# Systemic sclerosis

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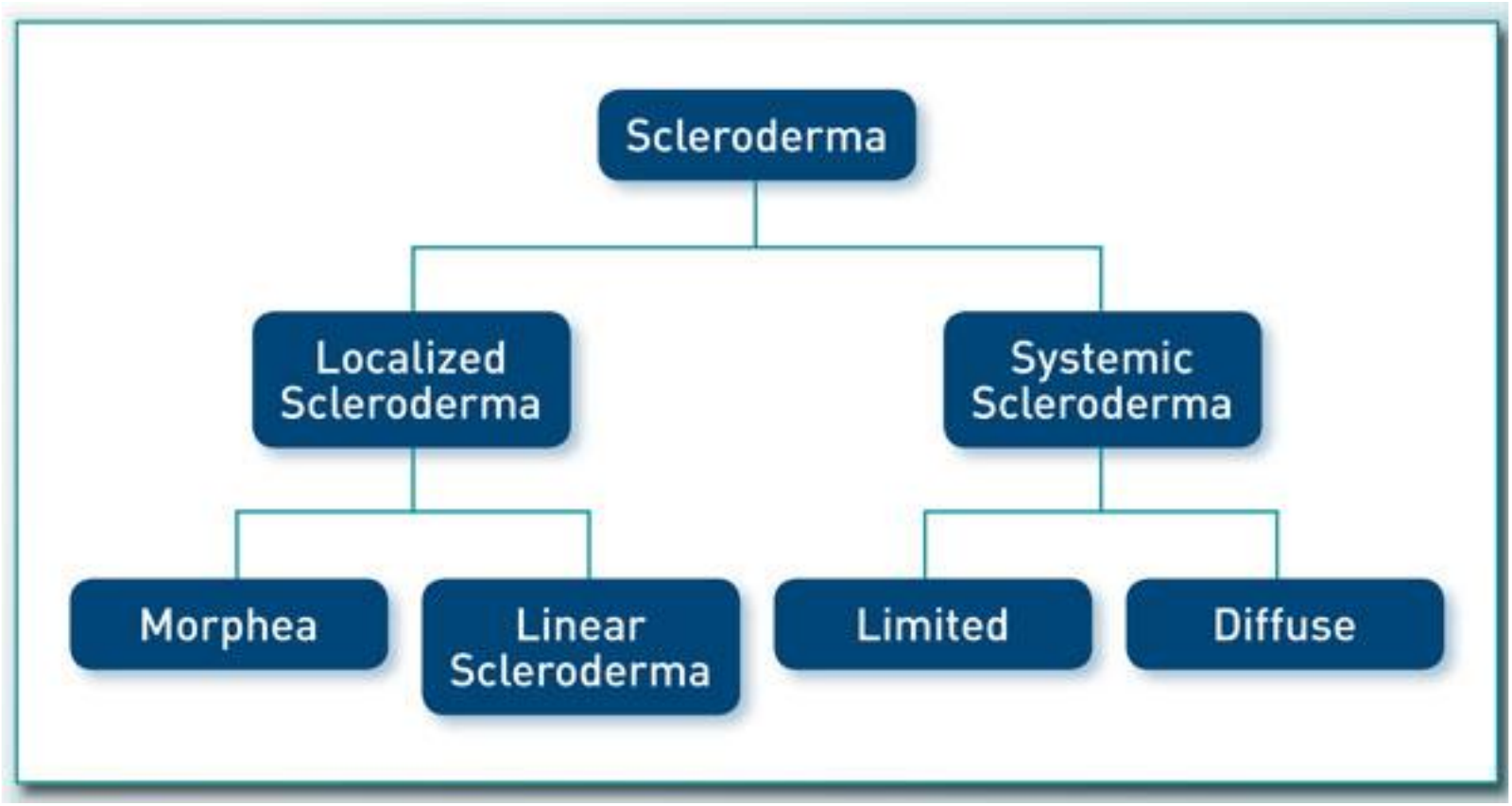
# Systemic sclerosis

- Is an autoimmune disease characterized by **microvascular injury and excessive connective tissue deposition in the skin and internal organs.**
- SSc presents with a variety of symptoms and show considerable heterogenity in clinical complications, autoantibody profiles, natural history, and prognosis.
- **Raynaud phenomenon, skin induration, esophageal problems, and pulmonary and cardiac fibrosis are common complications with no effective therapy.**
- Scleroderma **renal crisis** and **pulmonary hypertension** are major complications that can be managed with current therapies.
- Early recognition, symptomatic treatment and integrated care from is associated with improved outcomes and survival in SSc.

# Scleroderma



# Classification of systemic sclerosis

(adapted according to J.R. Seibold, 1994)

**I. diffuse** – skin thickening on the trunk, face and limbs.

**II. limited -** skin thickening localized distally of elbows and knees, with face involvement, (CREST syndrom).

**III. sine scleroderma –** without skin involvement (except of face), fibrotic changes of visceral organs.

**IV. overlap syndrome -** fulfilled criteria of systemic sclerosis and of SLE, RA or polymyositis.

**V. undifferentiated connective tissue disease-** Raynaud's phenomenon with clinical and/or laboratory abnormalities – anticentromere antibodies, skin vascular trophic changes.

# Clinical features

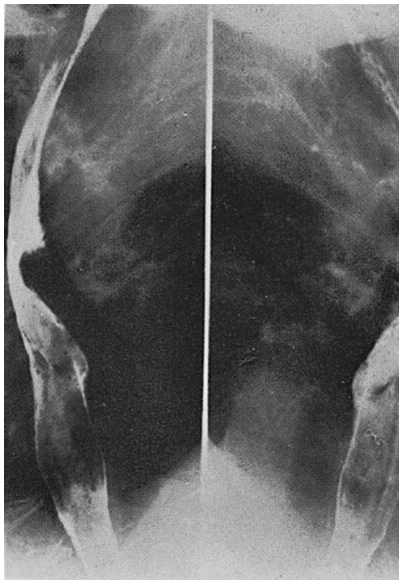
- **Early symptoms**:
  - **Raynaud phenomenon**, **skin tightening**,
  - systemic features: malaise, fatigue, arthralgia, and myalgia.

- **Vascular system:**
  - **Raynaud phenomenon** is present in greater than **95%** of patients with SSc
  - cold-induced and, less commonly, stress-induced, vasospasm in the digits.
  - **digital pits , digital ulcers, dry gangrene and auto-amputation**.

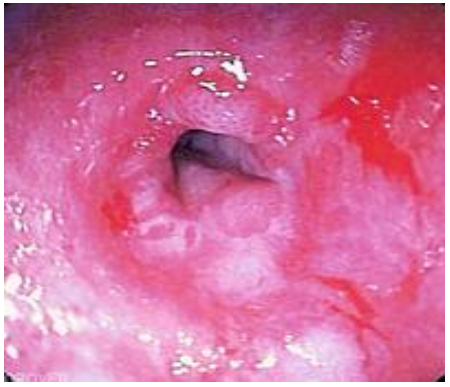
- **Cutaneous features:**
  - Fingers appear puffy and there may be loss of the skin creases on the fingers.
  - Diffuse skin changes there may be involvement of the skin on the hands, forearms, arms, chest, abdomen, thighs, legs, and feet.
  - Patients with limited cutaneous disease have skin changes limited to the face, neck, and distal extremities (distal to the elbows and knees).
  - Other skin manifestations include **telangiectases**, **digital pits**, **and calcinosis**.

# Systemic features - GIT

- **Gastrointestinal involement:**
- Reduced oral aperture from skin tightening, mandibular atrophy and a shortened frenulum.
- Esophageal dysmotility
- Gastroesophageal reflux and dyspepsia.
- Gastric involvement -bloating, nausea, emesis, anorexia, and weight loss.
- Intestinal dysmotility
- The liver is rarely primarily involved in SSc; however, an association does exist between primary biliary cirrhosis (PBC) and SSc, and a significant proportion of patients with PBC have an anti-centromere antibody.



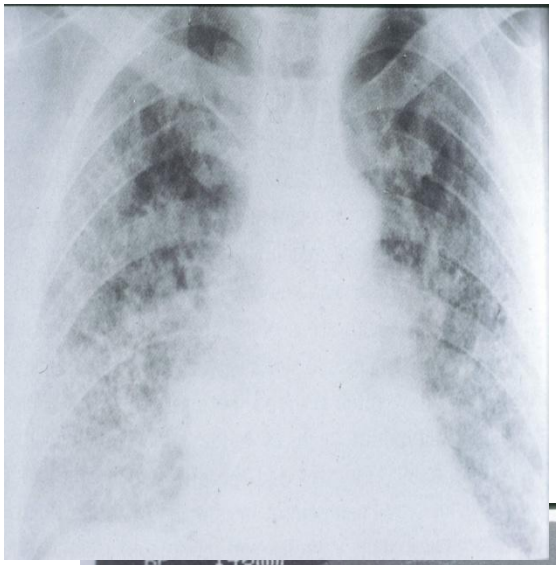
Postinflammatory stenosis and achalasia of esophagus

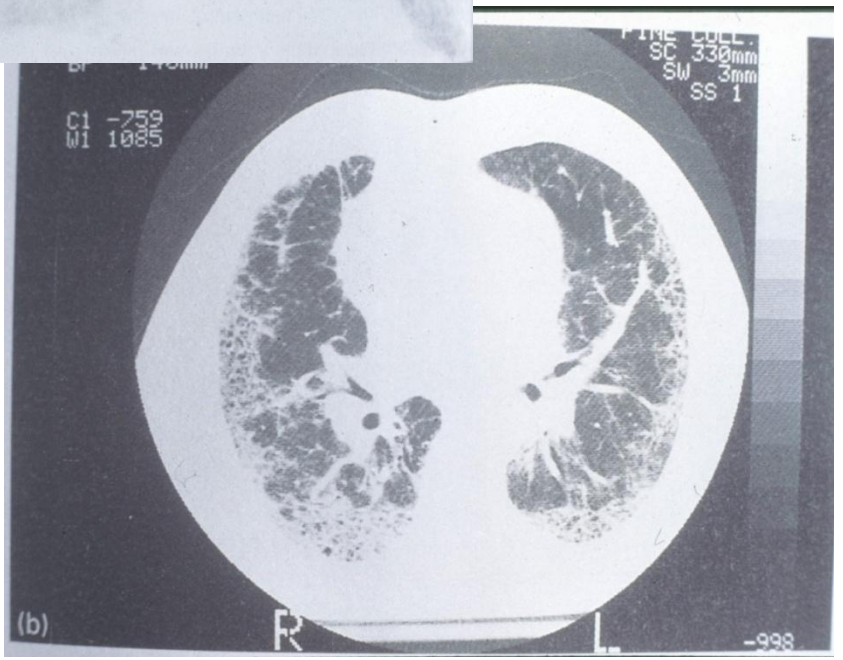


Endoscopic image of peptic stricture, ot narrowing of the esophagus near the junction with the stomach due the chronic gastroezophageal reflux. This is the most common cause of dysphagia

# Systemic features - lungs

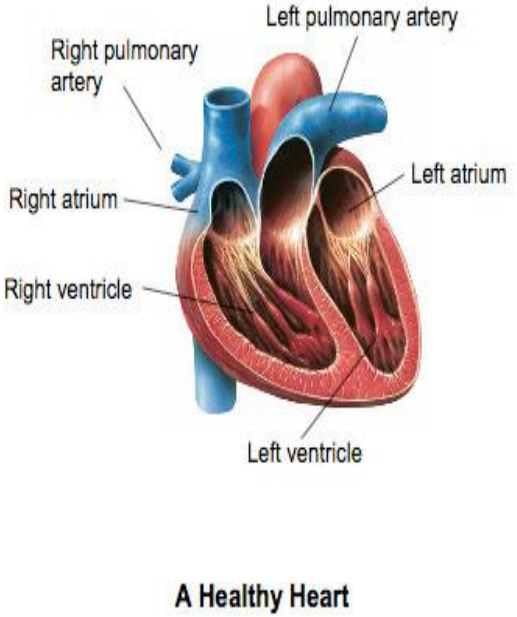
- **Pulmonary involvement**
- **interstitial lung disease** (ILD) **and/or pulmonary arterial hypertension (PAH)**. Other less common manifestations of lung involvement include aspiration pneumonia, pleural disease, obstructive airways disease, endobronchial telangiectasia with hemoptysis.
- ILD characterically begins as **basilar pulmonary fibrosis**
- pulmonary function testing with spirometry, lung volumes, and tests of gas exchange is the best method to screen for ILD. The most sensitive and earliest change is a reduction in diffusion capacity.
- bronchoalveolar lavage (BAL)



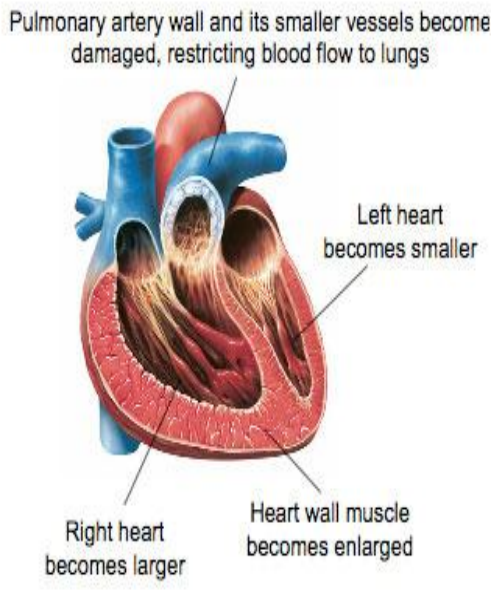


# Pulmonary vascular disease

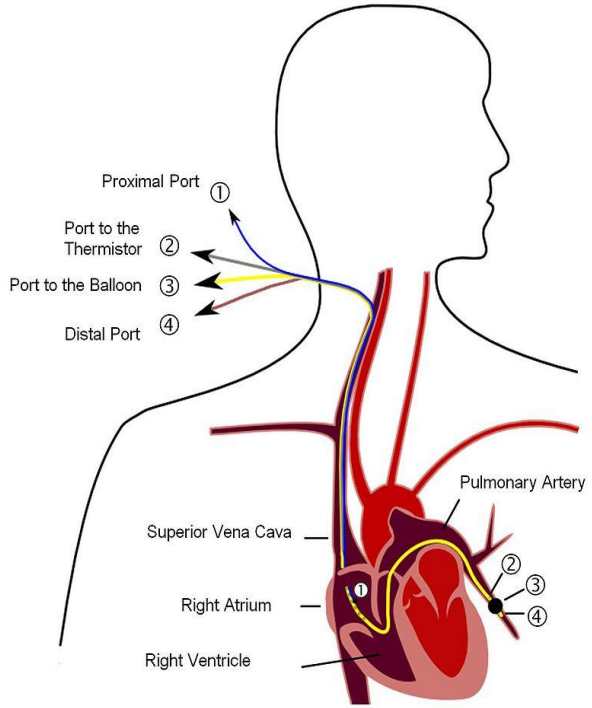
- **Pulmonary vascular disease** may occur either as a **primary vasculopathy** or **secondary to underlying cardiac disease** or **ILD**.
- Isolated pulmonary hypertension more commonly occurs in patients with limited cutaneous SSc, and typically presents many years after the onset of Raynaud phenomenon.




A Healthy Heart




A Heart with PAH*



# Other systemic organ involvement

- **Cardiac manifestations -**not often clinically evident, is a poor prognostic indicator. Include pericardial disease, a dilated cardiomyopathy, autonomic neuropathy, and arrhythmias.

- **Renal involvement: Scleroderma renal crisis** is one of the cardinal vascular manifestations of SSc. It is characterized by a high renin state, and the pathologic changes in the blood vessels are similar to that seen in other vessels in patients with SSc. It is estimated that 10% of patients with SSc will develop SRC.

- **Musculoskeletal symptoms -**arthralgia and myalgia, and some patients may develop a true inflammatory arthropathy and/or myopathy. The most common joints involved include the proximal interphalangeal, metacarpophalangeal, wrist, and ankle joints.

# Additional examinations

- **Skin:** capillaroscopy, biopsy
- **GIT:** baryum swallow, endoscopy, scintigraphy of esophagus, esophageal manometry
- **Musculoskeletal system**: X-ray - resorption of distal phalangi and calcifications
- **Lungs:** functional tests including DLCO, HRCT and bronchoscopy with cytology of BAL fluid
- **Heart:** ECG, ECHO and ECG-Holter monitoring
- **Kidneys:** biopsy - pathology: vasculitis of interlobar arteries and afferent arterioli

# Laboratory tests

- Light increase of acute-phase reactants
- Anemia
- Thrombocytopenia
- Autoantibodies:

  - anti-centromere antibody (limited cutaneous SSc)

  - anti-topoisomerase antibody (diffuse skin involvement and interstitial lung disease)

  - anti-RNA polymerase III (diffuse skin changes and renal crisis)

# Autoantibodies

| Antibodies | Prevalence (%) | Clinical association |
|---|---|---|
| Anticentromere | 20–30 | Limited scleroderma, Crest syndrome, pulmonary hypertension |
| Antitopoisomerase (anti-Scl-70) | 15–20 | Diffuse scleroderma, interstitial lung disease |
| Anti-PM-Scl | 2–3 | Polymyositis/scleroderma overlap |
| Anti-To/Th | 2–5 | Limited scleroderma |
| Anti-RNA polymerase | 20 | Diffuse scleroderma |
| Antifibrillarin | 4 | Diffuse scleroderma, myositis, pulmonary hypertension, renal disease |
| Anti-Ku, anti-Sm, anti-U1RNP | Rare | Overlap syndromes with features of scleroderma |
| Anticardiolipin antibodies | 20–25 | Limited/diffuse subsets, features of secondary antiphospholipid antibody syndrome rare |

# ACR/EULAR criteria

RheumTutor.com

**2013 ACR / EULAR Criteria For The Classification Of Systemic Sclerosis (Scleroderma)***

| Item | Sub-items(s) | 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 higher score)* | Puffy fingers | 2 |
| | Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints) | 4 |
| Fingertip lesions *(only count the higher score)* | Digital tip ulcers | 2 |
| | Fingertip pitting scars | 3 |
| Telangiectasia | - | 2 |
| Abnormal nailfold capillaries | - | 2 |
| Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)* | Pulmonary arterial hypertension | 2 |
| | Interstitial lung disease | 2 |
| Raynaud's phenomenon | - | 3 |
| SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)* | Anticentromere 3<br>Anti–topoisomerase I<br>Anti–RNA polymerase III | 3 |

* The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

† The total score is determined by adding the maximum weight (score) in each category.
**Patients with a total score of ≥ 9 are classified as having definite scleroderma.**

Sensitivity 91% Specificity 92%

Van den Hoogen et al. 2013 Classification Criteria for Systemic Sclerosis. Arthritis and Rheumatism. Vol. 65, No. 11, November 2013, pp 2737–2747

# Therapy

## Immunomodulatory drugs

- **Cyklophosphamid**- a number of retrospective series have suggested that cyclophosphamide was effective for SSc-associated lung fibrosis.
- **Methotrexate** - skin involement.
- **Mycophenolate mofetil** - efficiency for skin, lung involement.
- **Azathioprin**

# Therapy

## Treatments for organ-specific complications

- **Raynaud´s phenomenom and acral ulcerations** – calcium chanell blockers, pentoxifyllin, sartans, prostaglandins analogs, bosentan, sildenafil, statins
- **Gastrointestinal disease-** proton pump inhibitors, procinnetics, antacids
- **Intersticial lung disease-** oxgenotherapy
- **Pulmonary arterial hypertension-** prostanoids, bosentan, ambriestan, sildanefil
- **Renal crisis** –ACE inhibitors