting.
  - N.B.: require confirmation via Western blot.
  - A negative Lyme serology argues strongly against the Dx of Lyme disease.

Ankle Arthritis

- Bilateral swollen ankles with tenderness, but normal ROM.
- ?dx test.