SYSTEMIC SCLEROSIS: MAKING AN EARLY DIAGNOSIS AND SCREENING FOR SYSTEMIC MANIFESTATIONS

AAD 2016
I have no conflicts of interest or disclosures

I will be discussing non-FDA approved uses of medications
Objectives

- Recognize the subsets of systemic sclerosis
- Confidently make a diagnosis of early systemic sclerosis
- Discuss systemic manifestations of systemic sclerosis, appropriate screening algorithms for these manifestations and treatments
- Evaluation and treatment of Raynaud’s phenomenon and digital ulceration
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Systemic Sclerosis

- Limited cutaneous systemic sclerosis
  - previously CREST

- Diffuse cutaneous systemic sclerosis

- Systemic sclerosis sine scleroderma
Systemic Sclerosis

- Limited cutaneous systemic sclerosis
  - previously CREST

- Diffuse cutaneous systemic sclerosis

- Systemic sclerosis sine scleroderma
Limited Cutaneous Systemic Sclerosis

Skin

Diffuse Cutaneous Systemic Sclerosis

By definition requires proximal involvement

Systemic Sclerosis: Red puffy hands
Sclerodactyly
Systemic Sclerosis: Sclerodactyly
Limited Cutaneous Systemic Sclerosis

Diffuse Cutaneous Systemic Sclerosis

Raynaud's

Long slow course (8 to 10 years) + nailfold capillary changes

Explosive course (1 to 2 years) + nailfold capillary changes

Systemic Sclerosis: Raynaud’s phenomenon and digital ulcers
Dermoscopy: Nailfold Capillary Changes

Normal

Nailfold Capillary Dilation

Dilation, hemorrhage, drop-out


Systemic Sclerosis: Acro-osteolysis
Limited Cutaneous Systemic Sclerosis

Autoantibodies

+ANA

+anti-centromere

+Scl-70

+RNA polymerase III

Diffuse Cutaneous Systemic Sclerosis

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Systemic Sclerosis: Making the Diagnosis

+ANA

+ anti-centromere
OR
+ Scl-70
OR
+ RNA polymerase

Early
Objectives

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Limited Cutaneous Systemic Sclerosis

Diffuse Cutaneous Systemic Sclerosis

Systemic comorbidities

ILD

Isolated PAH

Renal Crisis

Systemic Sclerosis: Highest disease specific mortality of all CTDs

Age, Sex Matched Controls

Isn’t their Rheumatologist going to do this?


Limited Cutaneous Systemic Sclerosis

Diffuse Cutaneous Systemic Sclerosis

Systemic comorbidities

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Systemic Sclerosis: ILD Screening

- Pulmonary Function Test with DLCO
  - At diagnosis
  - Annually thereafter

ILD and Pulmonary Function Tests (PFTs)

Decreased lung volumes

Decreased Forced Vital Capacity (FVC)

Decreased diffusion capacity for oxygen (DLCo)
**Systemic Sclerosis: ILD Screening**

- **Restrictive pattern**
  - Decreased lung volumes
  - FVC < 80% predicted
  - Reduced DLCO
    - Recommend HRCT for further evaluation

- **Isolated low DLCO**
  - Indicative of PAH or ILD
  - Recommend HRCT to evaluate for ILD
  - Recommend TTE for PAH screening

## SScl-Associated ILD Therapy

### Table 1: The final set of 14 recommendations from EULAR scleroderma trials and research group (EUSTAR), 2009

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV SScl-ILD</td>
<td>A</td>
</tr>
</tbody>
</table>

In view of the results from two high-quality RCTs and despite its known toxicity, cyclophosphamide should be considered for treatment of SScl-ILD.

### Treatment

#### Induction

- **Usually:** IV Cyclophosphamide (65%)
- **Occasionally:**
  1. Oral Cyclophosphamide (65%)
  2. Mycophenylate Mofetil (48%)
  3. Azathioprine (45%)

#### Maintenance

- **Usually:** Mycophenylate Mofetil (73%)
- **Occasionally:**
  1. Azathioprine (47%)
  2. IV Cyclophosphamide (40%)
  3. Oral Cyclophosphamide (32%)

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Rituximab

Imatinib

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http://dx.doi.org/10.1016/j.autrev.2015.02.002
Limited Cutaneous Systemic Sclerosis

Diffuse Cutaneous Systemic Sclerosis

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Isolated PAH

Renal Crisis

Pulmonary hypertension

- Several possible etiologies
  - Pulmonary artery hypertension
  - Left heart disease
  - Lung diseases and/or hypoxemia
  - Chronic thrombotic and/or embolic disease
Systemic Sclerosis: PAH Screening

Systemic Sclerosis: PAH Screening

- TTE – at diagnosis and annually
  - Estimated PAP of > 30mmHg
  - Hypertrophy/enlargement of RV
  - RA enlargement
  - Leftward shift of interventricular septum
  - Tricuspid valve insufficiency

- Referral to Cardiology
  - Right heart catheterization

SScl-Associated PAH Therapy

- Endothelin receptor antagonists (ERA)
  - Ambrisentan
  - Bosentan
  - Macitentan

- Phosphodiesterase inhibitors
  - Sildenafil
  - Tadalafil

- Prostanoids
  - Epoprostenol
  - Iloprost
  - Selexipag (oral)

- Guanylate cyclase stimulator
  - Riociguat

No head-to-head comparison trials

Limited Cutaneous Systemic Sclerosis

Diffuse Cutaneous Systemic Sclerosis

Systemic comorbidities

ILD

Isolated PAH

Renal Crisis

Systemic Sclerosis: Renal Crisis

Renal crisis

- New onset SBP >140, DBP >90
- Rise in SBP >30 mmHg or DBP > 20 mmHg
- AND 1 of 5:
  - Increased Cr by 50% over baseline
  - Dipstick proteinuria > 2+
  - Hematuria 2+ by dipstick or 10 per HPF
  - Thrombocytopenia < 100,000
  - Hemolysis

- Normotensive renal crisis = one of 5 above AND increase Cr >50% over baseline or >120% over upper limit of normal
Systemic Sclerosis: Renal Crisis Screening

- Renal crisis
  - Blood pressure each visit
  - Home BP cuff
  - Creatinine, UA, CBC at regular visits
  - Avoid treatment with corticosteroids

- Treatment: Admission and captopril
Systemic Sclerosis Screening Summary

- Detection of Interstitial Lung Disease (ILD)
  - Regular PFTs with DLCo
  - High resolution CT scan for restriction/low DLCo

- Detection of Pulmonary Artery Hypertension
  - Regular TTEs
  - Right heart cath for increased ePAP, or high pre-test prob

- Early detection of renal crisis
  - Home blood pressure cuffs
  - Office visit BP, CBC, Cr, UA
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Raynaud’s Phenomenon: Treatment
Raynaud’s Phenomenon: Treatment

Dermatology

Preventive Measures
- Avoid known triggers
- Avoid cold
- Dress in layers
- Smoking cessation
- Avoid vasoconstrictants (caffeine, antihistamines, decongestants, stimulants and beta-blockers)

CCB
- Consider adding ARB, SSRI, alpha blockers, topical nitrate, aspirin

Dihydropyridines (nifedipine, nicardipine, amlodipine)

PDE5 inhibitor
- Sildenafil (20 mg QD to TID), Tadalafil (10-20 mg QD)

Botulinum toxin-A


### Table 1 Summary of Available Reports Based on Study Design, Criteria for Botulinum Injection, and Patient Symptom Demographics

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Indications</th>
<th>Excluded</th>
<th>Diagnostic Testing</th>
<th>N</th>
<th>Symptom Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fregene et al (2009)</td>
<td>Retrospective</td>
<td>Failed MM, pain, chronic ulcers, gangrene</td>
<td>Previous sympathectomy, active infection</td>
<td>Ultrasound, angiography</td>
<td>26</td>
<td>Pain: 75% improved&lt;sup&gt;a&lt;/sup&gt; Color: 56% improved dTCO₂: 57% improved&lt;sup&gt;a&lt;/sup&gt; Ulcers: 48% healed</td>
</tr>
<tr>
<td>Neumeister et al (2009)</td>
<td>Retrospective</td>
<td>Ischemic pain, decreased pulses, chronic ulceration</td>
<td>History of botox allergy</td>
<td>MRA, angiography</td>
<td>19</td>
<td>Pain: 84% improved Ulcers: 100% improved Doppler: −48.15% to 317.39%</td>
</tr>
<tr>
<td>Sycha et al (2004)</td>
<td>Pilot/Prospective</td>
<td>Primary or secondary RP</td>
<td>None</td>
<td>None</td>
<td>2</td>
<td>Pain: Improved Stiffness: Improved Doppler: Treated fingers improved 58% vs untreated</td>
</tr>
<tr>
<td>Van Beek et al (2007)</td>
<td>Prospective</td>
<td>Failed MM, chronic ulcers</td>
<td>None</td>
<td>MRA, angiography</td>
<td>11</td>
<td>Pain: 100% improved Ulcers: 100% &quot;small&quot; ulcers healed</td>
</tr>
<tr>
<td>Neumeister et al (2010)</td>
<td>Retrospective</td>
<td>Failed MM, ischemic pain</td>
<td>None</td>
<td>MRA, angiography</td>
<td>33</td>
<td>Pain: 85% improved Ulcers: 100% improved Doppler: −48.15% to 317.39%</td>
</tr>
<tr>
<td>Uppal et al (2014)</td>
<td>Prospective</td>
<td>RP w/SScI</td>
<td>None</td>
<td>None</td>
<td>20</td>
<td>Non-stat sig sub</td>
</tr>
</tbody>
</table>

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Raynaud’s Phenomenon: Treatment

- Botulinum toxin-A 5 U/0.1 mL
- cumulative total dose 100 U/hand
- 10-20 U per site
Raynaud’s Phenomenon: Treatment

**Dermatology**

- **Preventive Measures**
  - CCB
  - Consider adding ARB, SSRI, alpha blockers, topical nitrate, aspirin
  - PDE5 inhibitor
  - Botulinum toxin-A

**Consultants**

- **Endothelin Receptor Antagonists**
  - Intravenous prostanoid
  - Anticoagulation
  - Debridement
  - Digital sympathectomy

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