Sclerosis (Sc)

- Epidemiology
  - adult white females (NB AA have earlier onset and worse prognosis)
- Pathogenesis
  - autoantibodies against PDGF receptor activate collagen gene expression
- Classification
  - Systemic (SSc)
    - chronic idiopathic disorders of connective tissue characterized by diffuse changes in dermal skin (scleroderma), joint, muscle, and certain viscera (1° GI, lung, heart, kidney) due to inflammation, fibrosis and degenerative changes of interstitium and vessels
    - seropositive (85% of pts have at least one antibody)
    - seen in adults

	Diffuse (dSSc) aka Severe	**Limited (lSSc) aka Mild**
Epidemiology	<50yo, F>M	>50yo, F>>>>M
Location (dividing line b/t distal/proximal is elbow or knee)	distal and proximal extremities + face + trunk	distal extremities (usually just fingers) + face
Viscera	earlier visceral involvement	later visceral involvement and mostly lungs
Skin	skin thickens more quickly and more thick such that they have a short history of Raynaud's or even scleroderma occurs b/f Raynaud's	skin thickens less quickly and less thick such that they have a long history of Raynaud's
Constitutional Symptoms	Significant	Mild
Prognosis	10yr survival 50% (most common cause of death: ILD)	10yr survival 95% (most common cause of death: Pulm HTN)
Auto-Antibodies	**Anti-Scl70/Topoisomerase I** **Anti-RNA Polymerase I/III** **Anti-U3RNP**	**Anti-Centromere** **Anti-Th**
Sub Groups		**CREST Syndrome** = Calcinosis Raynauds Esophageal hypomotility Sclerodactyly Telengectasia
	SSc Sine Scleroderma = SSc w/o skin involvement **Overlap Syndrome** = features of other CTD (esp SLE or PM/DM) are present **Anti-U1RNP** **Anti-PM-Scl**	

  - Localized (LSc)
    - similar changes are localized and only seen in skin with no joint, muscle, visceral involvement
    - seronegative
    - seen in children

Morpha	**Linear Scleroderma**
single or multiple oval plaques of dermal fibrosis with erythematous rim	single or multiple bands of dermal fibrosis (**NB En Coup de Sabre** – scar like lesion that begins on one side of face and can extend down to the trunk)

- Differential Diagnosis of Scleroderma
  - Systemic Diseases: DM, HypoTH, amyoidosis, etc
  - Eosinophilic Fascitis
    - Fascial fibrosis (feels more deep on PEx) that spares the hands/face
    - Associated w/ Eosinophilia
    - Bx: fascial fibrosis
  - Bushke's Scleroderma
    - Dermal Fibrosis of neck, shoulder, upper arm
    - Associated w/ DM and monoclonal gammopathy
    - Bx: large collagen fibers
  - Scleromyxedema
    - Dermal Fibrosis of neck, shoulder, upper arm
    - Associated w/ monoclonal gammopathy, neurologic dz, GI dz, cardiac dz
    - Bx: mucin deposition and stellate fibroblasts

- Dialysis Associated Systemic Fibrosis
  - Brawny Hyperpigmentation that spares the fingers
  - Associated w/ RF
  - Bx: disorganized collagen with increased clefts and spindle cells
- Eosinophilia Myalgia Syndrome
  - Syndrome affecting practically every organ but typically pts p/w severe myalgia, dyspnea, edema, fatigue, and skin rashes. After 3-6mo acute inflammatory symptoms resolve and pt have neuropathy, myopathy, scleroderma, and chronic fatigue. This syndrome manifested in the late 1980s and was found to be due to ingestion of L-tryptophan supplements. Supplementation was common in the 1980s for the treatment of insomnia, chronic pain, depression, etc. And in 1989 when this syndrome emerged it was initially thought that it was due to impurities in one specific brand. It is now that thought that because tryptophan interferes with histamine metabolism its toxic accumulation is the cause for this syndrome.
- Toxic Oil Syndrome
  - Syndrome similar to above along with pneumonia like symptoms. This syndrome manifested in Spain in 1981 and was due to the ingestion of rapeseed oil which is used for industrial purposes. In Spain it was falsely sold as "olive oil". There is a conspiracy theory surrounding how this type of oil ended up on kitchen tables. It is thought that the presence of aniline is the cause for this syndrome.
- Necrotizing Systemic Fibrosis (NSF)
  - Sclerosis after given Gandolinium contrast

- Signs & Symptoms
  - Skin
    - **Scleroderma**
      - early morning pitting/non-pitting edema → induration (sclerodactyly, beak-like nose, puckered lips aka microstomia, thinning of lips aka microcheilia, "face-lift", "salt-n-pepper" facial/neck skin of AA – as the skin fibrosis it pulls melanocytes out creating hypopigmented surrounded by hyperpigmented areas) leading to contractures, disability, and disfigurement → after awhile the skin actually returns to normal thickness and then actually thins
      - typically begins distally at end of digits and progresses proximally
      - variable between diffuse (quicker and thicker) and limited (slower and less thick)
      - biopsy is diagnostic
      - degree of skin involvement is very predictive of outcome hence diffuse is worse than limited
      - Tx: no true effective treatment but D-penicillamine has been shown to mildly decrease skin thickening and reduce renal problems
    - **Telengectasia** (face, chest, palms)
    - **Calcinosis** (pressure points)
      - Tx: Colchicine or Surgical Excision
  - Peripheral Vasculature
    - **Raynaud's** (seen in 95% of SSc and *is usually the first symptom to manifest)*
      - excessive vasospasm in response to cold/stress leading to ischemic pallor/blanching → venous dilation leading to cyanosis with accompanying pain, paresthesia, numbness, et al → hyperemia during rewarming leading to rubor →→→ if significant or chronic one can get ulceration/necrosis and infections → "pitted scars" (WBR)
      - NB Raynaud's can also affect visceral vessels
      - DDx
        - Primary = Raynaud's Disease (50%) F>M, all digits, frequent attacks, ulceration rare, levido reticularis common
          - 30yo, 5F:M, typically more mild with no tissue injury, must r/o secondary causes
        - Secondary = Raynaud's Phenomenon (50%) M>F, single digit, infrequent attacks, ulceration common, livedo reticularis rare
          - CVD: Scleroderma, SLE, RA, PM/DM
          - Arterial Dz: Peripheral Atherosclerosis, Thromboangiitis Obliterans
          - Hematologic Dz: Cryoglobulinemia, Waldenstrom's, APS
          - Trauma: repetitive vibrational motions
          - Drugs: ergot alkaloids
      - Prevention
        - STOP Smoking
        - Avoid Quick Temperature Changes
      - Treatment
        - Mild: Low Dose CCB and ASA
        - Mod: Nitrates (Topical Nitro Paste or PO Viagra)
        - Severe: Endothlial Receptor Antagonist (Bosentan), (Prostacyclin Agonists (Iloprost, Epoprostenol, Trepostinil), Digital/Thoracic Sympathectomy, Amputation
        - Other: ARBs, alpha-blockers, fish oil

- Pulm *(most common cause of morbidity/mortality)*
  - Must distinguish between ILD and Pulmonary HTN by S/S, CXR, HRCT, PFTS, BAL, Auto-Abs but the main distinguishing feature is the onset of dyspnea
    - **ILD** (dyspnea is slowly progressive over 2-10yrs)
      - Tx: cyclophosphamide w/ or w/o steroids
    - **Pulmonary HTN** (dyspnea is rapidly progressive over 6-12mo)
      - Tx: (refer to pulm notes)
- Skeletal
  - Symmetric Polyarthralgias
  - Pts often describe a "squeaking" sensation upon moving their extremities
  - On physical exam crepitus over tendons aka "tendon friction rub" can be palpated
- Muscle
  - Symmetric Polymyalgias
  - Atrophy 2/2 (1) disuse b/c of joint contracture and (2) muscle fibrosis
- GI
  - Epidemiology: 75-90% of pts have GI dz w/ 6-12% of pts having significant dz resulting in high M&M, when GI dz is present 5yr mortality is 50% w/ 5-10% of these pts dyeing from a direct GI complication
  - NB often pt's have a (1) mixed CTD process esp Sjogren's disease w/ xerostomia subsequent difficult mastication and oropharyngeal dysphagia and pancreatico-biliary dz and (2) increase r/o other autoimmune process esp PBC/AIH
  - Mechanism: collagen deposition and smooth muscle atrophy leads to global delayed gut transit time (primarily stomach/SI) and lower resting sphincter pressures (primarily LES/IAS)
  - **Pharynx**: gingivitis, loosening of teeth, poor dental hygiene b/c hard to brush teeth, xerostomia 2/2 fibrosis of glands or overlap with Sjogrens, microstomia/microcheilia (noted above)
  - **Esophagus**: hypomotility of smooth muscle esophagus (dysphagia, can also be due to complications of GERD) and incompetency of LES w/ decreased clearance (GERD) strong correlation b/t esophageal and pulmonary disease in SSc pts, a recent study indicates that significant GER could be the SOLE cause of ILD, seen in these pts, anti-reflux surgery is not advocated in this population given comorbidities (1° pulmonary dz) and concurrent hypomotility, there have been a few cases reported but with very poor results
  - **Stomach**: gastroparesis, GAVE
  - **SI**: hypomotility to CIPO leading to SIBO, malabsorption
  - **Colon**: alternating diarrhea and constipation, AEs, diverticulosis, Pneumatosis Cystoides Intestinalis, Fecal Incontinence 2/2 impaired IAS
- CV
  - Pericarditis w/ Effusions
  - Restrictive CM w/ Conduction Abnormalities and Systolic/Diastolic HF
- Kidney
  - **"Scleroderma Renal Crisis (SRC)"**
    - rapid malignant hypertension due to stenosis of renal artery resulting in a syndrome that mimics TTP/HUS and oliguric RF
    - Tx: ACE-I (before ACE-I, SRC was the most common cause of M/M)

- Treatment
  - Overall the pt has active dz for ~2-3yrs and then the pt is left with the damage afterwards
  - No true effective disease modifying agents
    - Immunosuppressants (IFN-gamma) are used in pts with early, rapidly progressive, life threatening dcSSc
    - NSAIDs and Steroids are fairly ineffective and their only role is in treating myopathy and serositis