Table 16. Classification Criteria of APLS*

Criteria	Description
CLINICAL	
Vascular thrombosis	Arterial: stroke/TIA, multi-infarct dementia, MI, valvular incompetence, limb ischemia Venous: DVT, PE, renal and retinal vein thrombosis Must be confirmed by imaging or histopathology
Pregnancy morbidity	Fetal death (>10 wk GA), recurrent spontaneous abortions (<10 wk GA) or premature birth (<34 wk GA)
LABORATORY	Labs must be positive on 2 occasions, at least 12 wk apart
SLE anticoagulant	Prolonged aPTT not corrected by the addition of normal plasma
Anti-cardiolipin Ab	IgG and/or IgM
Anti-β2 glycoprotein-I Ab	IgG and/or IgM
ANA	Most sensitive test (98%), not specific

* 1 clinical and 1 laboratory criteria must be present *J Thromb Haemost* 2006;4:295-306

Manifestations of APLA
- Thromboembolic events
- Spontaneous abortions
- Thrombocytopenia
- Associated with livedo reticularis, migrane headaches

Signs and Symptoms
- see clinical criteria in Table 16
- hematologic
  - thrombocytopenia, hemolytic anemia, neutropenia
- dermatologic
  - livedo reticularis, Raynaud's phenomenon, purpura, leg ulcers, and gangrene

Arterial and venous thrombosis are usually mutually exclusive

Treatment
- thrombosis
  - lifelong anti-coagulation with warfarin
  - target INR 2.0-3.0 for first venous event, >3.0 for recurrent and/or arterial event
- recurrent fetal loss
  - heparin/low molecular weight heparin ± ASA during pregnancy
- catastrophic APLA
  - high-dose steroids, anti-coagulation, cyclophosphamide, plasmapheresis

Scleroderma (i.e. Systemic Sclerosis)

Definition
- a non-inflammatory autoimmune disorder characterized by widespread small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction causing fibrosis

CREST Syndrome
Calcinosis
Raynaud's phenomenon
Esophageal dysmotility
Sclerodactyly
Telangiectasia

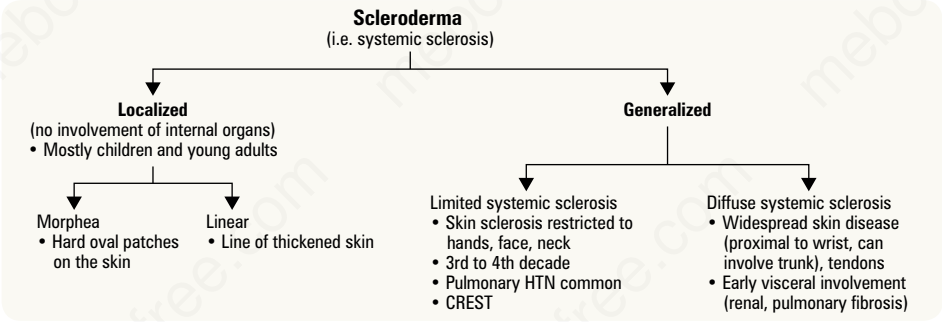

Figure 8. Forms of scleroderma

Table 17. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Criteria for Scleroderma*

Item	Sub-item	Score
1. Skin thickening of fingers of both hands extending proximal to the MCP (sufficient criterion)		9
2. Skin thickening of the fingers	Puffy fingers Sclerodactyly	2 4
3. Fingertip lesions	Digital tip ulcers Fingertip pitting scars	2 3
4. Telengiectasia		2
5. Abnormal nailfold capillaries		2
6. Pulmonary arterial HTN ± ILD (max score 2)	Pulmonary arterial HTN ILD	2 2
7. Raynaud's phenomenon		3
8. Scleroderma related Ab	Anti-centromere Anti-topoisomerase I Anti-RNA polymerase III	3

* Score of ≥9 is sufficient to classify a patient as having definite scleroderma (sensitivity 0.95, specificity 0.93)
Arthritis & Rheum 2013;65(11):2737-2747

Scleroderma is the most common cause of secondary Raynaud's phenomenon

Etiology and Pathophysiology

- idiopathic vasculopathy (not vasculitis) leading to atrophy and fibrosis of tissues
  - intimal proliferation and media mucinous degeneration → progressive obliteration of vessel lumen → fibrotic tissue
  - resembles malignant HTN
  - lung disease is the most common cause of morbidity and mortality

Epidemiology

- F:M = 3-4:1, peaking in 5th and 6th decades
- associated with HLA-DR1
- associated with environmental exposure (silica, epoxy resins, toxic oil, aromatic hydrocarbons, polyvinyl chloride)
- limited systemic sclerosis has a higher survival prognosis (>70% at 10 yr) than diffuse systemic sclerosis (40-60% at 10 yr)

Signs and Symptoms

Table 18. Clinical Manifestations of Scleroderma

System	Features
Dermatologic	Painless non-pitting edema → skin tightening Ulcerations, calcinosis, periungual erythema, hypo/hyperpigmentation, pruritus, telangiectasias Characteristic face: mask-like facies with tight lips, beak nose, radial perioral furrows
Vascular	Raynaud's phenomenon → digital pits, gangrene
Gastrointestinal (~90%)	Distal esophageal hypomotility → dysphagia Loss of lower esophageal sphincter function → GERD, ulcerations, strictures Small bowel hypomotility → bacterial overgrowth, diarrhea, bloating, cramps, malabsorption, weight loss Large bowel hypomotility → wide mouth diverticuli are pathognomonic radiographic finding on barium study
Renal	Mild proteinuria, Cr elevation, HTN "Scleroderma renal crisis" (10-15%) may lead to malignant arterial HTN, oliguria, and microangiopathic hemolytic anemia
Pulmonary	Interstitial fibrosis, pulmonary HTN, pleurisy, pleural effusions
Cardiac	Left ventricular dysfunction, pericarditis, pericardial effusion, arrhythmias
Musculoskeletal	Polyarthralgias "Resorption of distal tufts" (radiological finding) Proximal weakness 2º to disuse, atrophy, low grade myopathy
Endocrine	Hypothyroidism

Investigations

- blood work
  - CBC, Cr, ANA
  - anti-topoisomerase 1/anti-Scl-70: specific but not sensitive for diffuse systemic sclerosis
  - anti-centromere: favours diagnosis of CREST (limited systemic sclerosis)
- PFT
  - assess for interstitial lung disease
- imaging
  - CXR for fibrosis, echo for pulmonary HTN

Treatment

- dermatologic
  - good skin hygiene
  - low-dose prednisone (>20 mg may provoke renal crisis if susceptible), MTX (limited evidence)
- vascular
  - patient education on cold avoidance
  - vasodilators (CCBs, local nitroglycerine cream, systemic PGE2 inhibitors, PDE5 inhibitors)
- gastrointestinal
  - GERD: PPIs are first line, then H2-receptor agonists
  - small bowel bacterial overgrowth: broad spectrum antibiotics (tetracycline, metronidazole)
- renal disease
  - ACEI for hypertensive crisis
  - see Nephrology, NP32 for scleroderma renal crisis
- pulmonary
  - early interstitial disease: cyclophosphamide
  - pulmonary HTN: vasodilators (e.g. bosentan , epoprostenol, and PDE5 inhibitors)
- cardiac
  - pericarditis: systemic steroids
- musculoskeletal
  - arthritis: NSAIDs
  - myositis: systemic steroids

Cyclophosphamine versus Placebo in Scleroderma Lung Disease
NEJM 2006; 354:2655-66
Study: Double-blind, randomized, placebo-controlled trial
Outcome: Lung function and health-related symptoms
Results: The mean absolute difference in adjusted 12-month FVC percent predicted between cyclophosphamide and placebo groups was 2.53 percent, favouring cyclophosphamide. There were also treatment-related differences in physiological and symptom outcomes, and the difference in FVC was maintained at 24 months
Conclusion: Cyclophosphamide has a significant but modest beneficial effect on lung function, dyspnea, thickening of skin and health-related quality of life in patients with symptomatic, scleroderma-related interstitial lung disease

Raynaud's Phenomenon DDx

COLD HAND
Cryoglobulins/**C**ryofibrinogens
Obstruction/**O**ccupational
Lupus erythematosus, other connective tissue disease
Diabetes mellitus/**D**rugs
Hematologic problems (polycythemia, leukemia, etc.)
Arterial problems (atherosclerosis)/**A**norexia nervosa
Neurologic problems (vascular tone)
Disease of unknown origin (idiopathic)

Features of Pathologic Raynaud's Syndrome
- New onset
- Asymmetric
- Precipitated by stimuli other than cold or emotion
- Associated with distal pulp pitting or tissue reabsorption
- Digit ischemia
- Capillary dilatation by capillaroscopy