Rheumatologic Issues:
Systemic Immune-mediated Diseases

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Systemic Autoimmune Diseases

- SLE: Systemic Lupus Erythematosus
- Systemic Sclerosis (Scleroderma)
- Sjögren’s Syndrome
- Inflammatory Myopathies
Keys to Diagnosing Autoimmune Diseases

• Detailed history
• Careful physical exam
• Judicious use of Laboratory and Radiology
• Serologies should SUPPORT a clinical diagnosis, NOT suggest one!

SLE

• Multisystem autoimmune disease
• Protean manifestations
• Affects all age groups, peak ages of onset between 15 and 40
• 90% of all SLE patients are women of child-bearing age- F:M ratio = 5:1 during reproductive years, 2:1 in older and younger groups
• US prevalence 15-50/100,000, highest ethnic prevalence is African American
**Pathogenesis: Innate and Adaptive Immunity**

- SLE etiology: interactions between susceptibility genes and environmental factors resulting in abnormal immune responses, female gender permissive
- Genetics: Twins (monozygotic 25-30%, dizygotic 5%), familial (~2%), C’-deficiencies, HLA associations-HLA DR2,DR3
- Environment: Endocrine (female preponderance-estradiol), trauma (UV irradiation), drugs (Procainamide, INH, Hydralazine, Quinidine, Methyldopa,others)
- Immunologic: Autoantibodies, B-cell hyperactivity, T-cell dysfunction, defective apoptosis & IC clearance

**SLE: Diagnosis**

- Based on clinical features and autoantibodies
- Classification criteria for SLE diagnosis intended for confirming diagnosis for study inclusion
- ACR Criteria: 4/11 criteria at any time during course makes SLE likely: 95% specificity and 75% sensitivity
- SLICC Revision of ACR Criteria 2009
- Presence of antibodies with no clinical symptoms not diagnostic
ACR Criteria for the Classification of SLE (1982 / 1997)

• Malar Rash
• Discoid rash
• Photosensitivity
• Oral ulcers
• Arthritis
• Serositis — pleuritis, pericarditis
• Renal — >0.5 g prot, or cellular casts
• Neurological — Seizure, or psychosis
• Hematological — Hemolytic anemia, or leukopenia, or lymphopenia, or thrombocytopenia
• Immunologic — Anti-DNA, anti-Smith, or APLA
• ANA

SLICC (Systemic Lupus International Collaborating Clinic) Revision of ACR Criteria

• Classify a patient as having SLE if: biopsy-proven nephritis with ANA or anti-dsDNA OR patient satisfies 4 criteria including at least one clinical and one immunologic criteria

• Better sensitivity than ACR 11 (94% vs. 86%) and equal specificity (92%) with fewer misclassifications (p=.0082)
SLICC Criteria

• CLINICAL: Acute or subacute cutaneous LE, chronic cutaneous LE, oral/nasal ulcers, non-scarring alopecia, inflammatory synovitis, serositis, renal: Urine protein/creatinine ratio > 500/24 hr, neurological, hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia

SLICC Criteria: Immunologic

• ANA - above lab reference
• Anti dsDNA- above lab reference
• Anti-Sm
• Antiphospholipid Ab - lupus anticoagulant, false positive VDRL, Anticardiolipin at least twice normal, anti b2 glycoprotein 1
• Low complement (Low C3, C4 CH50)
• Direct Coombs in absence of hemolytic anemia
Systemic Lupus Erythematosus

• Clinical features on presentation in SLE:
  – Arthritis or arthralgia 55%
  – Skin Involvement 20%
  – Nephritis 5%
  – Fever 5%

• Major causes of mortality
  – Early: severe disease/ infection
  – Late: atherosclerosis

Organ Involvement in the Course of SLE

• Joints 90%

• Skin:
  – Rashes 70%
  – Discoid lesions 30%
  – Alopecia 40%

• Pleuropericardium 60%

• Kidney 50%

• Raynaud’s 20%

• Mucous Membranes 15%

• CNS (Seizures/Psychosis) 15%
Survival in SLE

- Improved survival: 5 year survival
  - 1950: 50%
  - 2000: 80-90%
- Improved survival related to:
  - Earlier diagnosis, Serologies
  - Dialysis
  - Steroids
  - Immunosuppressives: Cyclophosphamide, MMF
  - Blood pressure control
  - Antibiotics

Morbidity and Mortality in SLE

- Early:
  - Renal
  - SLE
  - Infection
- Later
  - Cardiovascular
  - Cancer
  - Osteoporosis
Cutaneous Manifestations

• SLE specific
  – Malar rash
  – Discoid rash
  – Subacute cutaneous LE

• SLE nonspecific
  – Livedo reticularis
  – Bullous lesions
  – Panniculitis
  – Photosensitivity
  – Oral ulcers
  – Alopecia
  – Urticaria
  – Digital ulcers
  – Purpura

Systemic Lupus Erythematosus: Rash and Erythema, Face
Systemic Lupus Erythematosus: Alopecia, Scalp

Systemic Lupus Erythematosus: Photosensitivity, Face and Neck
SLE: Musculoskeletal Features

- Arthralgias
- Arthritis (usually nonerosive, may have reducible deformities)
- AVN
- Myositis
- Fibromyalgia

Systemic Lupus Erythematosus: Jaccoud’s Arthropathy (Clinical and Radiograph)
**SLE: Renal Manifestations**

- Lupus Nephritis
  - WHO I (a):
    - Normal by all techniques; I(b) Normal by light microscopy, with ICs demonstrated by IF or EM
  - WHO II:
    - Mesangial
  - WHO III (a and b):
    - Focal Segmental (a) and Focal Proliferative (b) GN
  - WHO IV:
    - Diffuse Proliferative GN
  - WHO V:
    - Membranous GN

- ESRD usually results from Class III, IV disease
- Bx helps to identify potentially reversible abnormalities
  - Activity (cellular crescents, glomerular tuft proliferation, fibrinoid necrosis, karyorrhexis, leukocyte infiltrates in glomerulus and interstitium)
  - Chronicity (tubular atrophy, fibrous crescents, interstitial fibrosis, glomerulosclerosis)
International Society of Nephrology and Renal Pathology Society-ISN/RPS Classification of Lupus Nephritis

- **Class I**
  - Minimal mesangial LN

- **Class II**
  - Mesangial proliferative LN

- **Class III**
  - Focal LN

- **Class IV**
  - IV-S - diffuse segmental
  - IV-G - diffuse global (active and chronic)

ISN/RPS Lupus Nephritis

- Renal function more likely to deteriorate in IV-G than IV-S

- IV-G patients (A/C) had persistent proteinuria in spite of rx.

- Chronicity led to deteriorating function

Schwartz, MM, Semin Nephrol. 2007 Jan;27(1):22-34
Hiramatsu et al, Rheumatology. 2008 Apr 4. epub
Systemic Lupus Erythematosus: Red Blood Cell Cast, Urine

- Most SLE pts will have some abnormality on a renal bx
- Different histologies may co-exist in the same kidney, or even the same slide
- Histology may change over time
- Urinalysis is superior to BUN, Cr, 24 hr collections, in sensitivity of renal disease
  - Proteinuria, Casts (rbc, granular, tubular), Hematuria, Pyuria (in absence of infection)
Treatment of SLE Renal Disease-2010

• Steroids
• Immunosuppressive (Cyclophosphamide, Mycophenylate mofetil, or Azathioprine)
• Adjunctive therapy for proteinuria: ACE inhibitors, Angiotensin receptor blocker, spironolactone 25 mg or eplerenone 50 mg
• BP control
• Rituximab? – EXPLORER study negative, targeting B lymphocyte Stimulator (Blys) or (BAFF)?
• Transplant: survival of graft similar to those without SLE

MMF: Summary

• Compared with conventional CTX Rx:
  • Induction: “probably” equivalent (4 studies equivalent, one MMF superior to cyclophosphamide)
  • Maintenance: “may be” equivalent (death and CRF, CTX worse than MMF or Azathioprine) – relapse-free higher with MMF
• Less toxic (MMF fewer hospitalizations, less infection, GI SE and amenorrhea)
• Side effects (anemia, GI, leukopenia, HPTN)
• Current paradigm (MMF or Cytoxan induction, MMF equivalent to azathioprine for maintenance)

**SLE: Cardiac**

- Pericarditis- rare tamponade
- Libman Sacks endocarditis
- Valvular insufficiencies (mitral, aortic)
- Embolic events
- Myocarditis
- Coronary artery disease
  - Corticosteroids, Homocysteinemia
  - Accelerated atherosclerosis

**SLE: Cardiovascular**

- Elevated risk for CHD and stroke

- Overall risk of CVD:
  - 52.4-fold increased risk of MI in women ages 35-44
  - 4.2-fold increase in women ages 55-64 compared to Framingham Offspring Study (2)
  - Overall 10.1-fold increased risk nonfatal MI (1)
  - 17-fold increased risk death due to MI (1)
  - High in-hospital post-MI mortality risk: SLE:8.3%, DM 6.2%, control 5.1% (3)
SLE: Cardiovascular

- Excess risk not explained by traditional risk factors or prednisone treatment
- Prednisone Rx: ↑cholesterol of 7.5 mg% with each 10 mg dose increment, increased weight, BP, glucose
- Elevated biomarkers (CRP, homocysteine, mono chemo attractant protein-1, fibrinogen, etc.)
- Immune-complex endothelial damage, vasculitis, anti-phospholipid antibody-induced thrombosis, Libman-Sacks endocarditis, HPTN from renal involvement, hypercholesterolemia

Cardiovascular Risk in SLE

- Atherosclerotic and cerebrovascular diseases more common cause of late deaths than active SLE
- Higher incidence of sub-clinical CAD and carotid plaque
- Not explained by traditional risk factors
- aPL syndrome with arterial and venous thrombosis

Mok, C et al, Arth Rheum, 2005, 52(9) 2774-2782.
**SLE: Pulmonary**

- Acute lupus pneumonitis (alveolitis)
- Alveolar Hemorrhage Syndrome
  - Hemoptysis in only half; look for falling Hct, increased DLCO
- Pleurisy
- Interstitial Lung Disease (r/o PCP)
- Shrinking Lung syndrome
- Pulmonary HTN
- Pulmonary Embolism
- INFECTION

**SLE: Hematologic**

- Leukopenia (<4000 cells/mm³)
- Lymphopenia (<1500)
- Thrombocytopenia (<100,000)
- Anemia
  - AOCD, Coombs positive hemolysis
- Hyposplenism
**Antiphospholipid Antibody Syndrome**

- Syndrome characterized by recurrent arterial and/or venous thromboses, recurrent fetal loss, and thrombocytopenia in association with sustained elevated titers of antiphospholipid antibodies.

- “Antiphospholipid antibodies” encompass a family of antibodies (aPTT, RPR, anti-cardiolipin antibodies, and others)

- May also be detected: dRVVT, ELISA for b-2-glycoprotein I

- Other features: livedo, seizures, transverse myelitis, valvular heart disease, pulmonary HTN, Aortic insufficiency

**APAS**

- Primary vs. secondary

- Clinical manifestations best correlate with presence of high-titer IgG isotype.

- Drug-associated APAS generally not associated with disease.

- Treatment ranges from an aspirin a day, to SQ heparin plus aspirin, to full anticoagulation.

- Therapy for catastrophic antiphospholipid antibody syndrome
**SLE: Neuropsychiatric Manifestations**

- CVA
- Seizures
- Transverse myelitis
- Lupus headache
- Peripheral neuropathy
- Cranial neuropathy
- Depression
- OBS- most common CNS manifestation is cognitive dysfunction (memory, reasoning)
- Psychosis

**SLE: Gastrointestinal**

- Peritonitis
- Nausea, vomiting, diarrhea
- LFT abnormalities: AST and ALT elevations when disease is active
- Intestinal vasculitis- perforations, ischemia, bleeding
SLE: Ocular Manifestations

- Retinal vasculitis and optic neuritis – blindness can develop in days to weeks!
- SICCA
- Conjunctivitis
- Steroid complications: cataracts and glaucoma

SLE: ANA

- ANA’s are positive in > 95% of patients with SLE during course of disease and usually at onset of symptoms (repeated negative tests make dx unlikely)
- Specific for SLE: Sm antigen and high titer IgG antibodies to dsDNA
- Correlate with clinical manifestations
- Positive Predictive Value: 11%
ANA Titers in Healthy Individuals

- 1:40  20-30%
- 1:80  10-12%
- 1:160  5%
- 1:320  3%

ANA Positivity in other Disease States

- Autoimmune diseases: RA, other Rheumatologic disorders,
- Graves’, Hashimoto’s
- Primary biliary cirrhosis, hepatitis
- Hematologic malignancies
- Multiple Sclerosis, Myasthenia Gravis
- Drugs
- Prevalence increases with age
Significance of Autoantibodies in SLE

<table>
<thead>
<tr>
<th>Antigen</th>
<th>SLE</th>
<th>Clinical associations</th>
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<tbody>
<tr>
<td>Native DNA</td>
<td>40%</td>
<td>Nephritis (&amp; flare)</td>
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<tr>
<td>Denatured DNA</td>
<td>70%</td>
<td>Non-specific</td>
</tr>
<tr>
<td>Histones</td>
<td>70%</td>
<td>Drug-induced Lupus</td>
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<tr>
<td>Sm Antigen</td>
<td>30%</td>
<td>Severe SLE</td>
</tr>
<tr>
<td>Nuclear RNP</td>
<td>30%</td>
<td>Arthritis</td>
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<tr>
<td>Ribosomal RNP</td>
<td>10%</td>
<td>MCTD</td>
</tr>
<tr>
<td>SSA/Ro</td>
<td>35%</td>
<td>SCLE, Sjogren’s, NLS</td>
</tr>
<tr>
<td>SSB/La</td>
<td>15%</td>
<td>SCLE, Sjogren’s, NLS</td>
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Lupus Serologies

- ANA
- anti-dsDNA
- anti-ssDNA
- SSA/Ro, SSB/La, RNP, Sm, ribosomal P
- antiphospholipid antibodies
- C₃, C₄
Anti-dsDNA Antibodies

- Strong biomarkers
- Clinical predictors
- High titer IgG anti-dsDNA predict nephritis
- High affinity anti-dsDNA associated with flare
- Glomerular IC enriched for anti-dsDNA

SLE vs. Drug - Induced Lupus

- Manifestations of SLE *seldom* seen in Drug-induced lupus:
  - hypocomplementemia
  - renal disease
  - CNS disease
  - False + VDRL

- Treatment is removal of offending drug +/- *short-term* NSAIDs +/- Corticosteroids
Prevalence of Autoantibodies in SLE and Drug-Induced LE

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<th>SLE</th>
<th>Drug-Induced</th>
</tr>
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<tbody>
<tr>
<td>Native DNA</td>
<td>40%</td>
<td>No</td>
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<tr>
<td>Denatured DNA</td>
<td>70%</td>
<td>75-80%</td>
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<tr>
<td>Histones</td>
<td>70%</td>
<td>&gt;95%</td>
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<tr>
<td>Sm Antigen</td>
<td>30%</td>
<td>No</td>
</tr>
<tr>
<td>Nuclear RNP</td>
<td>30%</td>
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Malignancy and SLE

- Striking increased risk hematologic malignancies, esp NHL (SIR 3.64)
- Increased risk lung cancer (SIR 1.37)
- Highest risk earliest in course, esp first year
- Slight increase all cancers (SIR 1.15)
- Women with SLE get LESS cancer screening
- Breast cancer less likely localized
- Cyclophosphamide and cervical dysplasia

Osteoporosis and SLE

- Five-fold increased risk in fractures in women with SLE compared with US population

- Glucocorticoid-induced osteoporosis – cumulative and highest Prednisone

- Vitamin D (sun avoidance in SLE patients)

Therapy to Address Bone Density Issues in Patient with in SLE

- Calcium, Vitamin D, Exercise
- Prophylaxis for steroid-treated patients
- Premenopausal women: Rx issues, oral contraceptives
- Bisphosphonates – PO, IV (ONJ, atrial fibrillation) – not with renal insufficiency!
- Anabolic Therapy
SLE and Pregnancy, HT

• Pregnancy increases risk for SLE flares, no difference in fertility rates
• Increased risk for pre-eclampsia with LN and APS
• Higher risk of miscarriage, stillbirth, prematurity, IUGR, fetal heart block
• NO MTX, cyclophosphamide or MMF in pregnancy
• Relationship to disease activity at conception
• SELENA trial:
  – Oral contraceptives - no increase in SLE flares
  – Postmenopausal HT – mild to moderate-severe flares

SLE: Management Strategies

• Hydroxychloroquine as long-term maintenance drug
• Minimize steroids in mild-to-moderate lupus
• Mycophenolate mofetil for managing renal lupus
• Prevent ovarian failure from cyclophosphamide by using leuprolide acetate
• Prevent flares by avoiding triggers
• Some RA treatments appropriate to treat lupus arthritis
• Cancer preventive strategies critical because SLE increases cancer risk
• Address accelerated atherosclerosis, cardiovascular risks
• Coexistent fibromyalgia
• Address, evaluate and treat cognitive impairment
SLE: Pharmacologic Treatment

• Analgesics, NSAIDs: for arthralgias, arthritis
• Hydroxychloroquine: constitutional sx, derm, and in longterm management, musculoskeletal, serositis, hematologic systems
• Prednisone: hematologic, renal, neurological, serositis. Use judiciously and taper to lowest tolerated dose (preferably off)
• Methotrexate: Arthritis
• Cyclophosphamide: major organ or life-threatening flares in CNS, Kidneys.
• Mycophenylate Mofetil (MMF)

Skin

• Sunscreen
• Hydroxychloroquine. (<6.5 mg/kg/day)
• Topical corticosteroids
• Intralesional corticosteroids
• Methotrexate, Azathioprine
• Dapsone
Rx – SLE Joint Manifestations

• Arthralgias
  – Acetominophen, NSAIDs

• Arthritis
  • Hydroxychloroquine
    – Methotrexate
    – Azathioprine
    – Low-dose corticosteroids (<10 mg/d)

SLE: Additional Treatments

• Myopathy, Myositis
  – Steroids, Methotrexate, Cyclophosphamide
  – DDx drug-induced myopathy
    – steroids
    – hydroxychloroquine
    – statins

• Raynaud’s Phenomenon
  – Calcium channel blockers
**Additional SLE Rx:**

- Recognize co-morbid conditions:
  - Secondary Fibromyalgia
  - Secondary Sjogren’s Syndrome
  - Hypertension
  - Hyperlipidemia

- Routine Health Maintenance Issues
  - Age-appropriate malignancy screening
  - Eye exams (HCQ, Cataracts, Glaucoma)
  - Pneumovax, H. flu, Meningococcal
  - Dental Care
  - Infections
  - Bone Health: DXA, calcium, Vitamin D, Rx
  - ASA 81 mg, Statins

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**Scleroderma**

- Rare disorder, striking 2 - 10 per million/year
- Female : male = 3 : 1
- Onset usually between 30 and 50
- Scleroderma features Raynaud’s phenomenon, sclerodactyly, and extensive fibrosis over arms, hands, legs and often the trunk
- Late complications include joint contractures, muscle atrophy, skin ulceration, progressive obliterative vasculopathy
- Organ complications include ILD, Gastric dysmotility, arrhythmias, malabsorption, pneumatosis cystoides intestinalis
Systemic Sclerosis

- Highest case-fatality of connective tissue diseases (55% 10 yr survival)
- 90% have ILD on autopsy
- Major risks: progressive skin involvement, contractures, autoantibodies to topoisomerase-1 (30-40% with diffuse disease have +Scl-70)
- Steroids increase risk of renal crisis- even in low doses!
- PAH-leading cause of death

Skin involvement in Systemic Sclerosis

- Skin as nearly universal feature: pruritis, edema in early stages
- Sclerodactyly, digital ulcers, pitting of fingertips, telangectasia, cutaneous cutis
- Rodnan skin score: 0-3 in 17 distinct areas of body
- Limited cutaneous:
Scleroderma: Mauskopf, Facial Changes

Scleroderma: Raynaud’s Phenomenon, Blanching of Hands
Vascular Disease in SSc

- Raynaud Phenomenon
- Pulmonary Artery Hypertension
- Scleroderma Renal Crisis
- Gastric Antral Vascular Ectasia
- Cardiac (secondary to HPTN or PAH, pericarditis, myocardial fibrosis, CHF, pericardial effusion, conduction disturbances, arrhythmias)

Other Extracutaneous Organ Involvement in SSc

- GI involvement:
  - 90% (hypomotility, incompetent LES, GERD, malabsorption, vascular ectasia
- Pulmonary:
  - ILD in 75%, pulmonary vascular, lung cancer (5-fold higher)
- Renal:
  - 50% with proteinuria, scleroderma renal crisis: ARF, mild proteinuria, abrupt HPTN
- Musculoskeletal
  - Contractures, friction rubs, myopathy
- Neurological
  - Neuropathy, CNS
- GU
**Limited Scleroderma (CREST)**

- Calcinosi
- Raynaud’s
- Esophageal Dysmotility
- Sclerodactaly
- Telangectasias
- Limited Cutaneous: Skin involvement distal to elbows/knees, renal crisis and pulmonary fibrosis less likely – overall better prognosis except PAH
- 60-80% have Anti-Centromere Ab
- Pulmonary hypertension more likely (may be late)
- Biliary Cirrhosis

**CREST Syndrome: Calcinosis Cutis, Fingers**
Pathogenesis of Scleroderma

- Fibroblasts: enhanced production of Type I collagen, myofibroblasts
- T cells: release cytokines (TGFβ, IL-2) that stimulate fibroblast activities
- Vasculopathy: earliest fibrosis is seen in perivascular areas, later obliteration of the original vessel lumen: Net loss of capillary bed
- Platelets release TGFβ that activates fibroblasts

Systemic Sclerosis Management

- No steroids!
- PAH – prostacyclin analogs (epoprostenol), bosentan (endothelin antagonist), sildenafil (phosphodiesterase inhib), ambrisentan
- Interstitial Lung Disease: Cytoxan- Scleroderma lung study- non-sustained benefit
- Raynaud’s: calcium channel blockers, nitrates, ACE inhibitors, phosphodiesterase inhibitor, serotonin antagonists, prostacycline analogues, epoprostenol, bosentan
Prognosis in Scleroderma

• Overall mortality 5 to 8-fold higher
• Five year mortality (10%) and ten year mortality (18%) with diffuse disease
• Most deaths due to pulmonary fibrosis, PAH (not renal crisis as in past)
• Risk factors for mortality: diffuse disease, cardiac or GI involvement, extent of skin involvement, PAH (higher 5 year mortality 90% vs 20%)

Scleroderma Renal Crisis

• Rapidly progressive renal insufficiency
• Sudden onset hypertension
  – normal BP in 10%
• Microangiopathic hemolytic anemia
• Thrombocytopenia
• Rapidly progressive cutaneous fibrosis
• Steroid therapy a risk factor
• ACE inhibitors are organ and life-saving
Scleroderma: Treatment

- ACE inhibitors
- Methotrexate for myositis (not if renal insufficiency)
- Cyclophosphamide for active pulmonary alveolitis? Disappointing results
- Ca-channel blockers for Raynaud’s
- Pulm HTN
- Penicillamine- not recommended: no benefit of 1g/d over 125 mg qod
  - toxicities: induction of autoimmune disease, peripheral neuropathy, membranous GN

Scleroderma: Treatment

- Gastrointestinal manifestations:
  - Pilocarpine
  - Reflux esophagitis
  - Metoclopramide (increase LES tone and promotes gastric emptying)
  - Proton-pump inhibitors
  - Malabsorption- hypomotility, overgrowth- cyclic antibiotics
  - Erythromycin- promotility agent
Sjogren’s Syndrome

- Autoimmune exocrinopathy characterized by infiltration of salivary glands by lymphocytes leading to acinar disruption, scarring, and failure of glandular function

- Xerostomia, xerophthalmia

- Xerotrachea, dry skin, pancreatic insufficiency
Classification

- Primary Sjogren’s
- Secondary Sjogren’s
  - RA, SLE, IIM
- Differentiate from other causes of salivary gland enlargement

Extraglandular Involvement in Primary SS

- Musculoskeletal
  - Arthralgias, non-erosive arthritis, Raynaud's
- Pulmonary
  - Xerotrachea, alveolitis, pseudolymphoma
- GI
  - PBC, subclinical pancreatitis, atrophic gastritis
- Renal
  - Interstitial nephritis, RTA, NDI
- Endocrine
  - Autoimmune thyroid disease
Extraglandular Involvement in Primary SS

- Vasculitis
  - Palpable purpura, ulcers, gangrene, mononeuritis multiplex, mesenteric arteritis, GN

- CNS
  - optic neuropathy, may have oligoclonal bands
  - aseptic meningitis
  - seizures, transverse myelitis

- Non-Hodgkin’s Lymphoma

Sjogren’s Syndrome Labs

- ANA (90%)
- SSA/Ro (80%), SSB/La (60-70%)
- SPEP
- APRs
- RF (60%)
- Schirmer’s testing
- Minor salivary gland (lip) bx
- Rose-Bengal staining
Sjogren Syndrome Mimics

- Salivary gland enlargement:
  - viral infection (mumps, EBV, CMV, coxsackie A, HIV, influenza)
  - TB, histoplasmosis, actinomycosis
  - Bacterial parotitis
  - Sarcoidosis, amyloidosis
  - DM, Hyperlipidemia types II, IV, V
  - Alcoholism, anorexia, bulimia, pancreatitis
  - Tumors (lymphoma, adenocarcinoma) (usually unilateral)

Idiopathic Inflammatory Myopathies

- Polymyositis
- Dermatomyositis
- Inclusion body myositis
- IIM associated with malignancy
- Childhood PM/DM
- Amyopathic Dermatomyositis
- Overlap syndromes with other CVDs
Clinical Features of PM/DM

- Gradually progressive painless proximal muscle weakness
- CPK elevation, often 1000 - 10,000 mg/dl or more
- EMG/NCV abnormalities
- Lymphocytic infiltrates on muscle bx, myophagocytosis, centralization of nuclei
- Typical rash findings in DM

Polymyositis vs. PMR

- **Polymyositis**
  - painless weakness
  - sxs unchanging over course of the day
  - younger
  - CPK elevation

- **PMR**
  - Painful “weakness”
  - Not weak on exam
  - Sxs worst in am, better later in day
  - older (>50)
  - CPK normal
**Hallmarks of Dermatomyositis**

- Heliotrope rash
- Gottron’s papules and Gottron’s rash
- Shawl sign
- Nailford capillary abnormalities  
  – short DDx: DM, SLE, RP, UCTD
- Calcinosi Cutis
- Malignancy in up to 15%

**Dermatomyositis: heliotrope rash**

© ACR
Dermatomyositis: rash, hands

Dermatomyositis: rash, chest
Laboratory Features

- CPK 1000 - 10,000+ mg/dl
- CPK-MB
- Less sensitive/specific markers
  - Aldolase: glycolytic pathway enzyme found in muscle fast twitch fibers
  - also found in liver, kidney, brain, intestine, fetus
  - ALT, AST
  - ESR

Myositis Specific Autoantibodies

- Anti-Jo-1, Anti-PL-7, Anti-PL-12, Anti-OJ
- Members of the anti-synthetase family
- Jo-1 seen in 20% of PM pts
- Anti-synthetase syndrome
  - fever, inflammatory arthritis, ILD, RP
- Anti-Jo-1 is directed against histidyl tRNA synthetase (cytoplasmic antigen)
Malignancy in Dermatomyositis (DM) and Polymyositis (PM)

- Increased risk of malignancy with inflammatory myopathies
- DM higher risk than PM (RR 2.4) and SIR higher for DM than PM (6.2 vs. 2.0)
- Peak incidence within 2 years of myopathy dx
- Risk factors: capillary damage on bx, Dm with necrosis on trunk, cutaneous leukocytoclastic vasculitis, older age at myopathy diagnosis, anti-p155 Ab
- Types of cancer: adenocarcinoma of cervix, lung, ovary, pancreas, bladder, stomach make-up 70%
- Age-appropriate screening, ? Limited additional

Treatment of DM, PM

- First line: Corticosteroids, mg/kg, daily

- Second-line agents:
  - methotrexate, azathioprine
  - Rituximab
  - IVIg
  - Cyclosporine, Tacrolimus, MMF
  - Hydroxychloroquine: cutaneous
**Steroid Myopathy**

- Dose and total exposure related
- Proximal muscles
- Lower extremity > upper extremity
- Painless
- Normal enzymes
- Non-inflammatory biopsy
- Primarily affects type II fibers (fast twitch, glycolytic)

**Glucocorticoid-induced myopathy**

- Subacute onset over several weeks, muscle weakness, no myalgias, muscle tenderness
- Unusual unless > 10 mg/day Prednisone, likely presence of Cushingoid features
- Higher doses of glucocorticoid, greater likelihood of developing myopathy
- Urinary creatine elevated in both glucocorticoid and inflammatory myopathy, decreased creatine excretion with decrease in steroid dose in steroid myopathy – will increase if steroid dose is decreased and weakness due to steroid myopathy
- Course: Muscle strength improves in 3-4 weeks with steroid reduction.
Summary

- Multi-system disease presentation may be Systemic Immune-mediated disease, but may be infection, malignancy, other etiology
- History and PE more important than lab evaluation
- Importance of collaborative consultations, patient-centered care

Polymyalgia Rheumatica and Giant Cell Arteritis

- "My grandfather has headaches and his arms are sore"
- PMR
  - proximal muscle pain
  - stiffness
  - elevated ESR
  - Incidence 1/1000 people over 50
  - Rx: Prednisone moderate to low doses
- GCA
  - Systemic vasculitis, incidence 2.2/10,000
  - Visual loss in 40% untreated – ischemic optic neuropathy
  - Fever, ESR over 50, temporal artery, scalp tenderness, jaw and/or limb claudication, bruit, weight loss, malaise, FUO in elderly
  - Rx: High dose Prednisone + biopsy within 1 week
  - 50% patients with GCA have PMR-like presentation
  - Biopsy is critical
GIANT CELL ARTERITIS Temporal Artery Biopsy

- Arteries have skip lesions
- Ultrasound/Doppler may help identify involved areas
- If positive, confirms diagnosis — helpful in management of future disease
- If negative, doesn’t exclude diagnosis, but need to think about an alternative diagnosis

GIANT CELL ARTERITIS- Histopathology

- Granulomatous cell infiltration
- Giant cells
- Disruption of internal elastic lamina
- Proliferation of intima
- Occlusion of lumen
CASE DISCUSSION

History

• 37yo obese CF from Buffalo, NY
• PMH of PCOS, Hypothyroidism, Childhood Asthma
• June 2010: Acute SOB
  – Treated with 3 courses of antibiotics and steroids
  – Each time steroids were tapered, SOB would recur
• Aug 2010: Started on Daily Prednisone 20mg
• Sept 2010: Generalized myalgias & weakness
  – After Pred was cut in half with plans to taper
History

- Oct 2010 to Jan 2011:
  - rapidly progressive decline in muscle strength- noting increasing difficulty climbing stairs, getting up from a chair, progressing to the point now that she cannot lift her leg from the bed, comb her hair
  - noted puffy swelling of her hands as well as peeling, erythema of fingertips; Raynaud’s
  - denies fevers
- Jan 18, 2011
  - Seem in Interdisciplinary Rheumatology/ Pulmonary Clinic
  - Sent to CCF ED then admitted to medicine

OSH Pulmonary W/U

- 7/22/10: CT showed diffuse b/l scattered alveolar lung infiltrates; findings likely inflammatory
- 8/6/10: Bronchoscopy w/ biopsy showed chronic inflammation with histiocytic infiltrate; no granulomatous inflammation or malignancy
- 8/31/10: CT showed bilateral groundglass appearance in perihilar regions, upper lobes, and lingula anteriorly
- 9/29/10: Open lung biopsy showed changes most consistent with resolving acute and organizing bronchopneumonia. Possible collagen vascular disease.

- PFT showed only mild obstruction (FEV1 66%) but decreased DLCO 49%
Physical Exam

- V/S: BP 110/90 | Pulse 129 | Temp(Src) 97.7 °F (36.5 °C) (Oral) | Resp 18 | SpO2 98%
- Gen: obese, tearful
- Skin: mechanic's hands
- Chest: few scattered crackles
- CVS: distant heart sounds - no rub, murmur
- Abdominal: soft, NT, no organomegaly masses.
- Joints: no swelling - tender over knees, ankles - no effusions
- Muscle strength: UE 4+/5 prox, 5-/5 distal; LE 4-/5 prox, 4+/5 distal
- Ext: Upper arm and thigh tenderness
- Neuro: Sensory grossly intact to LT, DTR's 2+=bil UE and LE
CT-CHEST

- Mild basal predominant subpleural ground-glass opacity with associated fine subpleural reticulation (may represent NSIP).
- Additional multifocal areas of ill-defined subpleural ground-glass opacities in the mid to upper lungs (sequelae of prior known organizing pneumonia or interstitial pneumonitis)
ECHO

- Technically difficult due to body habitus.
- LV normal in size, mild concentric LVH
- Left ventricular systolic function is normal.
- EF = 60%
- Normal RV
- Trivial TR and MR.
- Trivial pericardial effusion with no evidence of cardiac tamponade.

LABS

<table>
<thead>
<tr>
<th>Component</th>
<th>Latest Ref Rng</th>
<th>1/19/2011</th>
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<tbody>
<tr>
<td>SM ANTIBODY</td>
<td>Low: &lt;1.0 AL</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>RNP Antibody</td>
<td>Low: &lt;1.0 AL</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>SSA ANTIBODY</td>
<td>Low: &lt;1.0 AL</td>
<td>&gt;8.0 (H)</td>
</tr>
<tr>
<td>SSF ANTIBODY</td>
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<td>&lt;0.2</td>
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<tr>
<td>Centromere</td>
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<td>&lt;0.2</td>
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<tr>
<td>Scleroderma IgG Ab</td>
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<td>&lt;0.2</td>
</tr>
<tr>
<td>Jo 1 Antibody</td>
<td>Low: &lt;1.0 AL</td>
<td>&gt;8.0 (H)</td>
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<tr>
<td>Ribosomal RNP</td>
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<td>&lt;0.2</td>
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<tr>
<td>Chromatin Antibody</td>
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<td>&lt;0.2</td>
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<tr>
<td>CK</td>
<td>30 - 220 U/L</td>
<td></td>
</tr>
<tr>
<td>MB</td>
<td>0.0 - 8.8 ng/mL</td>
<td></td>
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<tr>
<td>CK MB %</td>
<td>0.0 - 4.0 %</td>
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</tr>
<tr>
<td>Aldolase</td>
<td>2.0 - 6.0 U/L</td>
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<tr>
<td>LD</td>
<td>100 - 220 U/L</td>
<td>480 (H)</td>
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<tr>
<td>ANA by EIA</td>
<td>Low: &lt;1.5 OD Ratio</td>
<td>13.6 (H)</td>
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<tr>
<td>Anti-SSA</td>
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<td>&gt;8.0 (H)</td>
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<td>Anti-SM</td>
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<td>&lt;0.2</td>
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<tr>
<td>Anti-SSB</td>
<td>Low: &lt;1.0 AL</td>
<td>&lt;0.2</td>
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<td>Anti-RNP</td>
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<td>&lt;0.2</td>
</tr>
<tr>
<td>TSH</td>
<td>0.400 - 5.500 uU/mL</td>
<td>3.920</td>
</tr>
<tr>
<td>WSR</td>
<td>0 - 15 mm/hr</td>
<td>24 (H)</td>
</tr>
<tr>
<td>CRP</td>
<td>0.0 - 1.0 mg/dL</td>
<td>8.1 (H)</td>
</tr>
</tbody>
</table>
Anti-Synthetase Syndrome

Table 3—Proposed Criteria for the Antisynthetase Syndrome

Patient must have:
- Positive serologic testing for an anti-tRNA synthetase autoantibody
- Plus one or more of the following conditions:
  - Evidence of myositis by Bohan and Peter criteria
  - Evidence of ILD by ATS criteria
  - Evidence of arthritis by clinical examination, radiographic findings, or patient self-report
  - Unexplained, persistent fever
  - Raynaud phenomenon
  - Mechanic’s hands

Geoffrey R. Connors, Lisa Christopher-Stine, Chester V. Oddis and Sonye K. Danoff: Chest 2010;138;1464-1474
<table>
<thead>
<tr>
<th>Antibody</th>
<th>Antigen (tRNA Synthetase)</th>
<th>Prevalence in IIM, %</th>
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<tbody>
<tr>
<td>Jo-1</td>
<td>Histidyl</td>
<td>25-30</td>
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<tr>
<td>PL-7</td>
<td>Threonyl</td>
<td>2-5</td>
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<tr>
<td>PL-12</td>
<td>Alanyl</td>
<td>2.5</td>
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<tr>
<td>EJ</td>
<td>Glycyl</td>
<td>1</td>
</tr>
<tr>
<td>OJ</td>
<td>Isoleucyl</td>
<td>1</td>
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<tr>
<td>KS</td>
<td>Asparaginyl</td>
<td>1</td>
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<tr>
<td>Zo</td>
<td>Phenylalanyl</td>
<td>1</td>
</tr>
<tr>
<td>Tyr</td>
<td>Tyrosyl</td>
<td>1</td>
</tr>
</tbody>
</table>

IIM = idiopathic inflammatory myopathy.

*Geoffrey R. Connors, Lisa Christopher-Stine, Chester V. Oddis and Sonye K. Danoff: Chest 2010;138:1464-1474*