Lung Disease in Systemic Sclerosis: New Insights and Treatment Options

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Lung Disease in Systemic Sclerosis: New Insights and Treatment Options

- Pathophysiology
- Lung Disease
- Current therapies
- Future targets for therapy
Man knows much more than he understands.

ALFRED ADLER
Human Fibroblast Cell
Systemic Sclerosis Pathophysiology: What goes wrong?

- Auto antibodies
- Skin thickening
- Abnormal blood vessels
Systemic Sclerosis Pathophysiology: What goes wrong?

- Auto antibodies
- Skin thickening
- Abnormal blood vessels
Auto Antibodies

- Self-made proteins
- Attach and “attack”
- Auto antibodies attack self
- Most common ABs in SScl
  - Scl-70
  - Anti-centromere
  - U3-RNP
Other Auto-Immune Diseases

- Rheumatoid arthritis
- Sjogren’s disease
- Systemic lupus
- Inflammatory bowel disease
- Thyroid disease
- Celiac sprue
- Etc., etc., etc.
How do we know the immune system is involved in SScl?

- Auto antibodies >90% pts with SScl
- Immunologic activation is present
  - Elevated levels of growth factors, chemokines, cytokines, white blood cells
- Suppressing the immune system may help in some patients
Pathophysiology: What goes wrong?

- Auto antibodies
- Skin thickening
- Abnormal blood vessels
Human Fibroblast Cell
- Made by fibroblasts
- 25-35% of all protein in the body
- Only made by animals
- Gives structure to tendons, skin, bones, cartilage
Normal Aging

- Thinning of all layers of the skin
- Loss of collagen support in the epidermis and dermis
Scleroderma Skin Changes

- Epidermis
- Dermis
- Fat cells

○ = Collagen
Normal Lung

Interstitial Lung Disease
Pathophysiology: What goes wrong?

- Auto antibodies
- Skin thickening
- Fibroblasts gone wild
- Abnormal blood vessels
Pathophysiology: What goes wrong?

- Auto antibodies
- Skin thickening: Fibroblasts gone wild
- Abnormal blood vessels
Nailfold Capillaroscopy

- increased diameter
- reduced numbers
- increased visibility
- bushy and bizarre shapes
- punctate haemorrhages
Common vascular pathology in multiple sites

- Kidney
- Normal vessel
- Finger
- Pulmonary Artery
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Clinical Signs of Lung Involvement

- Shortness of breath
- Cough
- Fatigue
- Chest tightness or discomfort
- Exercise intolerance
Non-Pulmonary Causes of Symptoms

- Anemia
- Chest restriction due to skin involvement
- Arthritis/Fibromyalgia
- Obesity
- Heart disease
Systemic Sclerosis and Lung Disease

- Interstitial lung disease
- Pulmonary hypertension
- Less common lung conditions
  - BOOP, alveolar hemorrhage, bronchiectasis
Normal Lung

Interstitial Lung Disease
Diagnosing ILD

- High Resolution Cat Scan (HRCT)
- Pulmonary function testing
- Bronchoscopy
- Lung biopsy
Interstitial Lung Disease

- Increased fibroblasts and collagen in the walls of the airs sacs of the lung
- Other names: Scleroderma lung, pulmonary fibrosis, fibrotic lung disease
55-90% of all SScl patients have ILD

Associated with Scl-70 antibody

GERD/aspiration is a cofactor

Progressive disease:
- >20% on initial CT increases risk for progression
- more common with dcSScl
- warrants consideration of treatment
Pulmonary Hypertension = Pulmonary Artery Hypertension (PAH)

- Increased fibroblasts and collagen in the arteries of the lung

- Obstruction to flow:
  - Increased pressure in the blood vessels
  - Back-up of fluid in the legs
  - Impaired oxygen uptake
150 µm

intimal and medial thickening

normal
Symptoms of Pulmonary Hypertension

- Palpitations
- Pain or discomfort
- Lungs: shortness of breath is a common symptom
- Kidneys: sodium and fluid retention are common symptoms
- Liver: tenderness and pain are symptoms caused by congestion
- Swollen ankles are sometimes a symptom
Pulmonary Artery Hypertension (PAH)

- Prevalence estimates 5-50% in SScl
- Higher prevalence in limited systemic sclerosis (IcSScl) versus diffuse cutaneous (dcSScl)
- Associated with anticentromere antibody
- May occur with or without ILD
Right Heart Catheterization: Confirms pulmonary artery hypertension
Improved survival in systemic sclerosis is associated with better ascertainment of internal organ disease: a retrospective cohort study

Denton, et al.


<table>
<thead>
<tr>
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<th>Diffuse cutaneous (dcSSc)</th>
<th>Limited cutaneous (lcSSc)</th>
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<tbody>
<tr>
<td>5-yr survival</td>
<td>Improved 15% (84%)</td>
<td>No change (92%)</td>
</tr>
<tr>
<td>Pulmonary Fibrosis</td>
<td>7% vs. 38%</td>
<td>3% vs. 16%</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>&lt;1% vs. 7%</td>
<td>1% vs. 8%</td>
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Early Detection of Lung Involvement

- **At Diagnosis**: Pulmonary function testing (PFT), echocardiogram, 6 minute walk test, CT scan of the chest, overnight oxygen test

- **Annual Screening**: PFTs and echocardiogram
Why Screen?

• The age of nihilism is over
• Effective treatments for PAH are here
• Major paradigm switch:
  – Treatment focus is more than immunosuppression
  – Future therapies are not just science fiction
  – Clinical trials are available
Lung Disease in Systemic Sclerosis: New Insights and Treatment Options

- Pathophysiology
- Associated Lung Disease
- Current therapies
- Future targets
Scleroderma Treatments

- Immune Suppression
- Biologic Therapies
- Antifibrotic Agents
- Transplantation
  - stem cell transplant
  - lung
Immune Modulating for Interstitial Lung Disease

- Chemotherapies
  - Cyclophosphamide (cytoxan)*, mycophenylate (cellcept), azathioprine (imuran), methotrexate
- Biologic
  - Anti-tumor necrosis factor (infliximab), anti-CD 20 (rituxumab)

*positive study, -negative study
Cyclophosphamide versus Placebo in Scleroderma Lung Disease


- Oral cyclophosphamide x 1 year versus placebo

Results:
- 145/158 completed at least 6 months of treatment
- 2.53% improvement in lung function in cyclophosphamide group at 12-months
- Higher rate of side effects in treatment group

Unanswered questions:
- Is 2.53% lung function clinically meaningful
- Is iv cyclophosphamide as effective with less risk of side effects?
- Is there a better way to choose which patients are at risk for progressive disease
Penicillamine—blocks collagen cross-links
Relaxin—smooth muscle relaxant
ET-1 blockade (Bosentan)—blocks biologic cascade
Pirfenidone

*positive study, `negative study
Current Clinical Trials

• SCOT trial: Scleroderma Cyclophosphamide Or stem cell Transplantation

• ASTIS: Autologous Stem cell Transplantation International Scleroderma Trial
Why might stem cell transplant work?

- The immune system may not recognize self as abnormal and will stop attacking
The Autologous Transplant Process

1. Collection
   Stem cells are collected from the patient's bone marrow or blood.

2. Processing
   Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.

3. Cryopreservation
   Blood or bone marrow is frozen to preserve it.

4. Chemotherapy
   High dose chemotherapy and/or radiation therapy is given to the patient.

5. Reinfusion
   Thawed stem cells are reinfused into the patient.
Autologous Stem Cell Transplant

  - 81% with clinical benefit
  - 73% with more than 25% reduction in skin score
  - 5 year survival 96.2%, 7 year survival 85%
  - Less treatment related complications than prior experience
Current Therapies for PAH

- Supplemental Oxygen
- Diuretics
- Anticoagulation
- Calcium Channel Blockers

Prostacyclins—Intravenous epoprostenol/remodulin (Flolan/Remodulin), subcutaneous treprostinil (Remodulin), inhaled iloprost or remodulin (Ventavis/), oral remodulin (clinical trials)

Endothelin-1 receptor blocking agents—bosentan (Tracleer), ambrisentan (Letaris)

Oral phosphodiesterase 5 (PDE5) inhibitors—sildenafil (Revatio), tadalafil (Adcirca)

Lung Transplantation
## Current Therapies for PAH

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Current Therapies for PAH

**Prostacyclins:**
- intravenous epoprostenol/remodulin (Flolan/Remodulin)
- subcutaneous treprostinil (Remodulin)
- inhaled iloprost or remodulin (Ventavis/Tyvaso)
- oral remodulin (clinical trials)

**Endothelin-1 receptor blocking agents:**
- bosentan (Tracleer)
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**Oral phosphodiesterase 5 (PDE5) inhibitors:**
- sildenafil (Revatio)
- tadalafil (Adcirca)
Lung Transplants

- Significant risks
- More commonly done for ILD than PAH
- Exhaust other options before considering
- Timing: Not too well and not too sick
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Clinical Research Trials

- [http://clinicaltrials.gov](http://clinicaltrials.gov)
- 60+ trials current or future enrolling SScl pts
- Approx. 50% are treatment trials
Future Targets: Anti-growth factors

- Tyrosine Kinase Inhibitors—
  - Imatinib (Gleevec) and others
  - Block a pathway that lead to fibrosis
  - Clinical trials underway for use in skin, PAH and ILD
Screening for lung disease is important for both asymptomatic and symptomatic patients.

Discuss treatment options with your pulmonary physician.

Treat progressive disease.

Early treatment may be important.

Stay tuned...
If you think you can win, you can win.
Faith is necessary to victory.

WILLIAM HAZLITT
Prostacyclins
- Epoprostenol
- Treprostinil
- Iloprost

PDE-5 inhibitors
- Sildenafil
- Tadalafil

Endothelin receptor antagonists
- Bosentan
- Ambrisentan

Endothelin 1 (ET-1)

Endothelial cells

Endothelin A receptor (ETA)

Endothelin B receptor (ETB)

NITRIC OXIDE PATHWAY

VASODILATION AND ANTIPROLIFERATION

Prostacyclin pathway

Endothelin pathway

Nitric oxide pathway

SMP MUSCLE CELLS