Scleroderma

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None

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Objectives

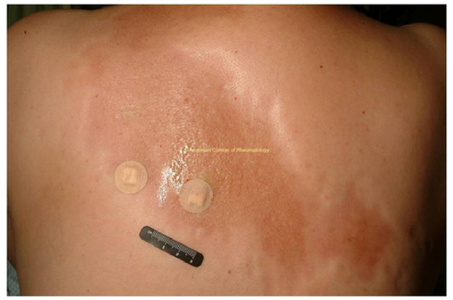
By the end of the session, learners will be able to:

1. Understand the major subtypes of scleroderma and their clinical manifestations
2. Discuss differential diagnosis and review the ACR/EULAR classification criteria
3. Understand the major systemic complications and approach to management of scleroderma

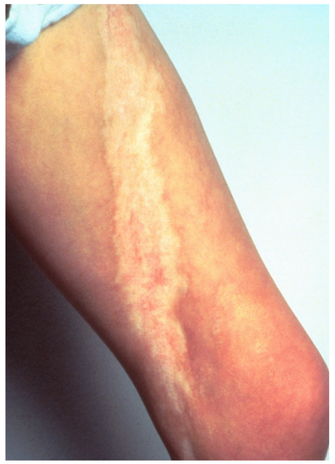
Scleroderma Phenotypes

Localized

Morphea



Linear



En Coup de Sabre

Systemic Sclerosis (SSc)

Limited (CREST)

Calcinosis
Raynauds
Esophageal dysmotility
Sclerodactyly
Telangiectasias

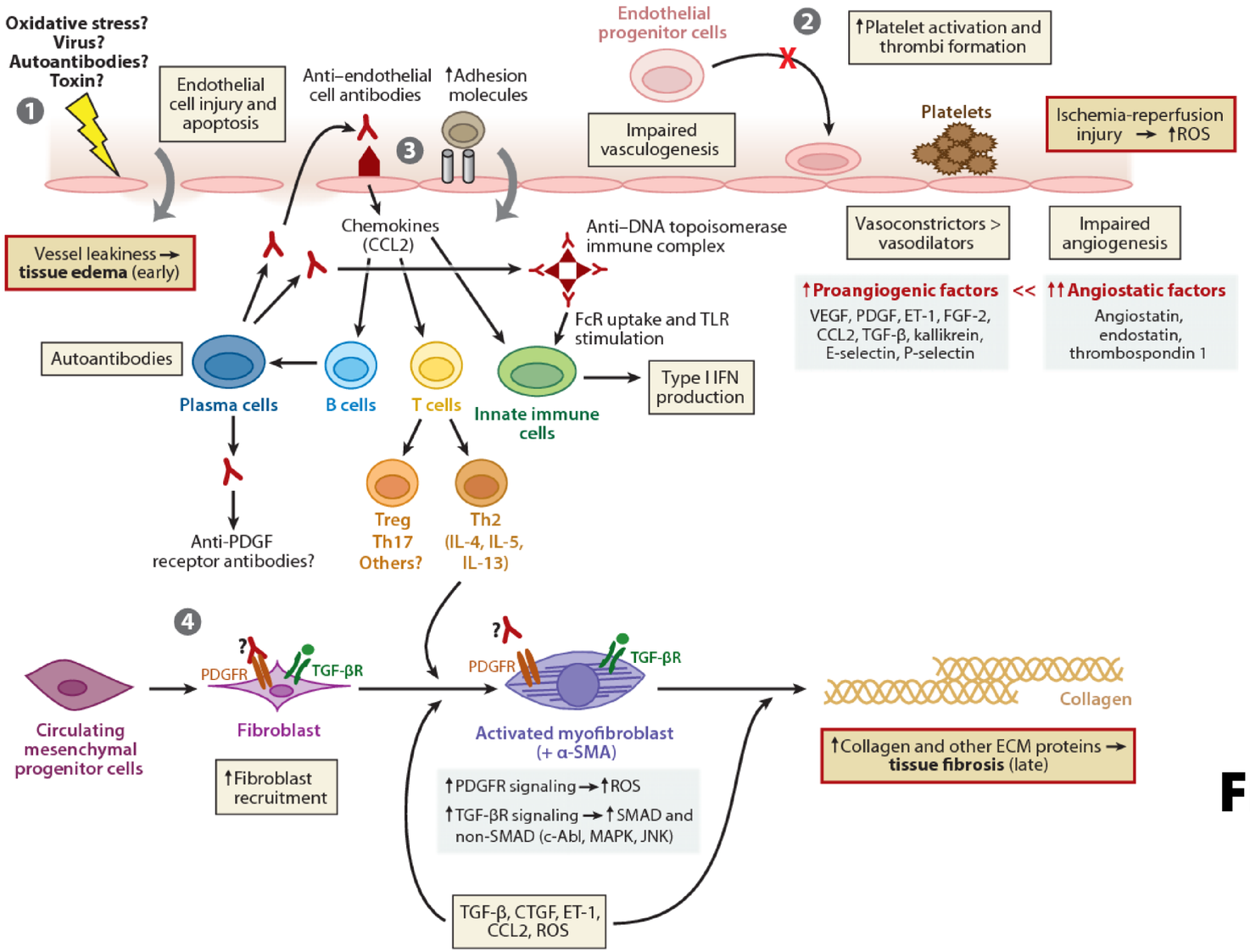
Diffuse

systemic sclerosis sine scleroderma

Epidemiology

- Rare disease
- More common in women and Black patients
- Poor prognosis
- 4x higher mortality than age/sex matched controls
  - Deaths related to ILD, pHTN and cardiovascular
  - Highest morbidity and mortality of all rheumatic diseases

Pathophysiology

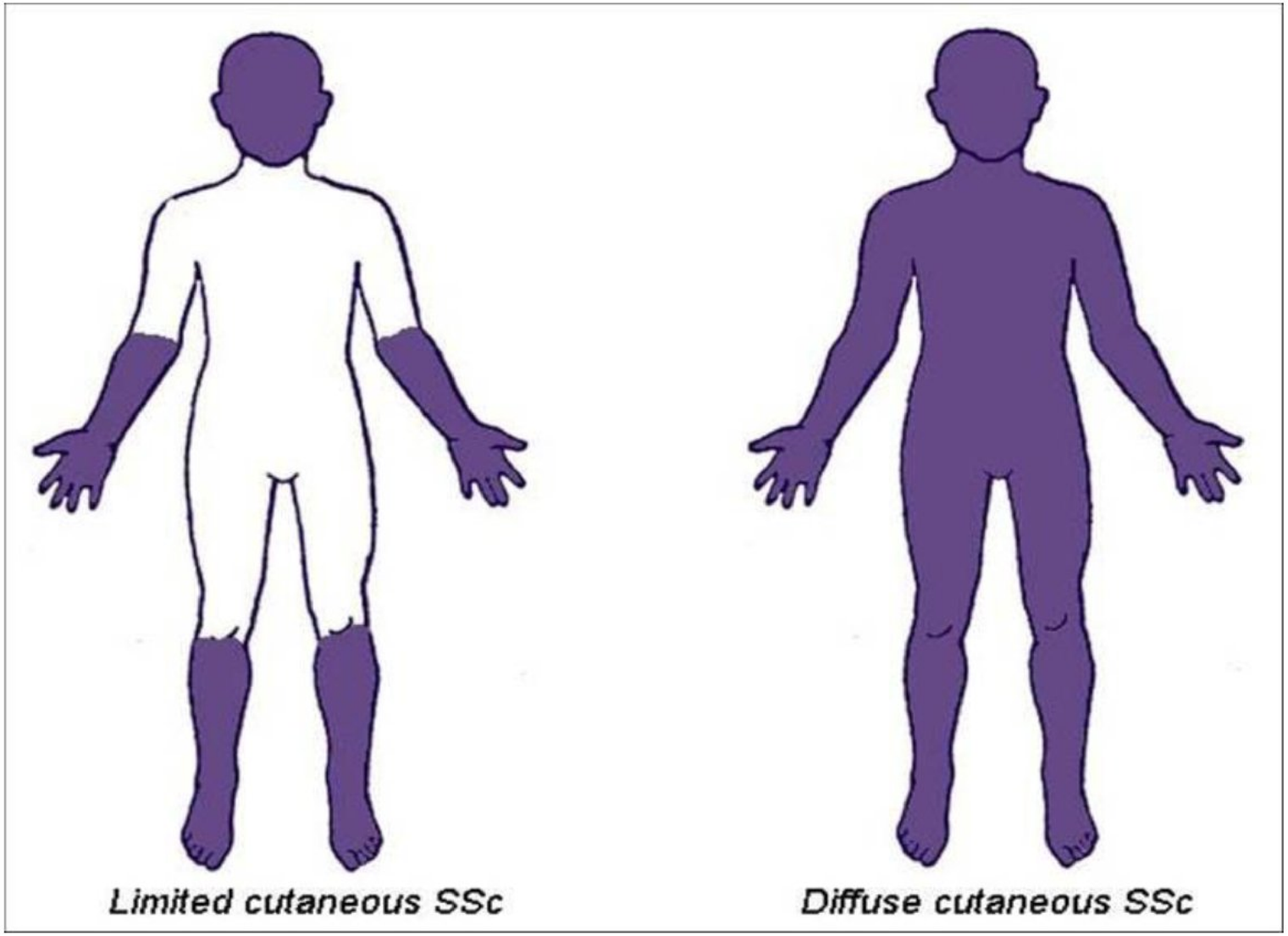


Autoimmunity

Fibrosis **Vasculopathy**

Katsumoto, Tamiko R., Michael L. Whitfield, and M. Kari Connolly. "The pathogenesis of systemic sclerosis." Annual Review of Pathology: Mechanisms of Disease 6 (2011): 509-537.

Limited vs Diffuse Scleroderma



Limited vs Diffuse Scleroderma

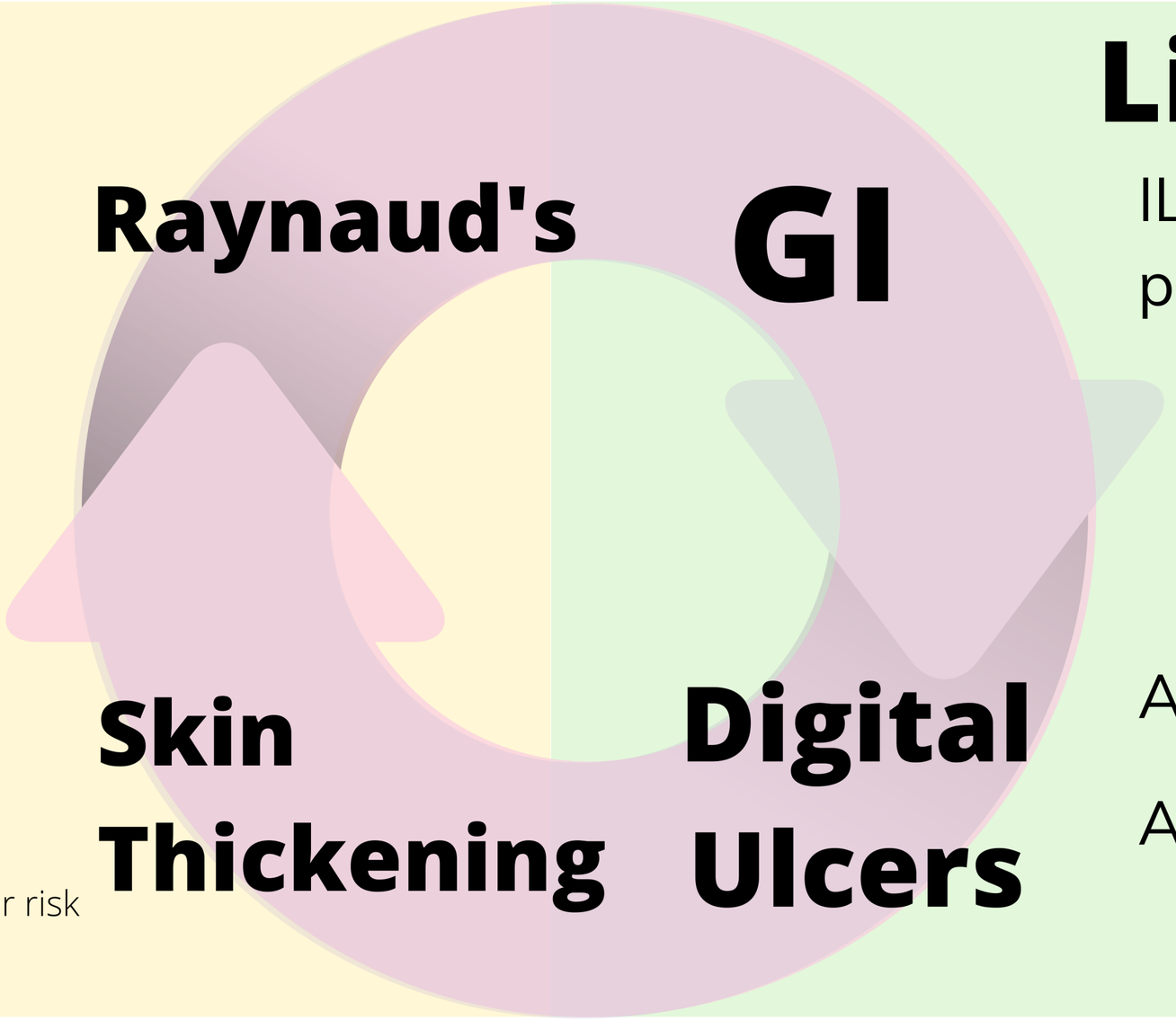
Diffuse

ILD - 50%
pHTN
RENAL
CARDIAC

Anti- Scl70
Pulmonary fibrosis

Anti- RNA Pol III
Severe skin, renal disease, cancer risk

Anti - U3 RNP



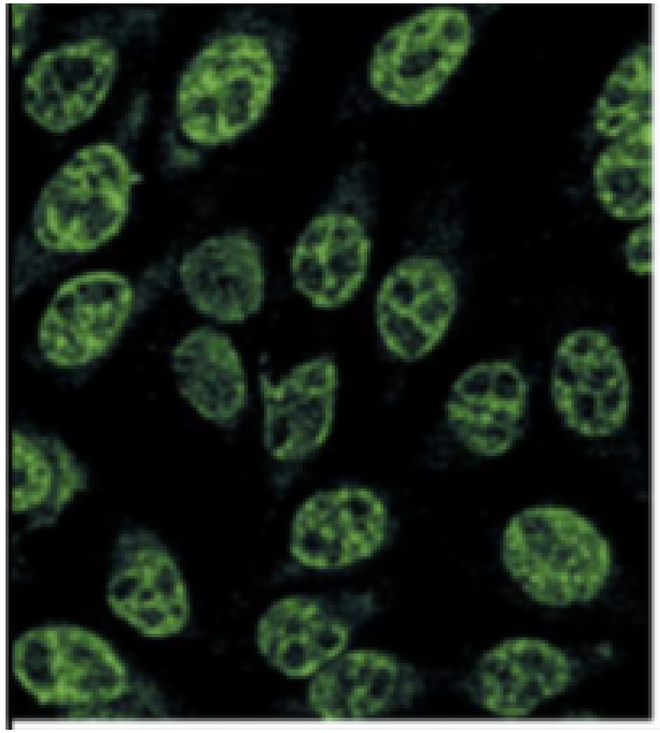
Limited

ILD
pHTN - 30-40%

Anti- Centromere
pHTN, PBC, digital ischemia

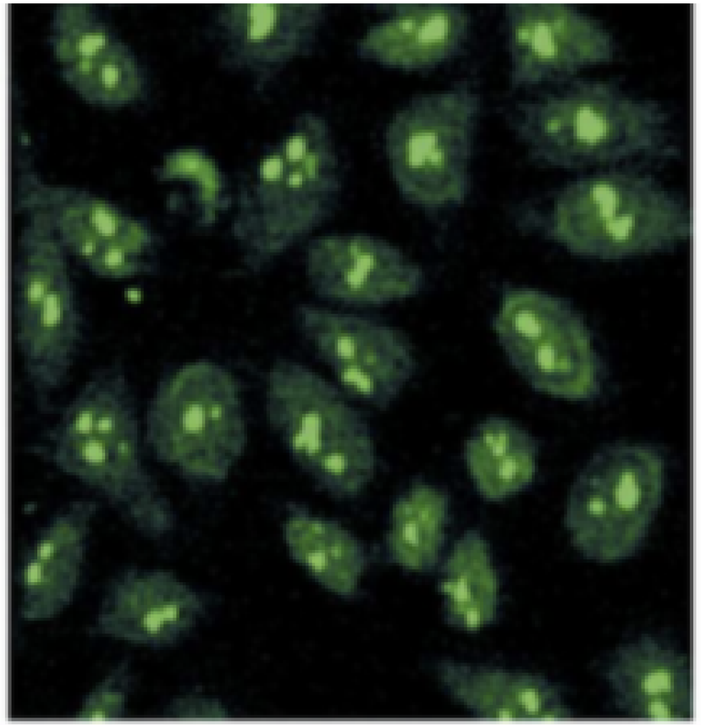
Anti-Th/To

Antibodies in SSc



Speckled

Scl-70

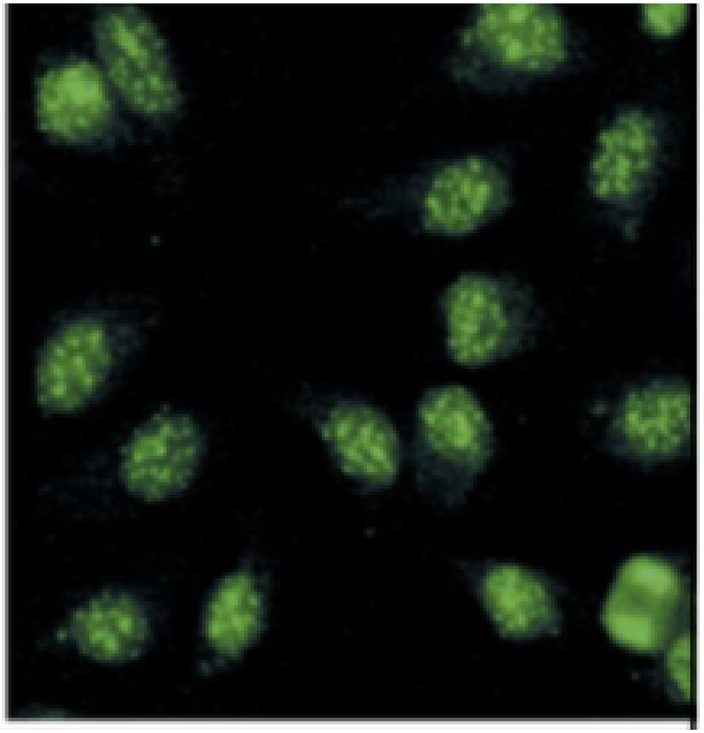


Nucleolar

RNA pol III

Th/To

PM-Scl



Centromere

2013 ACR/EULAR Classification Criteria

The ACR-EULAR Criteria for the classification of Systemic Sclerosis

1. These criteria are applicable to any patient considered for inclusion in a SSc study.

2. These criteria are not applicable to:

a) Patients having a SSc-like disorder better explaining their manifestations, such as: nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft versus host disease, and diabetic cheiropathy. b) Patients with `*Skin thickening sparing the fingers*',

Items	Sub-items	Weight / Score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*		9
Skin thickening of the fingers^ *(only count the highest score)*	Puffy fingers Sclerodactyly of the fingers (distal to MCP but proximal to the PIPs)	2 4
Finger tip lesions^ *(only count the highest score)*	Digital Tip Ulcers Finger Tip Pitting Scars	2 3
Telangiectasia		2
Abnormal nailfold capillaries		2
Pulmonary arterial hypertension and/or Interstitial lung Disease* (*Maximum score is 2)	PAH ILD	2
Raynaud's phenomenon		3
Scleroderma related antibodies** (any of anti-centromere, anti-topoisomerasel	Anti-centromere Anti-topoisomerasel	3
[anti-Sd 70], anti-RNA polymerase III) (**Maximum score is 3)	Anti-RNA polymerase III	
	TOTAL SCORE^:	

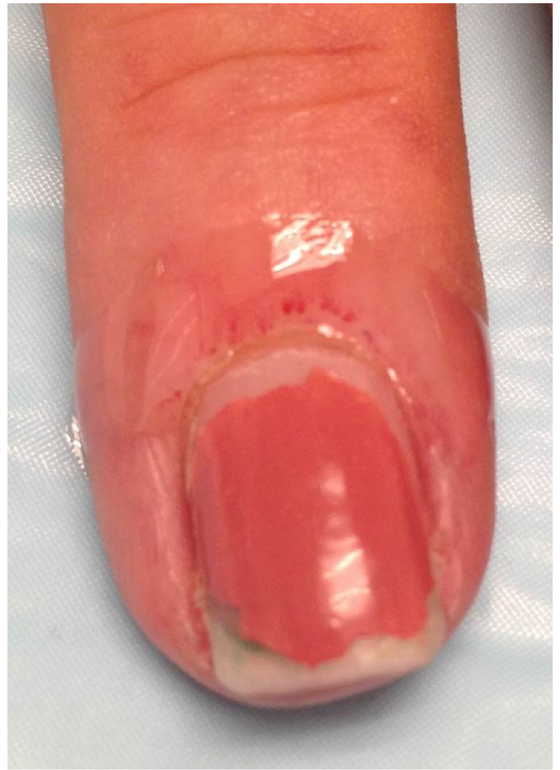
Patients having a total score of 9 or more are being classified as having definite systemic sclerosis.

Clinical Manifestations

- Skin
- Musculoskeletal
- Vascular
- Gastrointestinal
- Kidney
- Lung
- Cardiac

Case 1

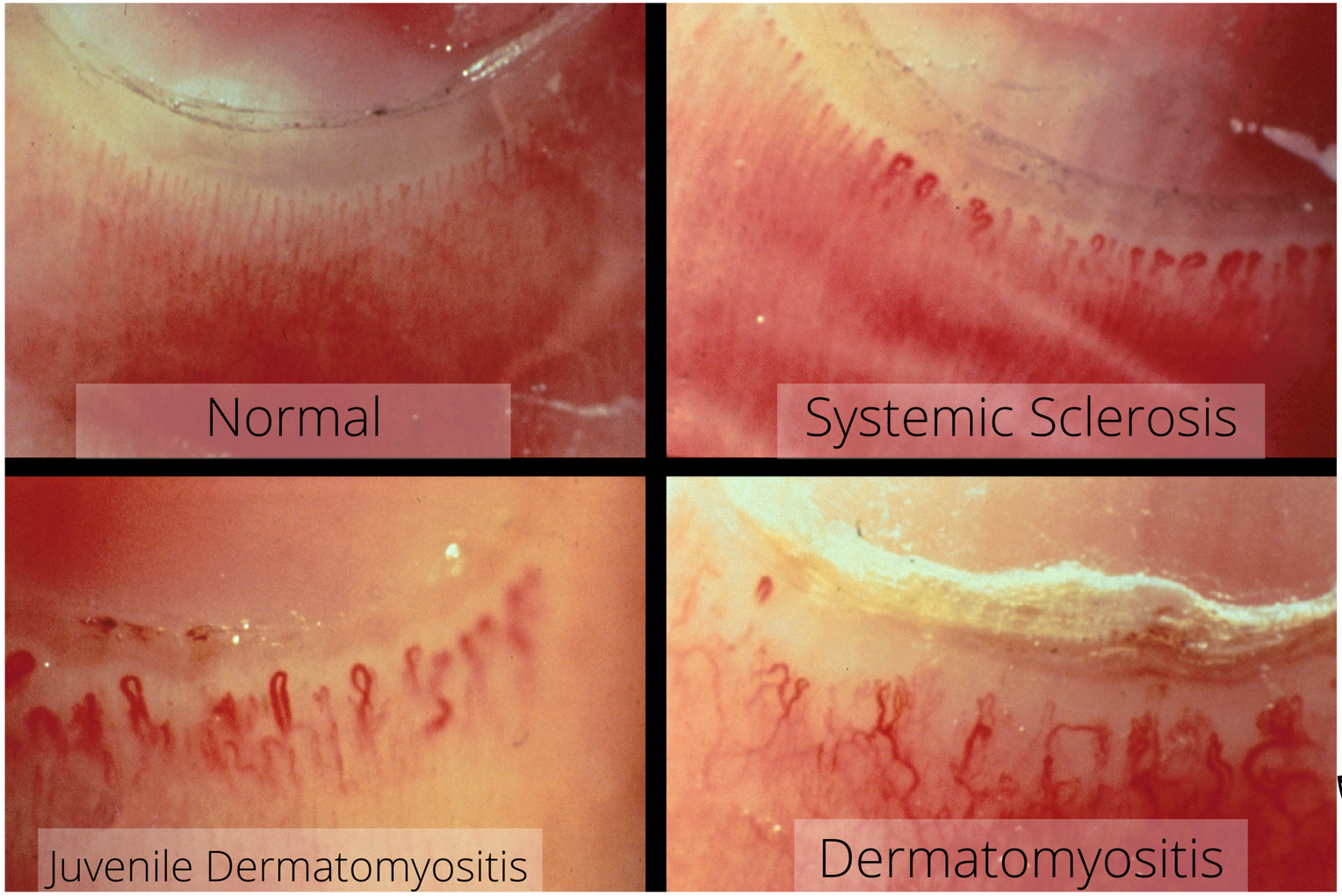
31 YO F who is referred to rheumatology by hand surgery due to a digital ulcer with poor wound healing. She has a 2 year history of Raynaud's phenomena. Labs with +ANA 1:320, centromere pattern. All other labs are unremarkable. Further review of systems reveals dyspnea on exertion and gastroesophageal reflux.
Physical exam demonstrates puffy fingers, but no digital ulcers or evidence of ischemia.



What is the likely diagnosis in this case?

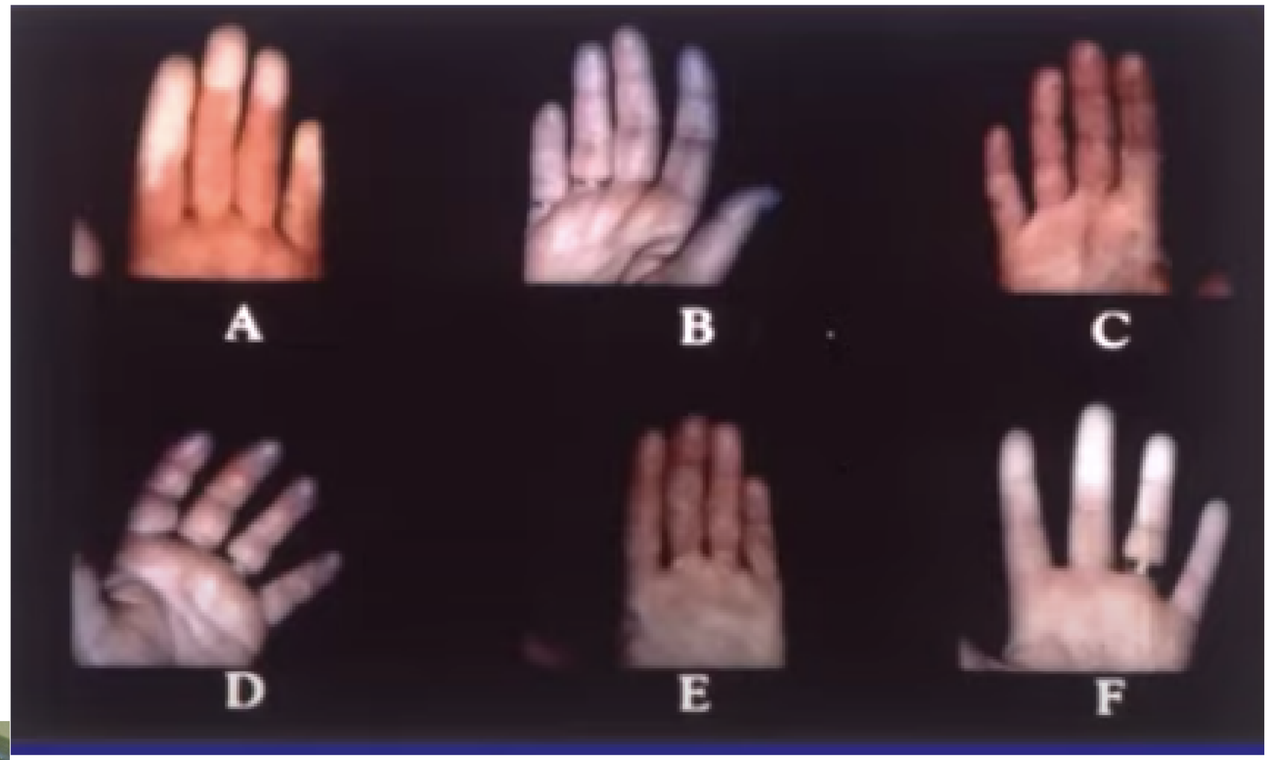
1. Limited cutaneous systemic sclerosis
2. Mixed connective tissue disease
3. Dermatomyositis
4. Systemic Lupus Erythematosus

Nail Capillary Microscopy



Raynaud's Phenomenon

- Vasospasm of small vessels of hands
- Pallor --> Cyanosis --> Erythema
- Obliterative vasculopathy
- First manifestation
  - Precedes other features by months to years



Maricq, H. R., and M. C. Weinrich. "Diagnosis of Raynaud's phenomenon assisted by color charts." The Journal of rheumatology 15.3 (1988): 454-459.

Raynaud's Treatment

Life style modifications and goals

- Avoid temperature changes
- Avoid smoking, caffeine
- Stress management
- Avoid sympathomimetics
- Dilate the blood vessels
- Prevent ulcers

Pharmacologic therapies

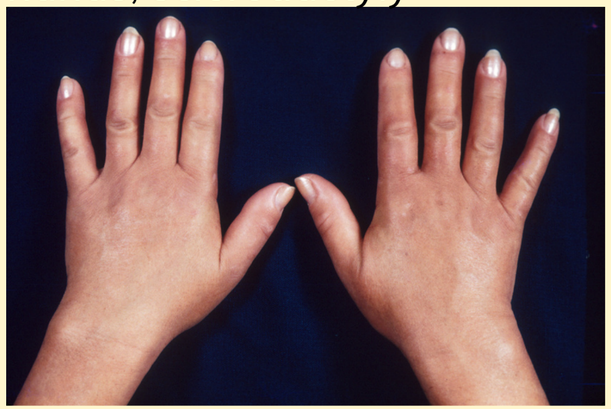
- Calcium channel blockers - Amlodipine/Nifedipine
- Phosphodiesterase inhibitors - Sildenafil
- Vasodilators - Topical nitroglycerin
- Endothelin receptor antagonists - Bosentan
- Prostacyclin analogs - Iloprost
- Sympathectomy

DIGITAL ISCHEMIA is an emergency and should be treated with urgency.

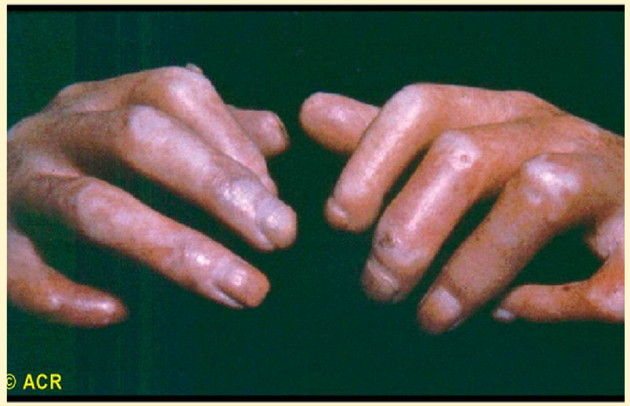
McMahan, Zsuzsanna H., and Fredrick M. Wigley. "Raynaud's phenomenon and digital ischemia: a practical approach to risk stratification, diagnosis and management." International journal of clinical rheumatology 5.3 (2010): 355.

Skin Manifestations

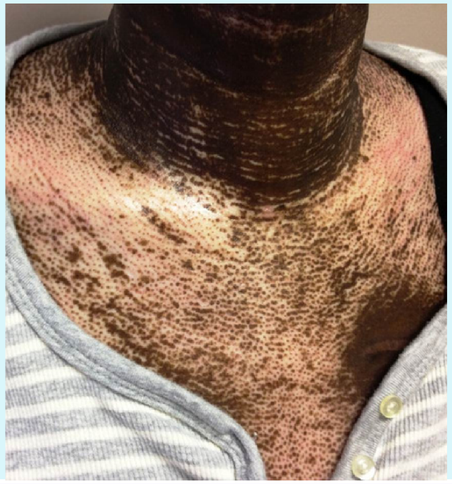
Initially diffusely swollen fingers and hands, sclerodactyly



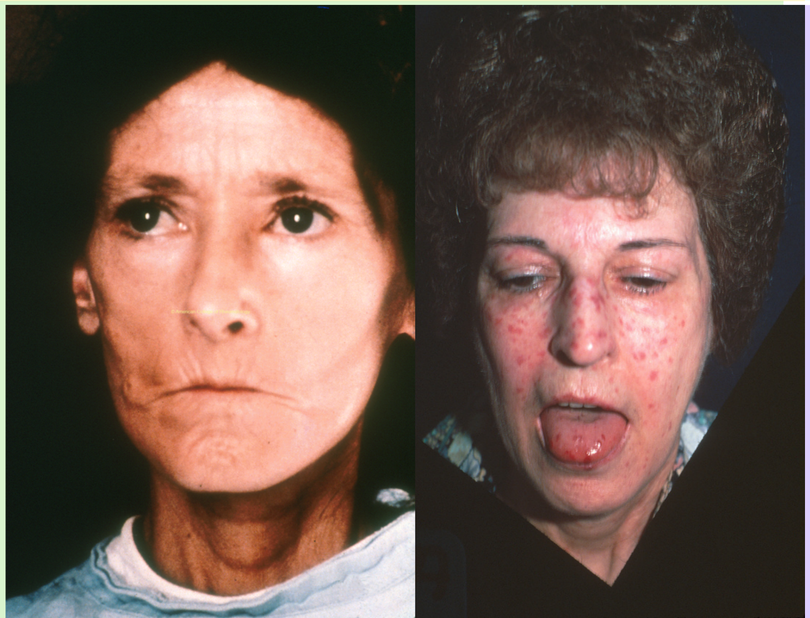
Skin thickening, atrophy, immobility and contractures



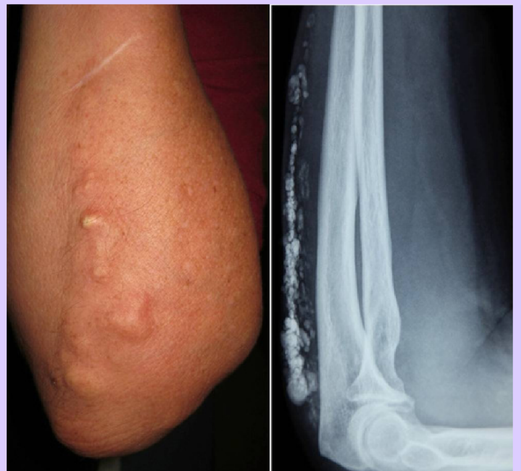
Poikiloderma (salt and pepper)

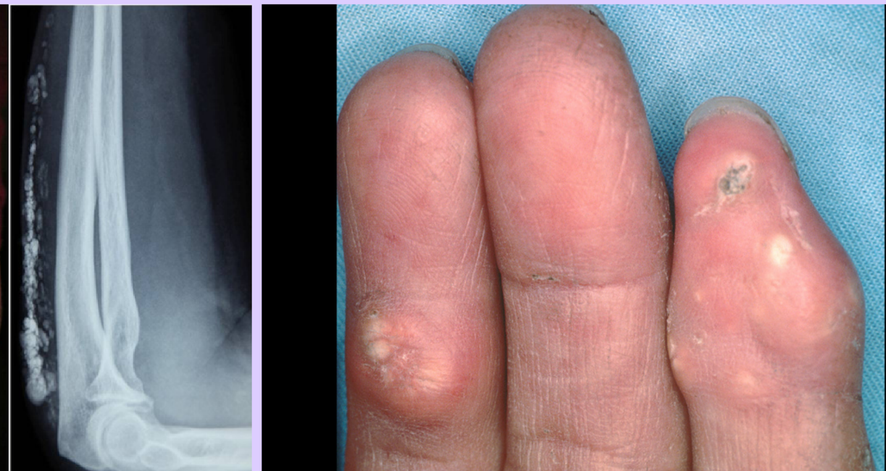


Decrease in oral aperture, devoid of wrinkles and telangectasias



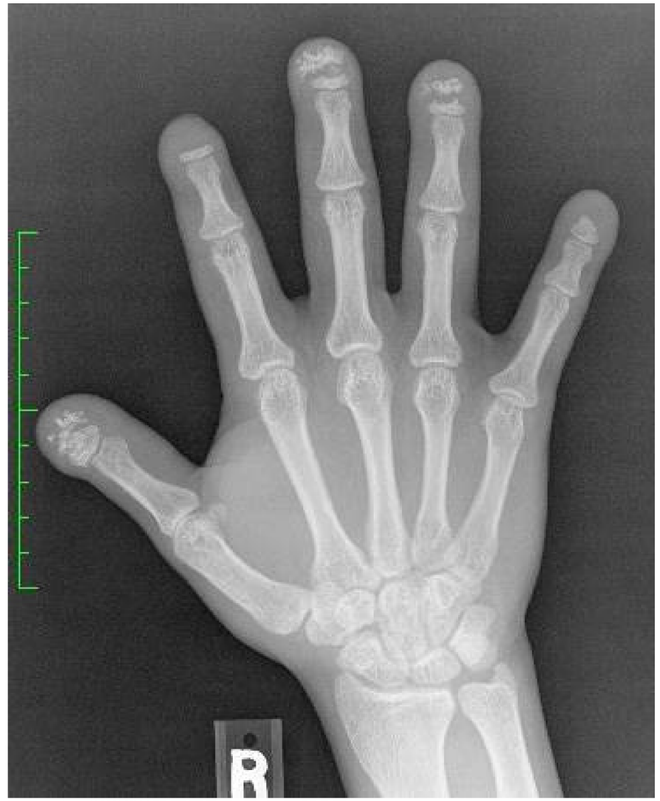
Calcinosis





Musculoskeletal

- Inflammatory arthritis
- Acroosteolysis (20-25% in severe disease)
- Myositis, anti-PM-Scl antibodies "Overlap myositis"
- Tendon friction rubs (RNP Pol III)



Gastrointestinal

- Esophageal dysmotility (dilated, patulous esophagus)
- GERD
- Gastroparesis
- Gastric antral vascular ectasia (GAVE)
- Small intestine bacterial overgrown (SIBO)
- Constipation
- Fecal incontinence

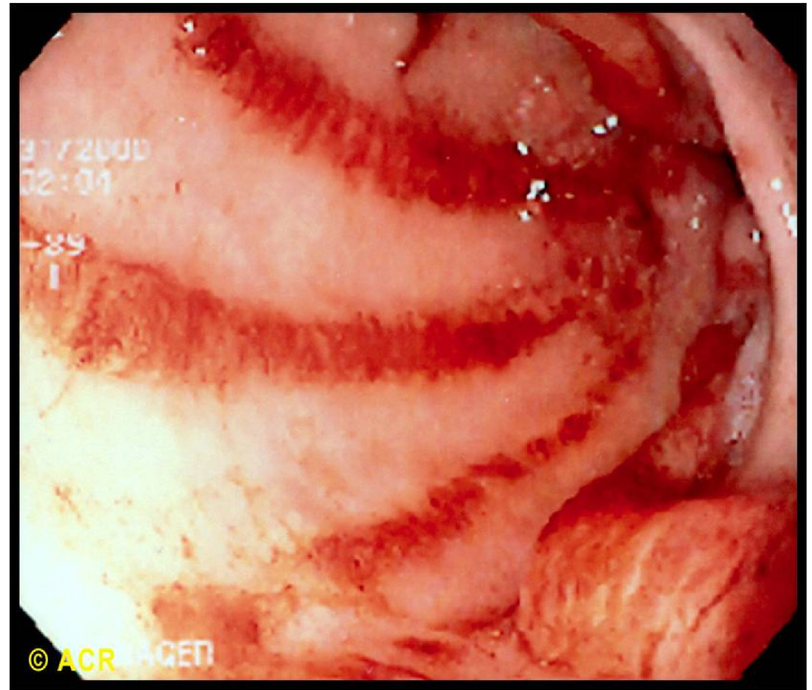
Forbes, Andrew, and I. Marie. "Gastrointestinal complications: the most frequent internal complications of systemic sclerosis." Rheumatology 48.suppl_3 (2006): iii36-iii39.

Case 2

41 YO M with history of diffuse SSc (+RNA pol III positive) who presents with fatigue, dyspnea and dark stools. He does not drink alcohol or use NSAIDs. Medications are omeprazole for GERD and amlodipine for raynaud's.

Physical exam: normal temp, 100/60 BP, 93 HR, 98% on RA. Skin changes related to diffuse SSc, no abdominal tenderness.
Labs: Hgb of 8.1, prior 10.0 (2 months prior)

EGD findings are shown.



What is the diagnosis? Treatment?

Case 3

50 YO M with 3 months of exertion dyspnea, he was diagnosed with diffuse cutaneous scleroderma 2 years ago. He has raynauds, GERD.
He is scl70 positive.

His vitals are normal. O2 sat 94% on RA. He has scattered telangectasias, sclerodactyly of the fingers and caclinosis on his elbows. Bibasilar crackles present.
EKG, Echo and chest xray are unrevealing.

What are you concerned about? What would your next steps be?

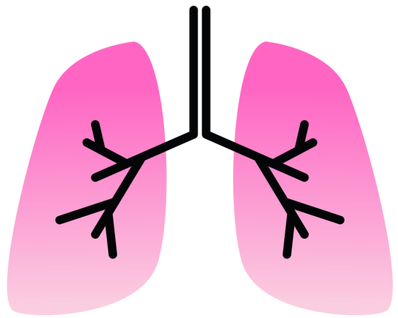
Dyspnea in SSc

Infection

ILD

pHTN

Aspiration /GERD



Cancer

Airway Disease

MSK

Pleural Effusion

SSc-ILD

- Leading cause of death and most frequent pulmonary manifestation
- Greatest risk in the first 4 years of diagnosis
- Symptoms:
  - Dyspnea on exertion
  - Non productive cough
  - Fatigue
  - Chest pain
  - Some have no symptoms
- NSIP most common pattern - 75%
- PFTs and HRCT at diagnosis
- PFTs with DLCO every 6-12 months x 5 years

SSc-ILD - Poor prognosis

- Diffuse skin involvement
- Late age of disease onset
- African American or Native American ethnicity
- DLCO<40% predicted
- Scl-70: Over 85% patients develop ILD
- PFTs: Early in course of disease
- HRCT: >20% lung volume

SSc-ILD

Pulmonary function tests (PFTs)

- Obtain at initial presentation in all patients – Include spirometry and DLCO
- Restrictive pattern – Decreased FVC
  - FEV1/FVC normal
- Thickening of interstitium --> decreased DLCO
- Changes of 10% in FVC and 15% in DLCO are significant

HRCT

- Earlier detection of ILD
- More accurate quantification
- Most common pattern
  - Non-specific interstitial pneumonia (NSIP)
    - Ground glass opacities and fibrosis
    - Bilateral, peripheral, lung bases
    - Extent of fibrosis on HRCT has negative correlation with FVC and DLCO

SSc-ILD Treatment

- **Mycophenolate mofetil (MMF),** By mouth, 0.5-1.5 g twice daily
- **Cyclophosphamide (CYC),** By mouth, 2mg/kg daily OR Intravenous, 500-750 mg/m2 of body surface area, monthly
- **Rituximab (RTX)**
- **Azathioprine (AZA),** By mouth, 2.5 mg/kg daily (max 150 mg/day)
- **Nintedanib,** By mouth, 150mg twice daily
- Tocilizumab , 162 mg SubQ weekly

- Autologous stem cell transplant

Tashkin, Donald P., et al. "Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial." The Lancet Respiratory Medicine 4.9 (2016): 708-719.
Distler, Oliver, et al. "Nintedanib for systemic sclerosis–associated interstitial lung disease." New England Journal of Medicine 380.26 (2019): 2518-2528.
Khanna, Dinesh, et al. "Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial." The Lancet 387.10038 (2016): 2630-2640.

Case 4

46 YO F with long standing diffuse SSc and ILD presents with worsening dyspnea for 2 months, with increased fatigue and lower extremity edema
Medication: Mycophenolate mofetil 750mg PO BID and Omeprazole 20mg PO qd

Physical exam: Fatigued, O2 sat 90% on room air, Diffuse skin thickening, Cardiac exam with prominent P2, JVP elevated at 10 cm above sternal angle and bibasilar crackles

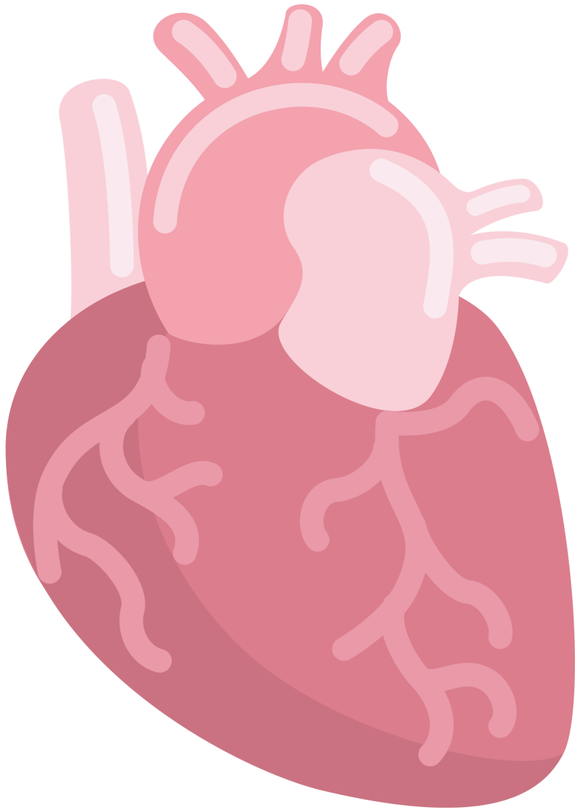
What are you concerned about? What is your next test?

SSc-Pulmonary Hypertension

- Most commonly Group 1 PAH, can see Group 2 and Group 3
- Screening with echo yearly
- Dx based on RHC: PAP > 20mmHg
- Risk factors for pHTN
  - Limited cutaneous scleroderma (especially >3 years)
  - Duration of Raynaud's phenomenon >8 years
  - Anticentromere antibody positivity
  - Isolated nucleolar pattern ANA positivity
  - Extensive telangiectasia
  - DLco% <60% in the absence of extensive ILD
  - FVC%/DLco% ratio >1.6

Cardiac

- Often silent
- Myocarditis, pericarditis and myocardial fibrosis are common
  - Heart failure and arrhythmia
- Increased coronary artery disease (3x HR)
- Screening with echo yearly



Case 5

33 YO F hospitalized for acute kidney injury and new hypertension, she was diagnosed with diffuse scleroderma about 2 years ago based on skin changes, Raynauds and RNA Pol III positive antibody. Her medications is amlodipine for Raynauds and pantoprazole for GERD.

Physical exam: Normal temp, 110bpm, 160/99 BP. Sclerodactyly is present, salt-and-pepper changes to her anterior chest, breath sounds with bibasilar crackles.

Hgb 8, Plts 50,000, Cr 2.8, UA + protein

What is likely diagnosis?

A. Hypertensive emergency
B. Scleroderma renal crisis
C. TTP
D. Posterior reversible encephalopathy syndrome

Case 5

33 YO F hospitalized for acute kidney injury and new hypertension, she was diagnosed with diffuse scleroderma about 2 years ago based on skin changes, Raynauds and RNA Pol III positive antibody. Her medications is amlodipine for Raynauds and pantoprazole for GERD.

Physical exam: Normal temp, 110bpm, 160/99 BP. Sclerodactyly is present, salt-and-pepper changes to her anterior chest, breath sounds with bibasilar crackles.

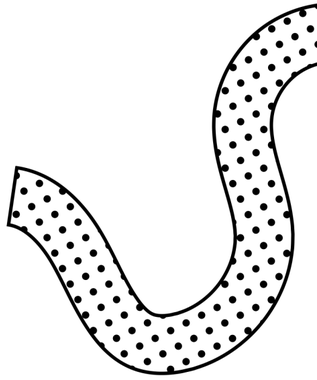
Hgb 8, Plts 50,000, Cr 2.8, UA + protein

What is your next step in treatment?

A. Start IV Hydralazine
B. Start Captopril
C. CT Head
D. Start metoprolol

Renal

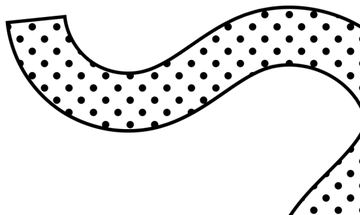
- 50% of patients with proteinuria, but most do not progress to CKD



Scleroderma Renal Crisis

- New onset BP > 150/85, increase greater than 20mmhg from
- Decline in renal function
- SRC is life threatening, occurs in about 10-15%, more frequent in diffuse SSc and Anti-RNA polymerase III antibodies.
- Occurs early in the disease
- Mortality of 90% if untreated
  - HTN
  - Proteinuria
  - Retinopathy
  - MAHA
  - Thrombocytopenia
- **Treat with ACE inhibitors (Captopril at first due to short half-life, titrate),** even with rising creatinine. Titrate to decrease the systolic blood pressure by 20 mmHg within the first 24 hours.

Avoid HIGH dose **prednisone** in SSc patients, can precipitate SRC



Mixed Connective Tissue Disease

- A distinct clinical condition!
  - Overlap of SLE, polymyositis and systemic sclerosis
  - High positive ANA, HIGH POSITIVE RNP

Two algorithms for establishing a diagnosis of mixed connective tissue disease (MCTD)

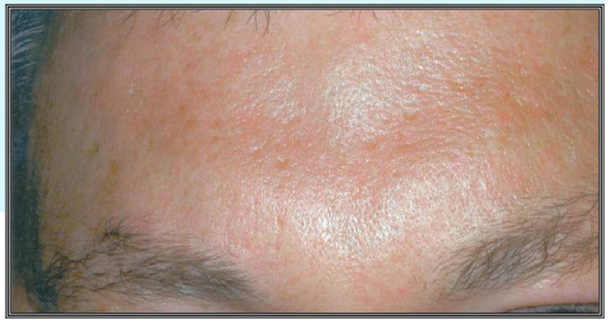
Alarcon-Segovia's criteria	Kahn's criteria
A. Serological criteria	**A. Serological criteria**
Anti-RNP antibodies with a hemagglutination titer of ≥1:1600	High titer anti-RNP corresponding to a speckled ANA of ≥1:1200 titer
B. Clinical criteria	**B. Clinical criteria**
1. Swollen hands	1. Swollen fingers
2. Synovitis	2. Synovitis
3. Myositis*	3. Myositis
4. Raynaud's phenomenon	4. Raynaud phenomenon
5. Acrosclerosis	
MCTD is present if:	**MCTD is present if:**
Criterion A is accompanied by three or more clinical criteria - one of which must include synovitis or myositis.	Criterion A is accompanied by Raynaud phenomenon and two or more of the three remaining clinical criteria.

- Mortality due to pHTN and ILD - screen yearly for pHTN

Scleroderma Mimics

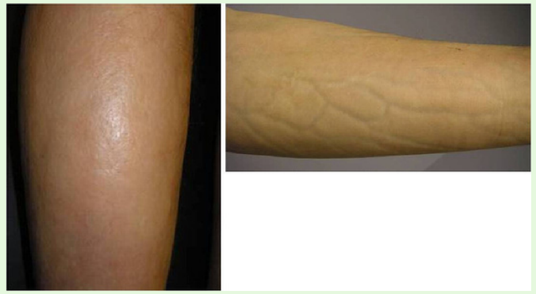
Scleredema

- Diabetes, infection, monoclonal gammopathy
- Diffuse, woody induration of the skin



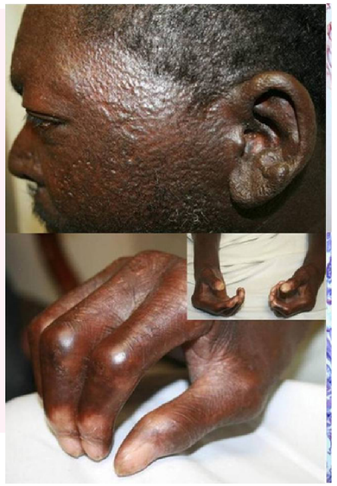
Eosinophilic fasciitis

- Symmetrical induration of the extremities with eosinophils
- Rapid onset, deep fascia
- Pitting edema progressing to indurated woody (peau d’orange) with a "groove" sign due to retraction of the subQ tissues



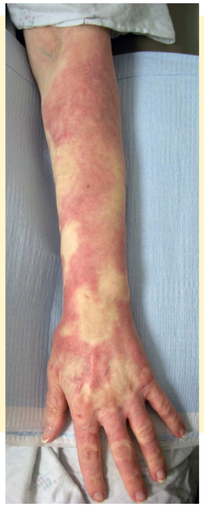
Scleromyxedema

- Cutaneous mucinosis associated with monoclonal gammopathy
- Waxy firm papules with mucin deposits



Nephrogenic Systemic Fibrosis

- Kidney failure and exposure to gadolinium-containing contrast
- Days to weeks
- Lower extremities and extend proximally



Conclusion

- **Multi-organ disease**, with team based approach
  - Treatment is mainly organ specific and symptomatic
- **Raynaud's phenomenon** is common and early manifestation of SSc, a lack of Raynaud's should prompt exploration of alternative diagnosis
- **Digital ischemia** and **scleroderma renal crisis** are emergencies

Questions?

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