

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

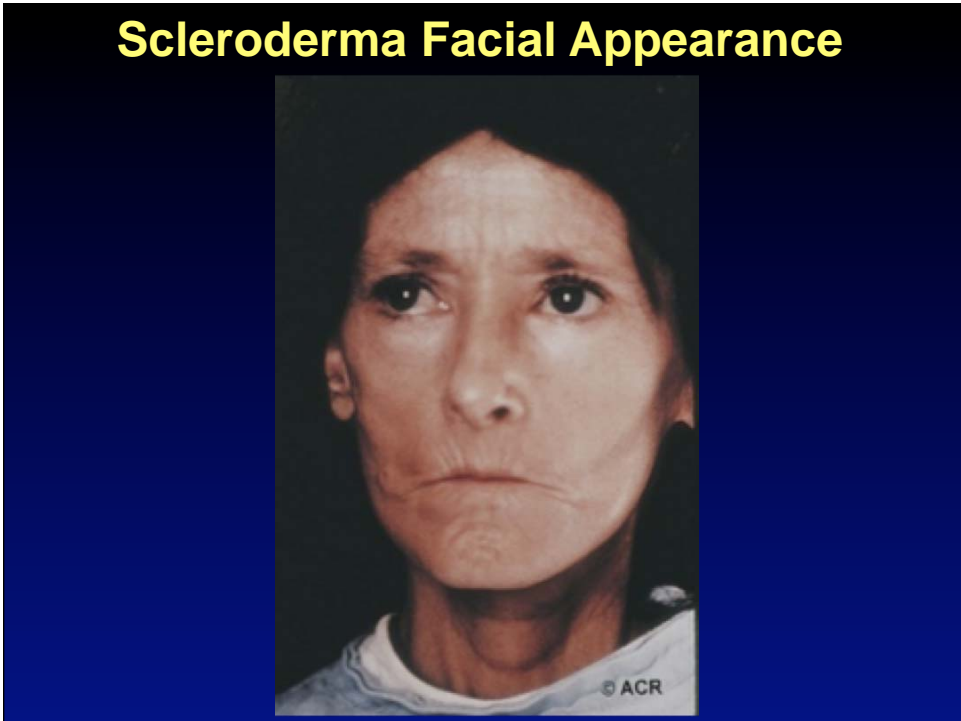
Swollen Digits in Scleroderma



Sclerodactyly



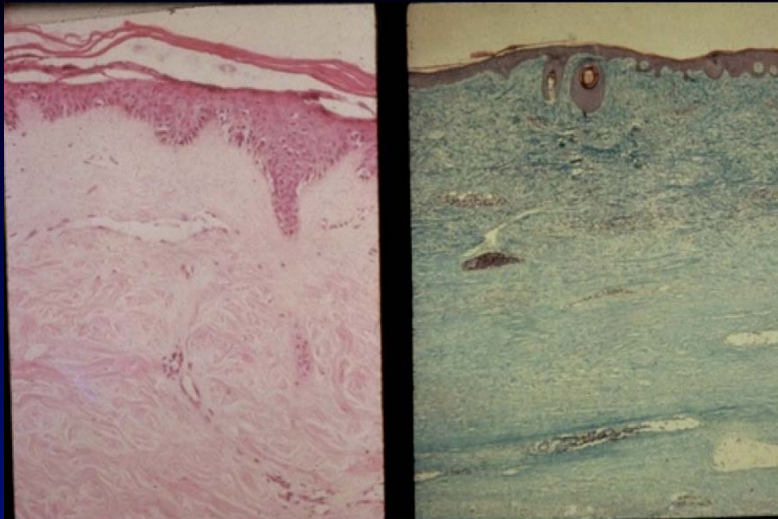
Scleroderma Facial Appearance



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



Raynaud's Phenomenon



Digital Arteriogram in Raynaud's Disease



Digital Capillary Microscopy in Scleroderma



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Normal



Capillary dilatation



Capillary "dropout"

Epidemiology of Scleroderma

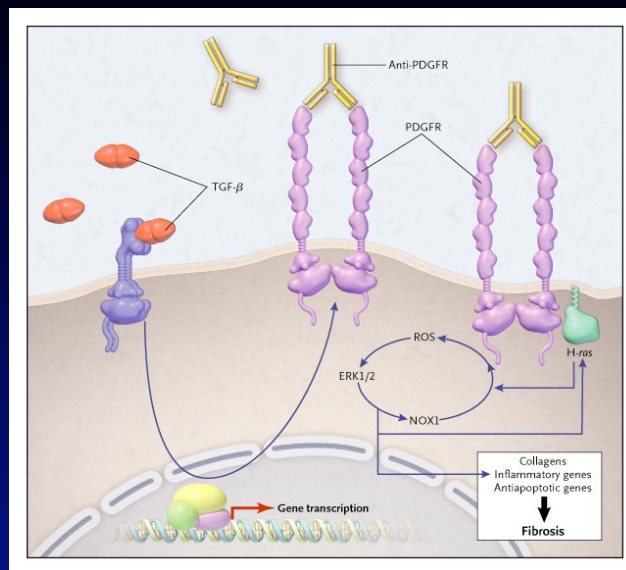
- Incidence: 2 per 100,000
- Prevalence: 25-75 per 100,000
- Sex: F:M 3:1
- Racial Distribution
 - Occurs in all populations
 - African Americans > Caucasians (2:1)
 - Choctaw Native Americans (Oklahoma)
 - Prevalence: 450 per 100,000

Autoantibodies in Scleroderma

- > 98% exhibit antinuclear antibodies (+ANA)
- Limited Scleroderma
 - 60-70% exhibit anticentromere Ab
- Diffuse scleroderma
 - 30% exhibit antitopoisomerase 1 Ab (anti-Scl 70 Ab)
 - 20-30% exhibit anti-RNA polymerase Ab

Autoantibodies in Scleroderma

Anti-PDGF Receptor Antibodies



Tan F. *N Engl J Med* 2006;354:2709-2711

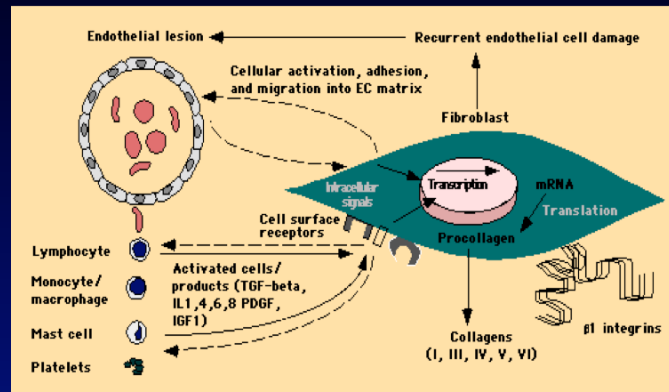
Immunogenetics of Scleroderma

- HLA associations:
 - Limited scleroderma (anticentromere Ab)
 - HLA-DR β 1*0101
 - HLA-DQ β 1*0501
 - Diffuse scleroderma (antitopoisomerase 1 Ab)
 - HLA-DR β 1*1101 (African Americans, Caucasians)
 - HLA-DR β 1*1104 (African Americans, Caucasians)
 - HLA-DQ β 1*0301 (African Americans, Caucasians)
 - HLA-DR β 1*1502 (Japanese)
 - HLA-DR β 1*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, TNF α , IL-1
- Fibroblast activation
 - Tissue fibrosis by excessive collagen deposition

Pathogenesis of Scleroderma



Limited vs. Diffuse Scleroderma

Limited Scleroderma

- Pulmonary
 - Pulmonary Hypertension
- Kidney disease uncommon
- Heart disease uncommon
- Gastrointestinal
 - Esophageal dysmotility and gastroesophageal reflux disease

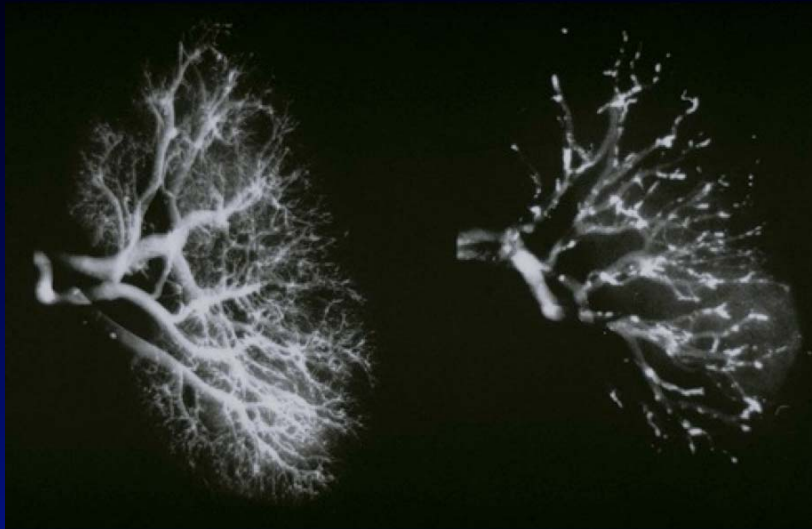
Diffuse Scleroderma

- Kidney
 - Acute renal failure 2° renovascular hypertension
- Pulmonary
 - Pulmonary Hypertension
 - Pulmonary Fibrosis
- Heart
 - Myocardial Fibrosis
- Gastrointestinal
 - Esophageal dysmotility and gastroesophageal reflux
 - Gastroparesis
 - Small bowel stasis and bacterial overgrowth
 - Colonic diverticular disease

Kidney Disease in Diffuse Scleroderma

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

Renal Arteriogram



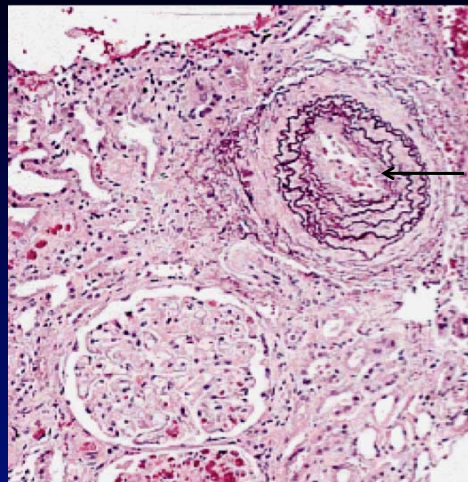
Normal

Scleroderma

Scleroderma Kidney Infarctions



Kidney Histopathology



vessel lumen occlusion

Approach to Scleroderma Kidney Disease

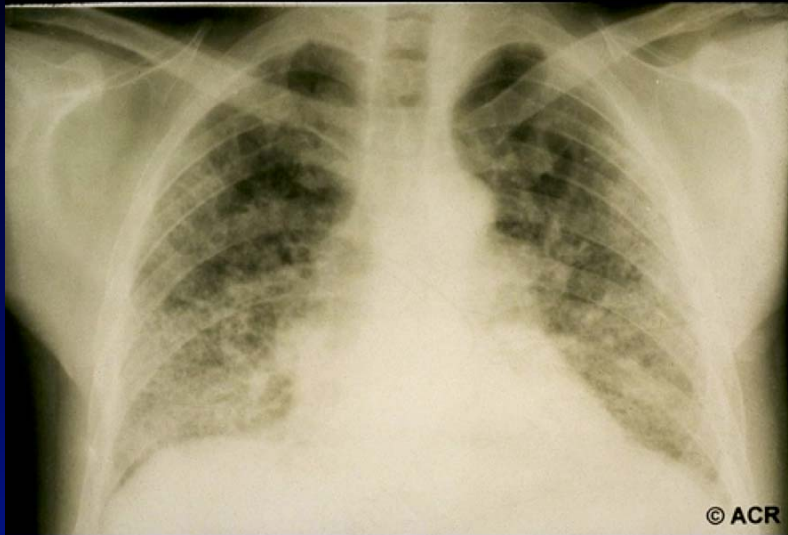
- Prophylactic administration of Angiotensin Converting Enzyme Inhibitors (ACE inhibitors)
 - Prior to ACE inhibitors: >90% mortality within one year
 - After ACE inhibitors: >60% survival after 10 years

Pulmonary Disease*

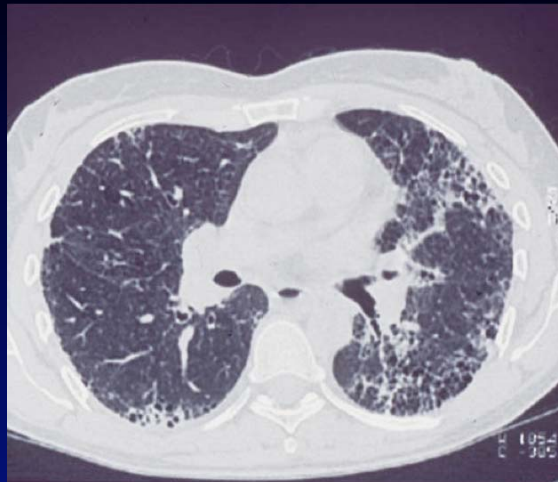
- Parenchymal involvement (interstitial lung disease)
 - Pulmonary fibrosis
- Vascular involvement
 - Pulmonary hypertension

**Major cause of mortality in Scleroderma*

Pulmonary Fibrosis

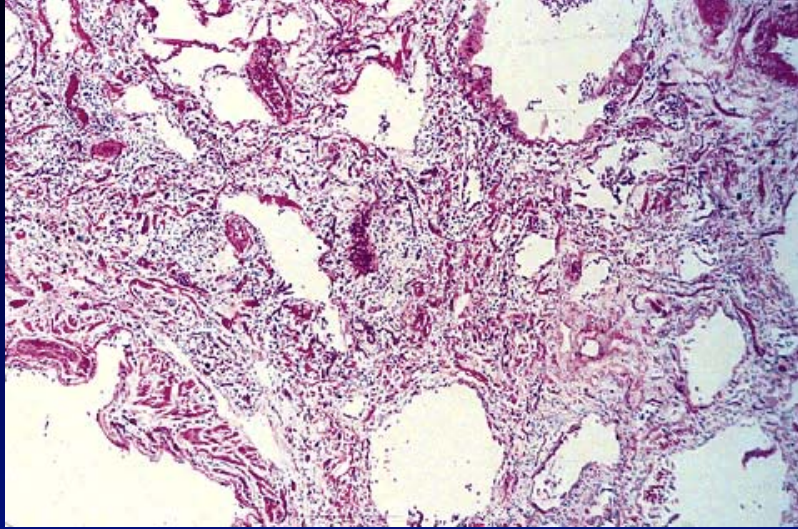


Pulmonary Fibrosis

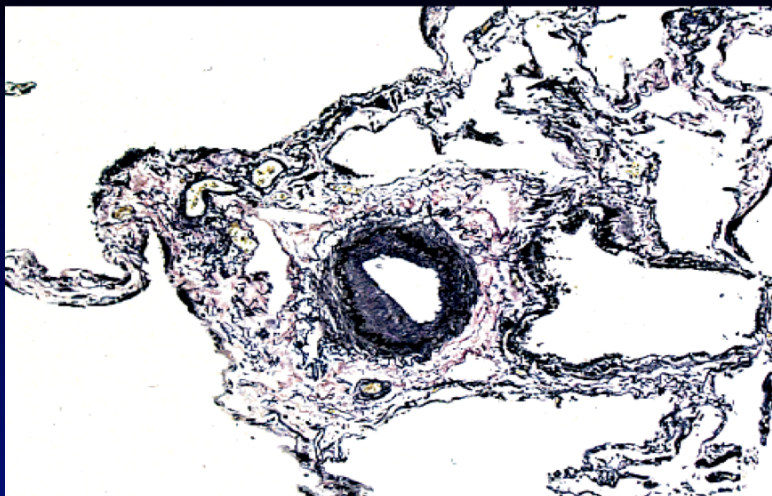


Chest CT scan

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

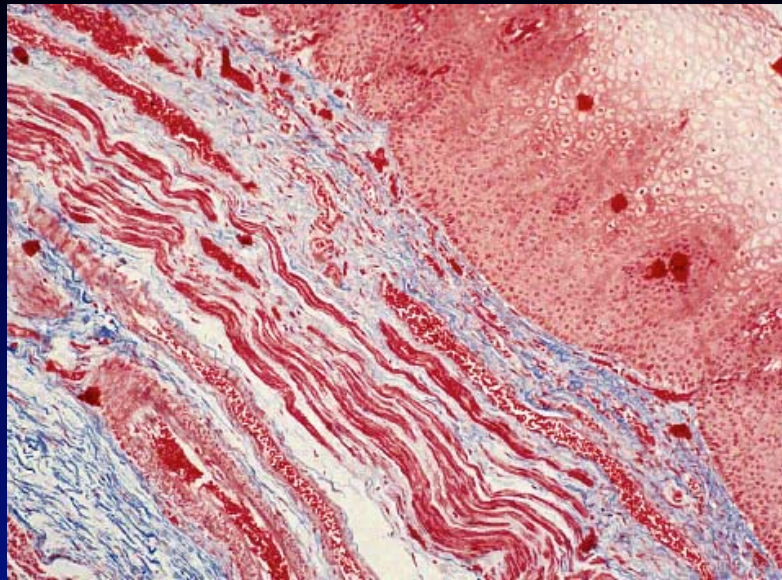
Esophageal Involvement

- Esophageal Dysmotility
 - Dysphagia
- Gastroesophageal Reflux due to incompetence of the lower esophageal sphincter
 - Dyspepsia or heartburn

Esophageal Disease



Esophageal Histopathology

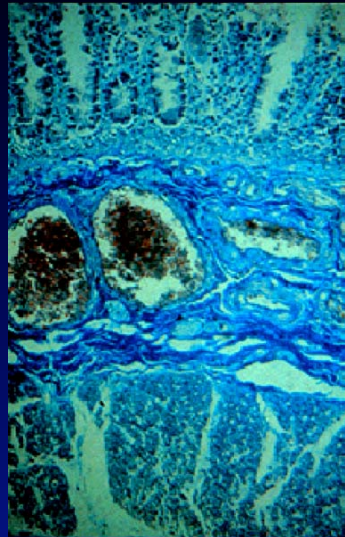


Small Intestine Involvement

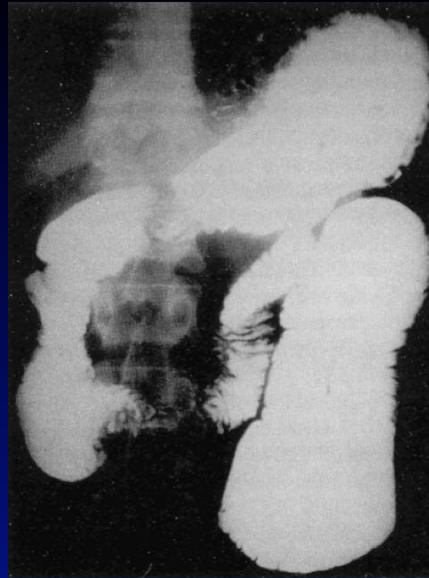
- Hypomotility
 - Stasis of intestinal contents
- Bacterial Overgrowth
 - Malabsorption
- Pseudo-obstruction
 - Abdominal pain

Duodenal Histopathology

Brunner's glands →



Dilatation of Proximal Jejunum



Large Intestine Involvement

- Diverticulae
 - Perforation

- Hypomotility
 - Constipation

- Pseudo-obstruction
 - Abdominal pain

Colonic Diverticulae



Colonic diverticuli



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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