Scleroderma in African Americans

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Scleroderma in African Americans

- Frequency and outcomes of Scleroderma in African Americans
- Specific clinical features and major problems that are different in African Americans
- Discussion of possible reasons why these differences occur
Incidence of Scleroderma by Age, Sex, and Race

SSc in AA
- More common,
- Younger onset than in whites
Mortality Rates

AAs have a worse prognosis.
Presentation of Scleroderma in African Americans

- AAs have non specific symptoms, joint pains and a positive ANA, so are often diagnosed initially with lupus.

- Initially treated with Plaquenil which may help joints but doesn’t do anything else, so delay of diagnosis of scleroderma and other problems,
Presentation of Scleroderma in African Americans

- **Raynaud’s**
  - Raynaud’s harder to recognize by A-As
  - Raynaud’s less common as first symptom and generally not for prolonged duration

- **Skin**
  - Pigment changes often first thing, both hyper and hypo-pigmentation
  - Skin thickening diffuse but less severe than Caucasian diffuse
Pigment Changes in Scleroderma
Body Image Dissatisfaction

Global Distress by Ethnicity

- Moderate to Severe Distress
- Mild Distress

Gordon, J, Arthritis Rheum 2006
Body Image Features which Caused Moderate to Severe Distress

<table>
<thead>
<tr>
<th>Feature</th>
<th>African-Americans</th>
<th>Caucasians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening</td>
<td>32%</td>
<td>33%</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>52%*</td>
<td>25%*</td>
</tr>
<tr>
<td>Facial changes</td>
<td>44%</td>
<td>31%</td>
</tr>
<tr>
<td>Wrinkles above upper lip</td>
<td>8 %*</td>
<td>36%*</td>
</tr>
<tr>
<td>Dark body pigment</td>
<td>48% *</td>
<td>16%</td>
</tr>
<tr>
<td>White body pigment</td>
<td>32% *</td>
<td>16%</td>
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</table>
Clinical Features, University of Pittsburgh

<table>
<thead>
<tr>
<th>Features</th>
<th>A-A</th>
<th>Caucasians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>202</td>
<td>2945</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>76</td>
<td>81</td>
</tr>
<tr>
<td>Age onset, yrs</td>
<td>38*</td>
<td>43*</td>
</tr>
<tr>
<td>Diffuse SSc %</td>
<td>51 *</td>
<td>43*</td>
</tr>
</tbody>
</table>

*p<0.01

## Severe Organ Involvement

<table>
<thead>
<tr>
<th>Organ (%)</th>
<th>African American</th>
<th>Caucasian</th>
</tr>
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<tbody>
<tr>
<td>Skin</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>Muscle</td>
<td>27***</td>
<td>12***</td>
</tr>
<tr>
<td>GI</td>
<td>17*</td>
<td>12*</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>32***</td>
<td>13***</td>
</tr>
<tr>
<td>PAH</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Heart</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Kidney</td>
<td>10</td>
<td>8</td>
</tr>
</tbody>
</table>

Muscle Involvement in African Americans

- **Inflammatory**
  - Overlap with myositis, Increased ↑CPK (muscle enzyme blood test), proximal weakness, needs steroids

- **Fibrotic**
  - Mild ↑CPK, mild weakness, but often leads to contractures. Treat with exercise and maybe low dose prednisone.

- ↑CPK only
  - ↑CPK without any weakness.
Treatment for Muscle

- Range of motion and strengthening exercises particularly for shoulders and arms.
- Anti-inflammatory and/or pain medication to help with discomfort so you can do the exercises.
- Walking to improve endurance and exercise capacity.
- Cardiopulmonary exercise programs.
GI - Small Bowel Symptoms

- Nausea
- Bloating
- Full feeling
- Vomiting
- Diarrhea
- Malabsorption
- Weight loss
- Constipation
Scleroderma Small Bowel
Treatment of Intestinal Problems

• Reflux/heartburn
  – Prevention-not eating before bed
  – Head of bed elevated
  – PPI-prilosec, Nexium etc

• Bloating/distention
  – Maybe probiotic

• Diarrhea (bacterial overgrowth)
  – Antibiotics

• Constipation - Fiber, miralax
**Lung Disease as Cause of Death in Scleroderma**

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>All SSc</th>
<th>Non-SSc causes</th>
<th>SSc causes</th>
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</thead>
<tbody>
<tr>
<td><strong>Pulmonary Hypertension</strong></td>
<td>25%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pulmonary Fibrosis</strong></td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heart</strong></td>
<td>14%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td>11%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lung Disease has many Symptoms

Symptoms are non specific

- Shortness of breath with exertion
- Fatigue
- Chest Pain
- Cough
- Fainting/near-fainting
- Edema
- Increased digital ulcers
SHORTNESS OF BREATH (SOB) - Dyspnea

- Shortness of breath with activity
- Scleroderma patients adapt to breathing difficulties; initially may deny SOB.
- Patients often don’t recognize SOB. May just feel fatigued/tired.
- So carefully think about breathing, can you climb stairs, carry bags, do things as fast or as easy as you did last year?
- Tell your doctor about changes in breathing
Lung Disease in Scleroderma
Pulmonary Fibrosis (scarring)
Inflammation in Pulmonary Fibrosis

- Inflammation occurs first and leads to scarring in lung, more severe in first 5-7 years of disease.

- Occurs more often in African-Americans.
Fibrosis Pathology

NORMAL

Air Cells

Fibrosis

Air Cells

Air Cells
Cytokines arrays in lavage of A-A and Caucasian

Hepatocyte Growth Factor inhibits fibrosis by blocking the CTGF which is overexpressed.

HGF is decreased in African-Americans (arrow).

Bogathkevich GS, Silver RM, Arth Rheum, 2007
RISK FACTORS FOR SEVERE FIBROSIS

- Early disease, diffuse scleroderma, anti-Scl-70 or nucleolar antibody
- African Americans, more common and more severe
- FVC < 75% early in disease (<18m)
- FVC decreasing by > 10%/year
- Shortness of breath with exercise, cough, but often silent
Pulmonary Function Tests (PFTs)

Breathing tests help determine the kind of breathing problem that is present.
Pulmonary Function Tests (PFTs)

**Forced Vital Capacity (FVC)** - Measures how much air you can get in. With a lot of scar tissue (fibrosis), can’t get as much air in. Fibrosis causes decreased FVC

**Diffusing Capacity (DLCO)** – Measures whether oxygen diffuses from air cells to blood stream. Can be decreased in fibrosis or with thickened blood vessels.
Loss of volume from Scarring in 76 Patients With Severe Fibrosis

Median loss of vital capacity/yr:
- 0-2 years: (n=36)
- 2-4 years: (n=35)
- 4-6 years: (n=23)
- 6-8 years: (n=37)
- 8-10 years: (n=11)
- >10 years: (n=9)

Duration of disease (yr) during which PFTs were obtained:
- 0-2 years
- 2-4 years
- 4-6 years
- 6-8 years
- 8-10 years
- >10 years
High Resolution CT Scan of Chest (HRCT)

Many x-rays going throughout the lungs, Do NOT need contrast.
Medical treatment needs to be early and aggressive
Scleroderma Lung Study I

Double blind, placebo controlled, cytoxan vs placebo in patients with inflammation.

1 year of treatment and followed for 1 year

Toxicity - low blood counts, infections, bladder irritation, bleeding.
Summary of SLS Study

Cytoxan group improved

- FVC improved
- Shortness of breath improved
- Function improved
- Improvement on HRCT
Other Treatment

- Results of SLS II - mycophenolate mofetil (cellcept) as effective but better tolerated than cytoxan

- New clinical trials (added on to Cellcept)
  - Pirfenidone - ongoing clinical trial
  - Nintendinab
  - Anti Integrin receptor

Many drug companies interested in Scleroderma pulmonary fibrosis
What does this mean for YOU?

• Early disease (< 5 years)
  – Need baseline studies – PFT, CT scans –
  – If necessary, need aggressive treatment
  – Need repeat tests every 4-6 m, then every 12 months until stable, then every 1-2 yr.

• Later disease – chronic fibrosis – need to prevent aspiration, infection and watch for low oxygen, and pulmonary hypertension, and EXERCISE!!
Pulmonary Arterial Hypertension
Pulmonary Arterial Hypertension

Healthy Pulmonary Artery

Increase blood flow

Vessel dilates with increased flow, no increased pressure is required

Stiffens Thickens Pulmonary Vascular Disease

Increase blood flow

Vessel is unable to dilate, right heart has to push harder to compensate
Pulmonary Arterial Hypertension

**Lungs**

35/15

Thickened blood vessels

Veins bring back blood to heart

**Body**

130/80

Veins bring back blood to heart
Pulmonary Arterial Hypertension

Increased lung pressures: 85/30 mmHg

Lungs

Veins bring blood back to heart

Increased stress on right heart (harder to push blood through vessels)

Body

Veins bring blood back to heart

Thickened blood vessels
Pulmonary Hypertension
Risk Factors

- Long duration of Raynaud’s
- Limited Scleroderma (CREST Syndrome) - Anti-centromere antibody
- African-American patients with nucleolar antibodies
- Shortness of breath with exercise
Pulmonary Hypertension
Risk Factors

- Long duration of Raynaud’s
- Limited Scleroderma (CREST Syndrome) - Anti-centromere antibody
- African-American patients
- Shortness of breath with exercise
- DLCO < 60% predicted
- FVC%/DLCO% > 1.6
<table>
<thead>
<tr>
<th></th>
<th>PAH</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCO % pred.</td>
<td>52%</td>
<td>81%</td>
</tr>
<tr>
<td>Time to PAH (y)</td>
<td>4.5</td>
<td>6.0</td>
</tr>
</tbody>
</table>
DLCO (% predicted) in Patients Who Developed PAH vs Controls

Mean DLCO, % pred.

Years Prior to PAH

Controls
PAH
Echocardiogram
Echocardiogram Problems

- Screening echo important BUT
- Pulmonary artery pressure is ONLY an estimate.
- False values are common
- Other causes of increased pressure occur.
- Treatment of PAH should NOT be started without a right heart catheterization
Right Heart Catheterization - Diagnostic Gold Standard
PULMONARY ARTERIAL HYPERTENSION TREATMENT

Exciting Times
Treatment

Oral therapy
- Revatio or Adcirca
- Tracleer, Letairis or Macitentan
- Riociguat

Inhaled therapy
- Ventavis or Tyvaso

Subcutaneous therapy
- Treprostinal- Remodulin

Intravenous therapy
- Treprostensal-Remodulin
- Prostacyclin-Flolan
What does this mean for YOU?

- All patients need to have baseline PFTs and know what their DLCO and ratio is.
- If high risk, then PFTs and echo every year.
- If echo abnormal, need right heart catheterization.
- Very serious illness, but treatment is available.
Clinical Course of Scleroderma in African-Americans

African-Americans have a worse prognosis

• Occurs in younger people
• More patients with diffuse scleroderma
• More have severe small bowel involvement
• More have severe pulmonary fibrosis
• Pulmonary hypertension occurs earlier, in younger patients and diffuse SSc.
Disparities in Scleroderma in African-Americans

Potential reasons:
Socio-economic status
Access, coverage and quality of care
General health care attitudes
Cultural differences
Disease differences:
  Antibodies
  Genetics
ANTIBODIES in Scleroderma

Diffuse

Anti - Scl 70
anti-RNA pol III
Anti U3 - RNP
anti-U1-RNP

Limited

anti-Centromere
Nucleolar
anti-Th
# Antibodies in A-A and C Patients with SSc

<table>
<thead>
<tr>
<th></th>
<th>A-A</th>
<th>C</th>
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<tbody>
<tr>
<td>U1 RNP</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>U3 RNP</td>
<td>40%</td>
<td>2%</td>
</tr>
<tr>
<td>Scl 70</td>
<td>27%</td>
<td>21%</td>
</tr>
<tr>
<td>ACA</td>
<td>7%</td>
<td>25%</td>
</tr>
<tr>
<td>Th/To</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Pol III</td>
<td>3%</td>
<td>31%</td>
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</table>

A-A ABs

C ABs
Patients with Scl 70 (anti-topoisomerase) antibody

<table>
<thead>
<tr>
<th>Features</th>
<th>African-American (n= 48)</th>
<th>Caucasian (n= 490)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (mean ±SD)</td>
<td>36.6</td>
<td>43.3</td>
<td>0.005</td>
</tr>
<tr>
<td>Diffuse disease %</td>
<td>71 %</td>
<td>65%</td>
<td>NS</td>
</tr>
<tr>
<td>Severe pulmonary fibrosis</td>
<td>44%</td>
<td>18%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Steen V, Arth Rheum, 2012
Patients with U3 RNP antibody

<table>
<thead>
<tr>
<th>Features</th>
<th>African-American (n= 24)</th>
<th>Caucasian (n= 61)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (mean)</td>
<td>38.5</td>
<td>39.9</td>
<td>NS</td>
</tr>
<tr>
<td>Severe GI tract</td>
<td>26%</td>
<td>9%</td>
<td>0.05</td>
</tr>
<tr>
<td>Severe Pulmonary fibrosis</td>
<td>14%</td>
<td>9%</td>
<td>NS</td>
</tr>
</tbody>
</table>
Genetic Causes for Differences

- African Americans and Caucasians have different frequency of gene markers in general.
- The auto-antibodies are associated with specific gene markers, so African Americans have a different set of auto-antibodies.
- Thus, African-Americans have a different frequency of disease manifestations.
Genome Research in African American Scleroderma Patients (GRASP)

- NIH study - studying the genetic associations in African Americans
- Exciting opportunity to learn why scleroderma is different in African-Americans
- Hopefully will lead to new directions for treatment
Other Differences

• There are other diseases that African-American’s have earlier and more severe (hypertension, kidney disease)

• A factor, TGF beta, plays a role in scleroderma and these other diseases.

• AA have more TGF beta in blood and tissue than Caucasians perhaps contributing to earlier and more severe disease. Again a genetic reason.
Specific Fibrosis Differences

- Dr. Rick Silver found differences in A-A and Caucasian in the factors seen in lung fluids (from bronchoscopy).
- He found that these factors were abnormal in healthy A-A as well.
- So perhaps these inherent differences contribute to the more severe fibrosis.
- Trying to find ways to improve these factors.
Summary

• Scleroderma in African Americans is more common and more severe than in Caucasians
• Muscle, small bowel, pulmonary fibrosis and pulmonary hypertension cause severe problems
• Health disparities may play a role in the difference of outcomes
• Disease severity is largely because of different disease subtypes in African Americans
• Genetics may also play an important role
Pulmonary Fibrosis

Some requires chemotherapy to stop inflammation and prevent scarring.

Late in disease - need to prevent infections (pneumonia, reflux and aspiration) and prevent low oxygen in blood which puts strain on heart and leads to pulmonary hypertension.