Systemic Sclerosis (Scleroderma)

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Objectives

- Recognize the cutaneous manifestations of scleroderma
- Know that there are 2 clinical presentations of scleroderma and be able to describe the physical findings and organ involvement in each.
- Describe findings that are associated with a poorer prognosis.

Case

- 34 year old female presents with pain in bilateral wrists and ankles for the past six months (hand swelling for 4 months)
- Previously in good health until 1 year ago when she developed blue/purplish discoloration on cold exposure
- Describes classic triphasic color changes of Raynaud's phenomenon: white, blue, then red and painful upon rewarming

Case

- Raynaud's symptoms progress through the winter
- Joint symptoms wax and wane
- Notes 1 hour of morning stiffness with constant hand swelling
- Difficult for her to form a complete grip or to completely extend her fingers

Case

- PMH: otherwise negative
- SH: works as an office receptionist, +smoker at 1 pack per day for 14 years
- ROS: +intermittent heartburn for the past year, mild shortness of breath for the past two months

Case

- Physical Exam:
  - VS: RR-14, BP-120/70
  - Chest: fine late inspiratory crackles were heard at both lung bases
  - Extremities: hands and fingers were cool, diffusely swollen, and slightly dusky, but normal pulses were detected.
Case – PE (continued)

- Fingertip atrophy and small scars were present on the second digit of both hands.
- The skin of the fingers were mildly thickened, but elsewhere it appeared normal.
- Few telangiectasias on face and chest.
- No synovitis was present.
- Neuro exam was normal.

Labs

- Liver transaminases – normal
- Creatinine – normal at 0.9
- UA – normal
- ANA – 1:2,560, nucleolar pattern
  - Positive anti-scl-70
  - Anti-dsDNA, Anti-centromere antibody, and Anti-RNP - negative

Case - Diagnosis

Scleroderma

Systemic Sclerosis

- Skin lesions are often the presenting manifestation
- Organs commonly affected: GI tract, kidneys, heart, lung, muscles
- More common in women than men
- Age of onset typically 30-50 years

Systemic Sclerosis

- Pathogenesis - not well understood
- Key features:
  - Endothelial cell damage
  - Inflammation-precedes fibrosis
  - Excess deposition of collagen by fibroblasts

Systemic Sclerosis

- Scleroderma = “thickened skin”
- Autoimmune disease
- Characterized by extensive fibrosis
- Constellation of findings that affects internal organs and the skin
- Chronic condition
- Cause is unknown
Clinical Features - SSc

- Chronic multisystem disease
- Initial symptoms are nonspecific – Raynaud’s phenomenon, fatigue, and musculoskeletal complaints
- Skin thickening is usually first specific clinical clue to suggest diagnosis

ACR Classification Criteria

- For purposes of classification, patients are considered to have Scleroderma (Systemic Sclerosis) if they have one major or 2 or more minor criterion listed below
  - Major Criterion
    - Proximal scleroderma
  - Minor Criterion
    - Sclerodactyly
    - Digital pitting scars or loss of substance from the finger pad
    - Bibasilar pulmonary fibrosis

Scleroderma - Subsets

- Diffuse Cutaneous
- Limited Cutaneous (CREST)
- Overlap Syndromes
  - Scleroderma with one or more features of other connective tissue diseases
  - Mixed Connective tissue disease (MCTD)
    - SLE, Scleroderma, polymyositis and positive anti-RNP
  - Localized Scleroderma (Morphea)

Systemic Sclerosis: sclerodactyly

- Often initial phase of edema and inflammation
- Small vessels damaged, thickened, partly occluded
- Fibrosis-dermis becomes bound down, loss of normal epidermal appendages
- Fingertip ulcers/pits
Systemic Sclerosis - skin signs

- Sclerodactyly
- Facial disfigurement
  - Microstomia, pursed mouth
  - Lip retraction
  - Beaked nose

Systemic Sclerosis - vascular

- Telangiectases ("mat telangiectasia")
- Dilated capillary loops

Telangiectasias
Systemic Sclerosis - skin signs

- Pigmentary: leukoderma
  - "Salt and pepper" discoloration
  - The area around the follicular orifice is spared
  - Involves face/scalp/upper trunk/arms

Systemic Sclerosis - skin signs

- Calcinosis
- Common around joints

Systemic Sclerosis - skin signs

- Often apparent at presentation
- Disfiguring/functionally limiting
- Identification should trigger further evaluation

Scleroderma - Major Organ Involvement

- Pulmonary
- Gastrointestinal
- Cardiovascular
- Renal

Pulmonary Features

- Lung impairment is the leading cause of mortality in SSc
- Prevalence of pulmonary fibrosis is 25-90%
- Onset is within the first 3 years of disease in most patients
- Dyspnea on exertion is the most common initial symptom
- Cough is a late manifestation of SSc lung disease
Pulmonary

- Severe fibrosis is more common among patients with diffuse skin disease, African American or Native American patients, and patients with anti-topoisomerase antibodies.
- Reduction in normal gas transfer from the alveolar space into the pulmonary circulation
  - caused by a fibrosing alveolitis (causing restrictive lung disease) and/or
  - Pulmonary vasculopathy characterized by endothelial cell dysfunction and intimal fibrosis

Pulmonary Features

- Pulmonary Function Tests (PFTs) may detect significant reductions in lung volumes (restriction) or decreased diffusing capacity (poor gas transfer) even when clinical lung symptoms are silent.
- Chest x-rays findings include: bilateral interstitial fibrosis involving the lower 2/3s
- High resolution CT findings include: ground-glass opacities, subpleural and diffuse honeycombing

Other Pulmonary Features

- Pulmonary hypertension
  - elevated right ventricular pressure
  - low diffusing capacity
- Associated with a high mortality rate
- Isolated PAH without fibrosis is associated with the CREST syndrome

Gastrointestinal Features

- One of the most common problems (80%)
- Found in both diffuse and limited disease
- Difficulty swallowing (dysphagia) and heartburn (gastroesophageal reflux) are the most common symptoms

GI Pathology

- Early in disease –
  - Abnormal function of the smooth muscle in the distal 2/3’s of the esophagus likely due to neuromuscular dysfunction
- Later in disease –
  - Smooth muscle atrophy and fibrosis develops with excess collagen deposition in the lamina propria and submucosa
Esophagus – abnormal motility and dilatation

GI disease
- Gastroparesis
- Constipation
- Bacterial Overgrowth => malabsorption and diarrhea
- Pseudo-obstruction
- Wide-mouth diverticuli
- Vascular abnormalities – telangiectasias to Watermelon stomach

Wide mouth diverticuli

Watermelon Stomach

Cardiovascular
- Myocardial fibrosis/sclerosis unrelated to coronary artery disease which is patchy
- Pericardial disease
  - usually subclinical pericardial effusions
  - acute pericarditis is uncommon
- Conduction system disease and arrhythmias
- Raynaud’s

Systemic Sclerosis: Raynaud phenomenon
- Episodic vasoconstriction of small arteries/arterioles
- Distal fingers
- Often initial manifestation
- Triggered by cold
- Fingers turn white (ischemic), blue (cyanotic) and then red (reperfusion)
Nailfold Capillaries

Renal

- Scleroderma renal crisis (SRC)
  - Characterized by
    - Malignant hypertension
    - Renal insufficiency
    - Microangiopathic hemolytic anemia
  - Now successfully treated with Angiotensin Converting Enzyme (ACE) inhibitors.

Predictive Factors of Renal Crisis

- Diffuse skin involvement
- Rapid progression of skin involvement
- Disease duration <4 years
- Anti-RNA polymerase III antibody
- Antecedent high-dose corticosteroids

Musculoskeletal

- Musculoskeletal pain (out of proportion) can be related to evolving skin manifestations.
- Symmetric arthralgias/arthritis
- Calcinosis
- Coarse tendon friction rubs
- Muscle atrophy and weakness – late in the disease
- “Overlap” syndrome with an inflammatory myopathy.
Radiographic findings

Nonarticular
- Subcutaneous calcinosis
- Osseous resorption of the digital tuft – represents the most distinctive and dramatic radiographic abnormality

Articular
- Juxtaarticular demineralization
- Joint space narrowing
- Erosions

Autoantibodies

- Anti-nuclear antibodies
- Anti-Scl-70 (DNA topoisomerase 1)
  - diffuse
- Anti-centromere
  - CREST
- Anti-RNA polymerase III
- Renal Crisis
- Anti-RNP
- MCTD

Clinical Differences - Diffuse

- Onset of skin changes within 1 year of Raynaud’s
- Truncal and acral skin involvement
- Early and significant incidence of interstitial lung disease, Scleroderma Renal Crisis, diffuse GI disease, and myocardial involvement
- Tendon friction rubs
- 30% incidence of antitopoisomerase antibodies (anti-Scl-70)
Systemic Sclerosis - CREST

- **C**: Calcinosis (cutaneous)
- **R**: Raynaud phenomenon
- **E**: Esophageal dysmotility
- **S**: Sclerodactyly
- **T**: Telangiectasia (skin)

Clinical Differences - Limited

- Long duration of Raynaud’s --years to decades
- Limited skin involvement
- Slow pace of progression
- A significant late incidence of PAH
- A high incidence of anticentromere antibody (70-80%)

Treatment

- Tends to be targeted at the clinical manifestations
- Renal: monitor BP, ACE inhibitors
- GI (GERD): proton pump inhibitors (PPIs), histamine receptor antagonists (H2 blockers), prokinetic agents
- Musculoskeletal: NSAIDs, PT/OT, low dose steroids (but must watch BP/renal function)

Treatment

- Raynaud’s: smoking cessation, conservative precautions with keeping core body temp warm, calcium channel blockers, and angiotensin receptor blockers (ARBs)
- Lungs: cyclophosphamide, corticosteroids, (stem cell transplantation and lung transplantation)
- Pulmonary Hypertension: oxygen, calcium channel blockers, prostacyclin derivatives, endothelin antagonists, phosphodiesterase inhibitors