Scleroderma

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Nomenclature Synonyms

Scleroderma

Progressive Systemic Sclerosis

Systemic Sclerosis
Scleroderma

- Chronic systemic autoimmune disease characterized by fibrosis of the skin as well as internal organs, e.g., lung, heart, gastrointestinal tract, and kidneys.
Limited vs. Diffuse Scleroderma

- Cutaneous criteria:
  - **Limited**: involves skin distal to elbows and knees, as well as face
  - **Diffuse**: involves skin of proximal extremities and face, as well as trunk

- Implications regarding natural history and prognosis
Mortality in Scleroderma

- Limited scleroderma
  - 90% 5-year survival
  - 75% 10-year survival

- Diffuse scleroderma
  - 70% 5-year survival
  - 50% 10-year survival
Swollen Digits in Scleroderma
Scleroderma Facial Appearance
Diffuse Scleroderma
Dermatopathology

Excessive Dermal Deposition of Collagen and ECM proteins
Raynaud’s Phenomenon

- Early manifestation of disease in >97% of scleroderma patients, preceding sclerodactyly by months to years

- Vasospasm of the digital microvasculature resulting in:
  - Digital ischemia (pallor)
  - Digital hypoxia (cyanosis)
  - Digital reactive hyperemia (erythema)
Raynaud’s Phenomenon

Scleroderma
Raynaud’s Phenomenon

Scleroderma
Digital Arteriogram in Raynaud’s Disease
Digital Capillary Microscopy in Scleroderma

- Normal
- Capillary dilatation
- Capillary “dropout”
Facial Telangiectasias in Limited Scleroderma
Epidemiology of Scleroderma

- Incidence: 2 per 100,000
- Prevalence: 25-75 per 100,000
- Sex: F:M 3:1

Racial Distribution
- Occurs in all populations
- African Americans > Caucasians (2:1)
- Choctaw Native Americans (Oklahoma)
  - Prevalence: 450 per 100,000
Autoantibodies in Scleroderma

- > 98% exhibit antinuclear antibodies (+ANA)

- Limited Scleroderma
  - 60-70% exhibit anticentromere Ab

- Diffuse scleroderma
  - 30% exhibit antitopoiso merase 1 Ab (anti-Scl 70 Ab)
  - 20-30% exhibit anti-RNA polymerase Ab
Autoantibodies in Scleroderma

Anti-PDGF Receptor Antibodies

Immunogenetics of Scleroderma

- HLA associations:
  - Limited scleroderma (anticentromere Ab)
    - HLA-DRβ1*0101
    - HLA-DQβ1*0501
  - Diffuse scleroderma (antitopoisomerase 1 Ab)
    - HLA-DRβ1*1101 (African Americans, Caucasians)
    - HLA-DRβ1*1104 (African Americans, Caucasians)
    - HLA-DQβ1*0301 (African Americans, Caucasians)
    - HLA-DRβ1*1502 (Japanese)
    - HLA-DRβ1*1602 (Choctaw Native Americans)
Pathogenesis of Scleroderma

- Endothelial activation
  - Vasospasm in Raynaud’s disease

- Immune activation
  - B cells and autoantibody generation
  - T cells and HLA associations
  - Macrophages and cytokine secretion
    - TGF-β, PDGF, TNFα, IL-1

- Fibroblast activation
  - Tissue fibrosis by excessive collagen deposition
Pathogenesis of Scleroderma
# Limited vs. Diffuse Scleroderma

<table>
<thead>
<tr>
<th>Limited Scleroderma</th>
<th>Diffuse Scleroderma</th>
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<tr>
<td><strong>Pulmonary</strong></td>
<td><strong>Kidney</strong></td>
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<tr>
<td>- Pulmonary Hypertension</td>
<td>- Acute renal failure 2°</td>
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<tr>
<td>- Kidney disease uncommon</td>
<td>- renovascular hypertension</td>
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<tr>
<td>- Heart disease uncommon</td>
<td>- Pulmonary</td>
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<td>- Gastrointestinal</td>
<td>- Pulmonary Hypertension</td>
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<tr>
<td>- Esophageal dysmotility</td>
<td>- Pulmonary Fibrosis</td>
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<td>- and gastroesophageal</td>
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<td>- Small bowel stasis and</td>
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<td>- bacterial overgrowth</td>
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<td>- Colonic diverticular</td>
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<td>- disease</td>
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Kidney Disease in Diffuse Scleroderma

- Renovascular disease causing hypertensive crisis resulting in acute renal insufficiency
- Usually an early manifestation
Renal Arteriogram

Normal

Scleroderma
Scleroderma Kidney Infarctions
Kidney Histopathology

vessel lumen occlusion
Approach to Scleroderma Kidney Disease

- Prophylactic administration of Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)
  - Prior to ACE inhibitors: >90% mortality within one year
  - After ACE inhibitors: >60% survival after 10 years
Pulmonary Disease*

- Parenchymal involvement (interstitial lung disease)
  - Pulmonary fibrosis

- Vascular involvement
  - Pulmonary hypertension

*Major cause of mortality in Scleroderma
Pulmonary Fibrosis
Pulmonary Fibrosis

Chest CT scan
Interstitial Lung Disease
Pulmonary Artery Involvement
Therapy of Pulmonary Hypertension

- Calcium channel blockers (e.g., diltiazem)

- Endothelin receptor blockers
  - Bosentan (Tracleer)
  - Ambrisentan (Letairis)

- Phosphodiesterase 5 inhibitor
  - Sildenafil (Revatio)

- Prostacyclin analogs
  - Epoprostenol (Flolan) intravenous
  - Treprostinil (Remodulin) intravenous
  - Iloprost (Ventavis) inhalation
Therapy of Interstitial Lung Disease

- Corticosteroids plus cyclophosphamide?
- Autologous stem cell transplant?
Gastrointestinal Involvement

- Principal cause of symptoms is a fibrosing process of the medial layer of the GI tract resulting in the replacement of smooth muscle with collagen

- Can involve the entire gastrointestinal tract

- Significant cause of morbidity in scleroderma
Esophageal Involvement

- Esophageal Dyssmotility
  - Dysphagia

- Gastroesophageal Reflux due to incompetence of the lower esophageal sphincter
  - Dyspepsia or heartburn
Esophageal Disease
Esophageal Histopathology
Duodenal Histopathology

Brunner’s glands
Normal GI Manometry
GI Manometry in Scleroderma
Small Intestine Involvement

- Hypomotility
  - Stasis of intestinal contents

- Bacterial Overgrowth
  - Malabsorption

- Pseudo-obstruction
  - Abdominal pain
Dilatation of Proximal Jejunum
Large Intestine Involvement

- Diverticuli
  - Perforation

- Hypomotility
  - Constipation

- Pseudo-obstruction
  - Abdominal pain
Approach to Gastrointestinal Disease

- Gastroesophageal reflux
  - Antisecretory agents, e.g., proton pump inhibitors

- Malabsorption 2° to bacterial overgrowth
  - Antibiotic therapy

- Hypo- or dysmotility related symptoms
  - Symptom control
    - e.g., constipation ➔ laxatives
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