Navigating the Maze of Connective Tissue Diseases

Linda S. Brecher, D.O., FACOI, FACR
Connective Tissue Disease=Collagen Vascular Disease

• 1942 Dr Klemperer introduced “diffuse collagen disease” based upon tissue studies of SLE and SScl patients

• 1946 Dr Rich introduced “collagen-vascular disease” based upon vasculitis

• 1952 Dr Ehrich suggested term “connective tissue diseases”
Connective Tissue Diseases

- Systemic Lupus Erythematosus (SLE)
- Sjogren’s Syndrome (SS)
- Systemic Sclerosis (SScI)
- Rheumatoid Arthritis
- Dermatomyositis / Polymyositis (DM/PM)
- Mixed Connective Tissue Disease (MCTD)
Suggestive History

• Female 20-50 years old with
  – Polyarthritis / polyarthralgias
  – Photosensitivity
  – Raynaud’s / hand puffiness
  – Muscle weakness
  – Dry eyes / dry mouth
  – Unexplained fevers
  – Serositis
  – Family history of CTD
Laboratory Testing

• Positive Antinuclear antibody (ANA)
  – >98% sensitive for SLE
  – Non-specific
Antinuclear Antibody (ANA)

- Not specific for any rheumatic disease
- False + increase with age
- These diseases are based upon CLINICAL parameters and supported by suggestive laboratory findings
Non Rheumatic Conditions with +ANA

- Autoimmune Hepatitis
- Autoimmune Thyroid Disease
- Hepatitis C
- Lymphoma
- Idiopathic Pulmonary Fibrosis
- Aging
Systemic Lupus Erythematosus
SLE - Epidemiology

- F:M 6-10:1
- Peak incidence – 15-40 years old
- Affects 1 in 2000 individuals but prevalence varies with race, ethnicity, and socioeconomic status
- Incidence 2-4 times greater in African Americans and Hispanics than Caucasians in the U.S.
SLE Antibodies and Clinical Associations

- dsDNA (40-60%)
- Sm (smith)
- ssA (Ro) (30-45%)
- ssB (La) (10-15%)
- Phospholipids, B2-glycoprotein (30%)

- High specificity SLE can correlate with disease activity
- High specificity SLE
- Neonatal lupus, SS, SCLE, Photosensitivity
- Neonatal lupus, SS
- LAC, thrombosis, recurrent fetal loss, thrombocytopenia
SLE – Organ Involvement

- Skin – photosensitivity, malar rash, discoid rash, SCLE, panniculitis, vasculitis
- Mucosal – oral, nasopharyngeal ulcers
- Arthritis – non-erosive
- Serositis – pleuritis, pericarditis
- Renal – proteinuria (>0.5 gm/24 hr or >+3), cellular casts
- Neurologic – seizures, psychosis
- Hematologic – hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia
SLE – diagnostic criteria (4/11)

• Malar rash - Hematologic disorder
• Discoid rash - Immunologic disorder
• Photosensitivity - ANA
• Oral ulcers
• Arthritis
• Serositis
• Renal disorder
• Neurologic disorder
Treatment - SLE

• Symptomatic for non life- / non organ-threatening disorders
  – Education
  – Avoid UV exposure
  – Avoid cigarette exposure
  – NSAIDS
  – Plaquinil
  – Balance rest/activity
  – (Low dose steroids)
Treatment – SLE

• Aggressive treatment for life or organ threatening disorders
  – High dose corticosteroids
  – Azothioprim
  – Methotrexate
  – Cyclophosphomide
  – Mycophenylate Mofetil
  – Rituxamab
Sjogren’s Syndrome
Sjogren’s Syndrome (SS)

- Keratoconjunctivitis sicca (KCS) – systemic disease associated with dry eyes, dry mouth and arthritis
Sjogren’s Syndrome

• Epidemiology
  – 1-2 million in US
  – Primary disease 1/1000 – equivalent to SLE
  – Secondary disease (50%) – associated with another connective tissue disorder (SLE, RA)
  – F:M 9:1
  – Mean age of diagnosis = 50 years
Sjogren’s Syndrome - pathology

- Lymphocytic infiltration of glandular and nonglandular organs
- Lymphocytes predominantly CD4+ helper cells
- B cells account for 20% of the lymphocytes and are responsible for increased immunoglobulin production
Sjogren’s Syndrome

• Initial manifestations of primary disease
  – Xerophthalmia 47%
  – Xerostomia 42%
  – Arthralgia/arthritis 28%
  – Parotid enlargement 24%
  – Raynaud’s 21%
  – Fever/fatigue 10%
  – Dyspareunia 5%
Clinical Manifestations of Dry Mouth

- Difficulty swallowing food
- Inability to speak continuously
- Change in taste
- Burning
- Increased dental caries
- GERD
- Oral candidiasis
- Difficulty wearing dentures
Clinical Manifestations of Dry Eyes

- Foreign body sensation
- Burning
- Itching
- Blurred vision
- Redness
- Photophobia
- Blepharitis
- Corneal ulceration
Testing for Sjogren’s Syndrome

- **Eyes**
  - Schirmer’s
  - Schirmer’s II
  - Rose bengal

- **Mouth**
  - Salivary gland scan
  - Salivary gland biopsy-lymphocytic infiltration
### SS – Extraglandular Manifestations

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgias/arthritis</td>
<td>60-70%</td>
</tr>
<tr>
<td>Raynaud’s</td>
<td>35-40%</td>
</tr>
<tr>
<td>Esophageal dysfunction</td>
<td>30-35%</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>15-20%</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>5-10%</td>
</tr>
<tr>
<td>Lung involvement</td>
<td>10-20%</td>
</tr>
<tr>
<td>Kidney involvement</td>
<td>10-15%</td>
</tr>
<tr>
<td>Liver involvement</td>
<td>5-10%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>2-5%</td>
</tr>
<tr>
<td>Myositis</td>
<td>1-2%</td>
</tr>
<tr>
<td>Lymphoma (44X)</td>
<td>5-8%</td>
</tr>
</tbody>
</table>
SS – Laboratory Findings

- Rheumatoid factor: 85-90%
- ANA: 90%
- ssA: 50-90%
- ssB: 50-90%
SS – Laboratory Findings

• Nonspecific
  – Elevated ESR
  – Hypergammaglobulinemia
  – Anemia
  – Leukopenia
  – Thrombocytopenia
Sjogren’s Syndrome - Treatment

- Artificial tears
- Humidifiers
- Punctual occlusion
- Topical cyclosporine
- Dental care
- Avoid alcohol
- Avoid concentrated sweets
- Salivary substitutes
- Sugarless gum/candy
- Cholinergic drugs (pilocarpine/cevimeline)
Sjogren’s Syndrome - Treatment

- NSAIDS
- Antimalarials
- Treat secondary fibromyalgia
- Corticosteroids
- Immunosuppressives
Sjogren’s Mimics

• Diffuse infiltrative lymphocytosis syndrome (DILS)
• Seen in HIV positive individuals
• Fever, lymphadenopathy, weight loss, bilateral parotid gland enlargement
• Infiltrating lymphocytes are CD8+
• Lack antibodies for SS-A/SS-B
Scleroderma
Scleroderma

• An uncommon connective tissue disease characterized by thickening/fibrosis of the skin
Scleroderma - Epidemiology

• F:M – 3:1
• Peak incidence 35-64 years
• Slightly more common in African American women during child bearing years
• Over all ages, there is no significant predominance among racial groups
Classification of Scleroderma

• Localized
  – Morphea
  – Linear Scleroderma

• Systemic Sclerosis
  – Diffuse systemic sclerosis
  – Localized systemic sclerosis (CREST)

• Overlap
Scleroderma
Cutaneous Disease

- Thickened Skin – abnormal fibroblast activity → normal type I collagen, glycosaminoglycan & fibronectin
  - Loss of sweat glands/hair
  - Skin thickening *always* begins in fingers & progresses proximally
- Calcinosis – cutaneous deposits of basic calcium phosphate
- Telangectasias – dialated venules, capillaries, arterioles on hands, face, lips, oral mucosa
Raynaud’s Phenomenon

- Reversible vasomotor disturbance
- Color changes b/l fingers, toes, ears, nose, lips
- Pallor, cyanosis, erythema
- Response to cold/emotional stress
Raynaud’s Phenomenon
Clinical Factors Suggesting SScl

- +ANA, anticentromere ab, Scl 70
- Nailfold capillary abnormalities
- Tendon friction rubs
- Puffy swollen fingers
- GERD
Raynaud’s Phenomenon
Treatment

• Warmth – hands & body
• Smoking cessation
• Vasodilators
  – Calcium channel blockers
  – Antiadrenergics
  – ACE inhibitors
  – ASA
  – Niacin
<table>
<thead>
<tr>
<th>Clinical</th>
<th>Diffuse SScl</th>
<th>Limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>Telangiectasias</td>
<td>30%</td>
<td>80%</td>
</tr>
<tr>
<td>Calcinosis</td>
<td>5%</td>
<td>45%</td>
</tr>
<tr>
<td>Raynaud’s</td>
<td>85%</td>
<td>95%</td>
</tr>
<tr>
<td>Arthralgias/Arthritis</td>
<td>80%</td>
<td>60%</td>
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</table>
## Scleroderma Organ System Involvement

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Diffuse SScl</th>
<th>Limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tendon friction rub</td>
<td>65%</td>
<td>5%</td>
</tr>
<tr>
<td>Myopathy</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Esophageal</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Pulm fibrosis</td>
<td>35-59%</td>
<td>35%</td>
</tr>
<tr>
<td>Pulm HTN</td>
<td>&lt;1%</td>
<td>12%</td>
</tr>
<tr>
<td>CHF</td>
<td>10%</td>
<td>1%</td>
</tr>
<tr>
<td>Renal crisis</td>
<td>15%</td>
<td>1%</td>
</tr>
</tbody>
</table>
Scleroderma
Gastrointestinal Involvement

- Esophageal dysmotility
- Bowel dilatation
- Bacterial overgrowth
- Malabsorption
- Large bowel diverticuli
- Watermelon stomach – gastric antral venous ectasia
## Scleroderma Lung Disease

<table>
<thead>
<tr>
<th></th>
<th>Interstitial Lung Disease</th>
<th>Pulmonary Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized Disease</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Limited Disease</td>
<td>Bibasilar Nonprogressive</td>
<td>8-28% Poor prognosis</td>
</tr>
<tr>
<td>(CREST)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse SScl</td>
<td>31-59% can progress and lead to death</td>
<td>Rare</td>
</tr>
</tbody>
</table>
Scleroderma Lung Disease

- Interstitial Lung Disease
  - Limited basilar involvement
  - Progression to middle and upper lobes
    - Inflammatory findings suggest better response to immunosuppressive therapies – prednisone, cytoxan, MTX
Scleroderma Lung Disease

- Pulmonary artery hypertension
  - Associated with significant morbidity and mortality
  - Progressive increase in pulmonary vascular resistance, right heart failure, and death
  - Eight current FDA approved therapies for PAH
  - Early recognition and aggressive treatment by an experienced physician is key
Systemic Sclerosis
Cardiac Involvement

• 50% at autopsy
• Clinical symptoms uncommon
  – Pericardial effusion
  – Myocardial fibrosis
  – CAD/vasculopathy (steroids)
  – Conduction defects
  – CHF
Systemic Sclerosis
Renal Involvement

• Hypertension
• Acute renal crisis
  – ACE inhibitors (diastolic BP< 90mm Hg)
Systemic Sclerosis
Bone/Articular Involvement

- Bone resorption
  - Ribs, mandible, acromion, radius, ulna
- Arthralgias
- Hand deformities / skin tightening
- Tendon friction rubs (wrist, ankles, knees)
- Myopathy/myositis
Systemic Sclerosis
Traditional Drug Therapies

- Colchicine
- P-Aminobenzoic Acid
- D-Penicillamine
- Chlorambucil
- Corticosteroids (not favored due to potential complications)
Systemic Sclerosis
Experimental Therapies

- Relaxin
- Methotrexate
- Photophoresis
- 5-Fluorouracil
- Cyclosporine
- Gamma interferon
- Plasmapheresis
- Immunosuppression – cytoxan, mycophenolate mofitil, autologous hematopoietic stem cell trans.
- Biologics in development to neutralize TGF-B
- Recent reports of encouraging results with rituxamab / imatinab