Systemic Sclerosis

Scleroderma
Definition

- Chronic systemic disorder
- Unknown etiology
- Thickening of the skin = scleroderma
- Involvement of multiple internal organs
- Early stage: inflammation
- Later stage: fibrosis
In scleroderma, the abnormal build-up of fibrous tissue in the skin can cause the skin to tighten so severely that the fingers curl and lose their mobility.
Conditions associated with scleroderma-like induration

- Limited cutaneous SSc
- Diffuse cutaneous SSc
- Morphea (localized)
- Overlap syndromes: MCTD, SSc/PM
- Scleromyxedema
- Paraneoplastic syndrome
- Vinyl chloride-induced SSc
- Pentazocine-induces SSc
## Classification

<table>
<thead>
<tr>
<th></th>
<th>Raynaud</th>
<th>Scleroderma Sine Scleroderma</th>
<th>Limited Scleroderma</th>
<th>Diffuse Scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raynaud</td>
<td><strong>YES</strong></td>
<td><strong>POSSIBLE</strong></td>
<td><strong>YES</strong></td>
<td><strong>YES</strong></td>
</tr>
<tr>
<td>Skin Involvement</td>
<td><strong>NO</strong></td>
<td><strong>NO</strong></td>
<td><strong>YES (focal)</strong></td>
<td><strong>YES (diffuse)</strong></td>
</tr>
<tr>
<td>Musculo-Skeletal</td>
<td><strong>NO</strong></td>
<td><strong>NO</strong></td>
<td><strong>YES</strong></td>
<td><strong>YES</strong></td>
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<tr>
<td>Gastro-Intestinal</td>
<td><strong>NO</strong></td>
<td><strong>YES</strong></td>
<td><strong>YES</strong></td>
<td><strong>YES</strong></td>
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<tr>
<td>Cardio-Pulmonary</td>
<td><strong>NO</strong></td>
<td><strong>YES</strong></td>
<td><strong>YES</strong></td>
<td><strong>YES</strong></td>
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<tr>
<td>Renal</td>
<td><strong>NO</strong></td>
<td><strong>YES</strong></td>
<td><strong>RARE</strong></td>
<td><strong>YES</strong></td>
</tr>
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</table>
Limited cutaneous SSc

- Skin: limited to fingers, distal to elbows, face, slow progression
- Raynaud’s phenomenon: precedes skin involvement
- Pulmonary fibrosis: moderate
- Pulmonary arterial hypertension: frequent
- Scleroderma renal crisis: very rare
- Calcinosis cutis: frequent, prominent
- Autoantibodies: Anticentromere
Diffuse cutaneous SSc

- Skin: diffuse, fingers, extremities, face, trunk, rapid progression
- Raynaud’s phenomenon
- Pulmonary fibrosis: frequent, early, severe
- Scleroderms renal crisis: occurs in 15%
- Calcinosis cutis: mild
- Autoantibodies: Antitopoisomerase = Scl-70
CREST syndrome

- Calcinosis cutis
- Raynaud´s phenomenon
- Esophageal dysmotility
- Sclerodactyly
- Telangiectasia
The limited symptoms of scleroderma are referred to as **CREST**

- **C**alcinosis - Calcium deposits in the skin.
- **R**aynaud’s phenomenon - spasms of blood vessels in response to cold or stress.
- **E**sophageal dysfunction - acid reflux and decrease in motility of esophagus.
- **S**clerodactyly - thickening and tightening of the skin on the fingers and hands.
- **T**elangiectasias - dilation of capillaries causing red marks on surface of the skin.
Epidemiology

- Incidence: 9-19 cases/million/year
- Female predominance
- Greatest in the childbearing years
- Onset: range of 30-50 years
Environmental factors

- Toxic oil syndrome: rapeseed oil
- L-Tryptophan: eosinophilia-myalgia syndrome
- Silica, polyvinil chloride, epoxy resins
- Bleomycin
- Silicone breast implants
Pathogenesis

- Vascular injury
- Cellular and humoral immunity
- Progressive visceral and vascular fibrosis in multiple organs
Vasculopathy and Fibrosis

- Raynaud’s phenomenon: altered blood flow response to cold
- Endothelial cell injury
- Fibrosis affects multiple organs
- Fibroblasts proliferate
- Scar formation via producing collagen
- TGFβ
- Circulating autoantibodies
Pathology

- Obliterative vasculopathy of small arteries and arterioles → luminal narrowing
- Fibrosis in the skin and internal organs
- Progressive replacement of normal tissue architecture
- Skin: collagen fiber accumulation
- Lungs: interstitial fibrosis and vascular damage, nonspecific interstitial pneumonitis, pulmonary hypertension
Pathology 2

- Gastrointestinal tract: from the mouth to the rectum, lower esophagus, small bowel obstruction, gastroesophageal reflux, premalignant Barret’s metaplasia
- Kidneys: chronic renal ischemia, renal crisis
- Heart: myocardial fibrosis
- Other organs: synovitis, fibrosis of tendon sheaths, inflammatory myositis, fibrosis of the thyroid gland, fibrosis of the salivary glands
Clinical features

- SSc can affect every organ
- Great deal of variability in its clinical expression from one patient to the next
- dcSSc = diffuse cutaneous SSc
- lcSSC = limited cutaneous SSc
- SSc sine scleroderma
- Digital necrosis: sharply demarcated necrosis of the fingertip
Clinical features 2

- Sclerodactily: skin induration and fixed flexion contractures at the proximal and distal interphalangeal joints
- Raynaud’s phenomenon
- Soft tissue swelling, intense pruritus
- Skin on the fingers, hands, distal limbs, and face affected first
- Arthralgias
- Decline in sweating capacity
- Telangiectasia, calcinosis
- The course of the SSc indolent
- Overlap syndromes
Raynaud’s Phenomenon

- Episodic vasoconstriction in the fingers and toes
- Tip of the nose and earlobes
- Cold exposure
- Pallor $\rightarrow$ cyanosis $\rightarrow$ erythema rewarming of the fingers, vasoconstriction $\rightarrow$ ischemia $\rightarrow$ reperfusion
- Normal population: 3-5%, women
- Primary and/or secondary
- Nailbed cutaneous capillaries viewed stereoscopic microscope
Raynaud’s Phenomenon

1. Fingers can become white due to the lack of blood flow
2. The fingers may turn blue as the blood vessels dilate to keep the blood in the tissues
3. Finally the fingers may turn red as the blood begins to return

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Skin features

- Skin thickening from distal to proximal
- Dermal sclerosis due to collagen accumulation
- Hair loss, decreased sweating, dry skin
- Face: loss of wrinkles, expressionless facies, microstomia
- Skin ulceration
- Resorption of the terminal phalanges
- Calcium deposits ulcerate through the skin
Pulmonary features

- Exertional dyspnea, chronic dry cough
- Crackles at the lung bases
- Reductions in forced vital capacity
- ILD = interstitial lung disease  HRCT, pulmonary fibrosis
- Restrictive lung disease
- Nonspecific interstitial pneumonitis
- PAH = pulmonary arterial hypertension: pulmonary arterial pressure >25 mm Hg determined by right heart catheterization
- Right heart failure, tachypnea, prominent pulmonic S2 heart sound, elevated jugular venous pressure, edema
- Doppler echocardiography
- BNP = brain natriuretic peptide↑
Gastrointestinal involvement

- Abnormal motility of the esophagus, stomach, small and large intestines
- GERD: heartburn, regurgitation, dysphagia
- Distal two-thirds of the esophagus
- Barret’s esophagus $\rightarrow$ adenocarcinoma
- Endoscopy
- Gastroparesis, gastric ectasia, watermelon stomach
- Malabsorption, malnutrition, intestinal pseudoobstruction
Renal involvement

- Hypertension, proteinuria, microscopic hematuria
- SSc renal crisis
- Abrupt onset of malignant hypertension
- Rapidly progressive oliguric renal failure
- Creatinine↑
Cardiac involvement

- Myocardial fibrosis and pericardial effusion and conduction defects and arrhythmias
- Heart failure
- Echocardiography: left ventricular diastolic dysfunction
Laboratory features

- Anemia ← chronic inflammation
- Iron deficiency anemia → GI bleeding
- ESR normal
- Scl-70 Ab = topoisomerase-I
- Anticentromere Ab
Diagnosis of SSc

- Clinical picture
- Skin induration + typical visceral organ manifestations
- Rarely: full-thickness biopsy of the skin
- Digital tip pitting scars + HRCT pulmonary fibrosis in the lower lobes
<table>
<thead>
<tr>
<th>Major Criterion</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>Proximal sclerodermatous skin changes (proximal to</td>
<td>1. Sclerodactyly</td>
</tr>
<tr>
<td>the metacarpophalangeal joints)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Digital pitting scars of fingertips or loss of</td>
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<td></td>
<td>the distal finger pad</td>
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<td></td>
<td>3. Bibasilar pulmonary fibrosis</td>
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</table>
Treatment of SSc

- Disease-modifying treatments: Cyclophosphamide in interstitial lung disease and in skin induration 6-12 months, steroids?, Methotrexate, D-penicillamine→antifibrotic agent in skin induration
- Raynaud’s: dree warmly, calcium channel blockers, ARBs (angiotensin II receptor blockers) Losartan, iv. prostaglandins, low-dose aspirin
Treatment of GI complications

- PPI (proton pump inhibitors)
- H2 blockers
Treatment of pulmonary arterial hypertension

- Endothelin-1 receptor antagonist orally: Bosentan
- Oxygen supplementation
- Sildenafil: inhibitor of phosphodiesterase type 5
- Prostacyclin analogues iv.: Epoprostenol, Iloprost
- Lung transplantation
Treatment of renal crisis

- Medical emergency
- ACE inhibitors
- Short-term dialysis
- Kidney transplantation
Skin care

- Hydrophilic ointments and bath oils
Course and prognosis of SSc

- Difficult to predict
- Skin regression possible
- 5-year survival: 70-90%
- 10-year survival: 55-75%
Polymyositis (PM) and Dermatomyositis (DM)
Figure 1

(A) Severe reddish-purple rash around eyelids. (B) The heliotrope rash was resolved significantly 1 month after prednisone treatment. (C) Pulmonary involvement shown in CT of the chest. (D) Repeated CT scan result showed improvement after 1 month treatment.
Heliotrope rash in dermatomyositis

A reddish-purple eruption on the upper eyelid (the heliotrope rash), accompanied by swelling of the eyelid in a patient with dermatomyositis. This is the most specific rash in DM, although it is only present in a minority of patients.

Mechanic’s hands in a patient with polymyositis, and the anti-synthetase syndrome
Clinical features of PM/DM

- Prevalence: 1 in 100,000
- Progressive and symmetric muscle weakness
- Difficulty in getting up from a chair, climbing steps, lifting objects, combing hair
- Facial and ocular muscles unaffected
- Dysphagia, difficulty in holding up the head
- Rarely: respiratory muscles affected
- Severe weakness, muscle wasting
Polymyositis

- Age at onset: >18 yr
- Association with systemic autoimmune diseases
- Drugs: D-penicillamine, AZT (zidovudine) → inflammatory myopathy
Dermatomyositis

- Skin rash: heliotrop rash: a blue-purple discoloration on the upper eye-lids with edema, Gottron’s sign: erythematous flat-topped papules over the knuckles, periungual telangiectases,
- Muscle weakness
- Age at onset: adulthood and childhood
- Overlap syndromes: SSc, MCTD
- Malignancy: 15% of cases
Extramuscular manifestations

- Fever, weight loss, arthralgia, Raynaud’s
- Joint contractures
- Dysphagia and GI symptoms
- Cardiac disturbances: AV conduction defects, tachyarrythrmias, DCM, congestive heart failure
- Pulmonary dysfunction
Association with malignancies

- Ovarian cancer
- Breast cancer
- Melanoma
- Colon cancer
- NHL
Pathogenesis

- Autoimmune etiology
- 20% of patients: autoantibodies
- anti-Jo-1 Ab: directed against the histidyl-transfer RNA synthetase
- Endomysial inflammatory infiltrates, muscle-fiber necrosis
Differential diagnosis

- Chronic progressive muscle weakness: amyotrophic lateral sclerosis, spinal muscular atrophies, muscular dystrophies, mitochondrial diseases, endocrine myopathies, neoplasm, myasthenia gravis
- Acute muscle weakness: Guillain-Barré syndrome, transverse myelitis, poliomyelitis, parasitic polymyositis, suppurative pyomyositis, chronic alcoholics
- Necrotizing myositis: cancer, viral infection
- Drug-induced myopathies: d-penicillamine, procainamide, statins, fibrates, cyclosporine, steroids
- Weakness due to muscle pain and muscle tenderness: polymyalgia rheumatica, fibromyalgia, chronic fatigue syndrome
Diagnosis

- Serum muscle enzymes: CK↑ 50-fold, LDH, SGOT, SGPT, aldolase↑
- Needle EMG (electromyography): myopathic potentials
- Muscle biopsy: definitive test, inflammation + muscle fiber necrosis detected
Treatment of PM and DM

- **Goal:** improve muscle strength
- **Oral Prednisone:** 1 mg/kg per day, response after 3 months, steroid myopathy, steroid resistancy
- **Azathioprine:** 3 mg/kg daily
- **Methotrexate orally:** 7.5 mg/week → 25 mg weekly
- **Mycophenolate mofetil:** 2.5 mf/day
Treatment of PM and DM 2

- Rituximab = monoclonal anti-CD20 in DM
- Cyclosporine
- Cyclophosphamide: 0.5-1 g iv. monthly for 6 months
- Tacrolimus in PM
- IVIG (intravenous immunoglobulin)
- Plasmapheresis
Prognosis

- 5-year survival rate: 95%
- 10-year survival rate: 84%
- Dysphagia, respiratory difficulties, cancer
- DM responds better to therapy than PM
- Relapses at any time
Wegener’s granulomatosis (WG)
Wegener's Granulomatosis

Wegener's is infamous for its subtle presentation, and its lethality if it is not correctly diagnosed and treated.

It is caused by autoantibodies against proteinase 3.

* Sore Eye
* Sore Ear
* Stuffy Nose

* Abnormal Chest X-ray
* Sore Joint
* Trace of blood in urine

* Destruction of the Face
* Lung Cavities & Bleeding
* Permanent Kidney Damage & Failure
* Gangrene

Positive c-ANCA (Anti-neutrophil cytoplasm Test)

Granulomas & patchy necrosis in arteries & veins
Incidence and Prevalence of WG

- Prevalence: 3 per 100,000
- Age of onset: 40 years
- Primary vasculitis syndrome → damage of vessels
- Immunopathogenic mechanisms
- ANCA = antineutrophil cytoplasmic antibody
- c-ANCA = cytoplasmic ANCA
- Detectable antibodies to proteinase-3
- Granuloma formation
Pathology and pathogenesis

- Necrotizing vasculitis of small arteries and veins + granuloma formation
- Lung: multiple, bilateral, nodular cavitary infiltrates
- Biopsy: necrotizing granulomatous vasculitis
- Upper airway lesions: sinuses, nasopharynx
- Kidney: rapidly progressive crescentic glomerulonephritis
Clinical manifestations

- Upper airways 95%
- Purulent or bloody nasal discharge
- Nasal septal perforation
- Saddle nose deformity
- Serous oitis media, hearing loss
- Subglottic tracheal stenosis → severe airway obstruction
- Pulmonary involvement: hemoptysis, dyspnea 85-90%
- Eye: scleritis, conjunctivitis, retroorbital mass lesion
- Skin: palpable purpura, papules, vesicles, subcutaneous nodules
- Heart: pericarditis, coronary vasculitis
- CNS: mononeuritis multiplex, cerebral vasculitis
- Kidney disease: 77%, proteinuria, hematuria, red blood cell casts, rapidly progressive renal failure
Laboratory findings

- ESR↑
- Mild anemia, leukocytosis, thrombocytosis
- 90% positive antiproteinase-3 c-ANCA
Diagnosis of WG

- Tissue biopsy: necrotizing granulomatous vasculitis
- c-ANCA positivity
Treatment of WG

- Cyclophosphamide induction for severe disease: 2 mg/kg per day orally + steroids
- Cyclophosphamide for 1 year following the induction of complete remission
- Prednisone 1 mg/kg per day
- Improvement: 90%
- Complete remissions: 75%
- Later relapses
- Remission maintenance: Azathioprine, Methotrexate 2 years past remission
Treatment of WG 2

- Mycophenolate mofetil 1000 mg twice a day
- Rituximab (anti-CD20)
- Trimethoprim-sulfamethoxazole