The Lung in Scleroderma

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### Lung Disease as Cause of Death in Scleroderma

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>All SSc</th>
<th>SSc causes</th>
<th>Non-SSc causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Hypertension</td>
<td>25%</td>
<td></td>
<td>53%</td>
</tr>
<tr>
<td>Pulmonary Fibrosis</td>
<td>23%</td>
<td></td>
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<tr>
<td>Kidney</td>
<td>14%</td>
<td></td>
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<tr>
<td>Heart</td>
<td>14%</td>
<td></td>
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<tr>
<td>GI</td>
<td>11%</td>
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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)
Fibrosis Pathology

NORMAL

Air Cells

Air Cells

Fibrosis

Air Cells

Air Cells
RISK FACTORS FOR SEVERE FIBROSIS

- Early disease, diffuse scleroderma, anti-Scl-70 or nucleolar antibody
- African Americans, more common and more severe
- Abnormal breathing tests early in disease (usually 1st 5 years)
- Breathing (on PFTs) decreasing by > 10%/year
- Shortness of breath with exercise, cough, but often silent
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

Duration of disease (yr) during which PFTs were obtained

- 0-2 (n=36)
- 2-4 (n=35)
- 4-6 (n=23)
- 6-8 (n=37)
- 8-10 (n=11)
- >10 (n=9)
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
Inflammation in Pulmonary Fibrosis

- Inflammation occurs first and leads to scarring in lung, more severe in first 5-7 years of disease – so we have focused on stopping inflammation and preventing fibrosis.

- New drugs are trying to treat fibrosis.
Scleroderma Lung Study I

• Double blind, placebo controlled, 1 year cytoxan vs placebo in patients.
• Cytoxan group improved:
  – FVC difference of 2.94% predicted
  – Improved symptoms of shortness of breath, improved function
  – HRCT better at 12m
  – BUT no difference from placebo after 2 years

Scleroderma Lung Study II

Double blind, 1 year oral cytoxan (+1 year placebo) vs 2 years mycophenolate mofetil in patients with early (<7 years) SSc with ILD

142 patients: 52 years old, early disease, mean 2.5 years
FVC 66%, DLCO 54%
26% fibrosis on CT.
Scleroderma Lung Study II

Also, improved symptoms, and well being, and skin
Scleroderma Lung Study II: Side effects and withdrawal

• More patients in cytoxan group had severe side effects so that they withdrew from study
• Patients on mycophenolate had side effects (mild ones) but could remain on the drug.
• Serious low blood counts and infections in cytoxan group only
NEW TRIALS

• Nintedanib – SENSCIS Trial - drug approved for IPF, Patients can be on background mycophenolate; drug vs placebo

• Anti –integrin receptor - STRATUS- Experimental anti-fibrotic – on background mycophenolate, 4 out of 5 patients get the drug, but it is a monthly infusion.

• Pirfenidone – another drug approved for IPF- SLS III, New diagnosis, Upfront Mycophenolate, then pirfenidone vs placebo
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

RA, LV, RV
Pulmonary Arterial Hypertension

Increased lung pressures 85/30

Lungs 35/15

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

Thickened blood vessels

Veins bring back blood to heart

Body 130/80

Veins bring back blood to heart
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
## Evidence of PAH Prior to PAH Diagnosis

<table>
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<tr>
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<th>PAH</th>
<th>Controls</th>
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<tbody>
<tr>
<td>DLCO % pred.</td>
<td>52%</td>
<td>81%</td>
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<tr>
<td>Time to PAH (y)</td>
<td>4.5</td>
<td>6.0</td>
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</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, Adempus
  Tracleer, Letairis or Opsumat
  Orenitram, Uptravi
Inhaled therapy
  Ventavis or Tyvaso
Subcutaneous therapy-
  Treprostinal - Remodulin
Intravenous therapy
  Treprostenal-Remodulin
  Prostacyclin-Flolan
NEW TRIALS for PH

• Trials specifically for Connective Tissue Disease patients with PH.
  – Catalyst - Reata – Exciting study for patients with PAH from scleroderma with an add on drug, Bardoxolone
  – Lariat - Reata – Even more exciting study for patients with scleroderma who have pulmonary fibrosis AND PH (first study)
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.
Summary

• Lung disease is the most serious complication in scleroderma
• Pulmonary fibrosis needs to be identified early and treated early and aggressively, mycophenolate but new trials.
• Pulmonary arterial hypertension occurs later in disease and needs to be looked for in all long standing patients. LOTS of treatment and new study.
Clinical Trials at Georgetown

- Raynaud’s study
- Digital Ulcer study
- Pulmonary fibrosis – 3 different studies, less than 7 years of disease
- Pulmonary hypertension – add on therapy
- Contact Dr. Steen or coordinators. steenv@georgetown.edu, See Handout