Systemic sclerosis

4th year MBBS

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Case 1

• A 35-year-old woman presented with a 6-month history of bilateral hand stiffness and swelling

• She had a 15-year history of Raynaud’s phenomenon with blanching and cyanosis of the fingertips on cold exposure

• developed painful sores on several fingerpads which were slow to heal, and at times white chalky material would extrude from the ulcers.
• She complained of dysphagia and heartburn and was found on barium swallow to have esophageal dysmotility with GER
Examination

• puffy fingers with loss of skin creases over dorsum of fingers
• digital pitted scars on several fingerpads, some with ulceration chalky white exudate
• periungual erythema and telangiectasias on fingers, hands and face
• normal skin texture of the proximal arms and legs, chest, and abdomen.
• mild flexion contractures of the fingers
Investigations

- ANA 1:1280; centromere pattern.
- Radiographs: calcifications in the soft tissues
- PFTs normal
- Echocardiogram: normal
Diagnosis?
Objectives

• Definition & types
• Epidemiology
• Pathogenesis
• Genetics
• Clinical features
• Lab findings
• Treatment
Classification

- Localized scleroderma
  - morphea, diffuse morphea
  - Linear scleroderma, coup de sabre

- Systemic sclerosis
  - Limited cutaneous SSc
  - Diffuse cutaneous SSc
localized scleroderma

- A group of localized fibrosing skin disorders that primarily affect children

- **Morphea**: solitary or multiple circular patches of thickened skin and, less commonly, widespread induration (generalized morphea)
Morphea
Generalised morphea
Linear scleroderma

- streaks of thickened skin, typically in one or both lower extremities
- may affect the subcutaneous tissues with fibrosis and atrophy of supporting structures, muscle, and bone.
- In children, the growth of affected long bones can be retarded.
- When linear scleroderma lesions cross joints, contractures can develop.
Linear scleroderma
En coupe de sabre
Systemic sclerosis (SSc)

- A chronic systemic disorder of unknown etiology
- Characterized by thickening of the skin (scleroderma) and involvement of multiple internal organs, such as the lungs, GI tract, heart, and kidneys
## 2 subsets of SSc

1. Diffuse cutaneous SSc
2. Limited cutaneous SSc

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>LIMITED CUTANEOUS SSc</th>
<th>DIFFUSE CUTANEOUS SSc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin involvement</td>
<td>Limited to fingers, distal to elbows, face; slow progression</td>
<td>Diffuse: fingers, extremities, face, trunk; rapid progression</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Precedes skin involvement; associated with critical ischemia</td>
<td>Onset contemporaneous with skin involvement</td>
</tr>
<tr>
<td>Pulmonary fibrosis</td>
<td>May occur, moderate</td>
<td>Frequent, early and severe</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>Frequent, late, may be isolated</td>
<td>May occur, associated with pulmonary fibrosis</td>
</tr>
<tr>
<td>Scleroderma renal crisis</td>
<td>Very rare</td>
<td>Occurs in 15%; early</td>
</tr>
<tr>
<td>Calcinosis cutis</td>
<td>Frequent, prominent</td>
<td>May occur, mild</td>
</tr>
<tr>
<td>Characteristic autoantibodies</td>
<td>Anticentromere</td>
<td>Antitopoisomerase I (Scl-70)</td>
</tr>
</tbody>
</table>
Epidemiology

- Affects all races.
- Incidence is 9–19 cases per million per year
- Prevalence of 286 cases per million population.
- More in females
- Most common age of onset is in the range of 30–50 years.
- More common in blacks & has worse prognosis
- Blacks more likely to have the diffuse form with ILD
Pathogenesis

- **Vascular Injury**
  - Endothelial cell activation
  - Platelet activation

- **Leukocyte Recruitment**
  - CD4+ CD8+ T cells
  - Activated monocytes/macrophages
  - Activated B cells

- **Autoantibodies**

- **Th2 Cytokines**
  - TGF-β, CTGF, PDGF
  - Chemokines

- **Fibroblast activation**
  - Fibrocyte differentiation
  - Myofibroblast differentiation
  - Impaired mesenchymal cell apoptosis

- **Endothelin-1**

- **Obliterative Vasculopathy**

- **Tissue Hypoxia**

- **Collagen, connective tissue accumulation**
  - Extracellular matrix reorganization, contraction
  - Impaired matrix degradation

- **Tissue Fibrosis**
Genetics

- non-Mendelian pattern of inheritance.
- concordance rate for SSc among twins is low (4.7%)
- 1.6% of SSc patients have a first-degree relative with SSc.
- risk of other autoimmune diseases, including SLE and RA is increased.
Environmental factors

- CMV infection: molecular mimicry with Scl-70 antigen
- rapeseed oil: *toxic oil syndrome*
- L-tryptophan: *eosinophilia-myalgia syndrome*
- miners exposed to silica
- polyvinyl chloride
- epoxy resins
- aromatic hydrocarbons
- Drugs: bleomycin, pentazocine and cocaine
Clinical features
Raynaud’s phenomenon:

- Episodic vasoconstriction in the fingers and toes
- Attacks are triggered by exposure to cold, stress, and vibration.
- Attacks start with pallor, followed by cyanosis. Eventually erythema develops with rewarming.
- Underlying pathogenic mechanisms:
  - Vasoconstriction
  - Ischemia
  - Reperfusion.
- 3–5% of the general population have Raynaud’s phenomenon
Raynaud’s

• **Primary**

• **Secondary:**
  – CTDs: SSc, SLE, Sjogren, Cryoglobulinaemia
  – hematological disorders
  – endocrine conditions
  – Occupational: vibrating tools
  – beta blockers
  – anticancer drugs such as cisplatin and bleomycin
### Raynaud’s Phenomenon

<table>
<thead>
<tr>
<th></th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Female</td>
<td>Male and Female</td>
</tr>
<tr>
<td><strong>Age of Onset</strong></td>
<td>Menarche</td>
<td>Mid 20’s or later</td>
</tr>
<tr>
<td><strong>Finger Edema</strong></td>
<td>No</td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Periungual erythema</strong></td>
<td>Rare</td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Arthritis</strong></td>
<td>No</td>
<td>Frequent</td>
</tr>
<tr>
<td><strong>Nail fold capillaroscopy</strong></td>
<td>Normal</td>
<td>Dilated tortuous capillaries</td>
</tr>
<tr>
<td><strong>Autoantibodies</strong></td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>
Skin

- skin thickening: symmetrical and bilateral
- Loss of creases on the dorsum of the fingers
- fixed flexion contractures
- Face: taut and shiny skin, loss of wrinkles
- Microstomia
- Beaked nose
- Telangiectasia: face, hands, lips, and oral cavity.
- slow-healing ulcers, may become infected
- Calcinosis
Lung

• The leading cause of death
• two main types of pulmonary involvement:
  – ILD
  – PAH
• Other:
  – aspiration pneumonitis complicating GER
  – restrictive ventilatory defect due to chest wall fibrosis
ILD

• cause restrictive lung disease with impaired gas exchange
• PFT show decreased FVC and DLCO but unaffected flow rates
• **Risk factors:**
  – male gender
  – African-American race
  – diffuse skin involvement
  – Severe GER
  – SCI-70
  – low FVC or DLCO at initial presentation.
ILD
Pulmonary arterial hypertension (PAH)

- PAH: a mean pulmonary arterial pressure >25 mmHg at rest, as determined by right heart catheterization
- may occur in association with ILD or alone
- May lead to right heart failure and significant mortality.

- **Risk factors for PAH:**
  - limited cutaneous disease
  - anticentromere and RNP antibodies
  - late age at disease onset
  - severe Raynaud’s phenomenon
PAH

- PFT shows isolated reduction in DLCO
- CXR show PA enlargement
- PAP on Echocardiogram > 40 mmHg suggest diagnosis
- Right heart catheterization is required to confirm PAH
Enlarged pulmonary arteries

Enlarged right ventricle
Gastrointestinal tract

- Due to abnormal motility of the esophagus, stomach, and small and large intestines
- Atrophy and fibrosis of smooth muscle, intact mucosa, and small-vessel vasculopathy.
• Gastroesophageal reflux disease (GERD) ➔ heartburn, regurgitation, and dysphagia

• Gastroparesis ➔ early satiety, abdominal pain and distension

• Gastric antral vascular ectasia gives a watermelon appearance on endoscopy ➔ recurrent episodes of occult gastrointestinal bleeding ➔ unexplained anemia.

• malabsorption and chronic diarrhea secondary to bacterial overgrowth.

• intestinal pseudoobstruction.
Renal

• Scleroderma renal crisis
  – occurs within 4 years of the onset of the disease.
  – **Risk factors:**
    • African-American race
    • male gender
    • diffuse skin involvement
    • autoantibodies to RNA polymerase III.
  – presents with abrupt onset of malignant hypertension.
  – In 10% of patients, blood pressure is normal
Scleroderma renal crisis

- Urinalysis shows proteinuria and microscopic hematuria
- thrombocytopenia
- evidence of MAHA with fragmented red blood cells
- Rx: ACE inhibitors
Musculoskeletal

- Arthralgia
- Joint contractures
- Tendon friction rubs
- Severe erosive asymmetrical polyarthritis (rare)
- Inflammatory myositis
- Acro-osteolysis: Bone resorption in the terminal phalanges
Lab findings

- Normocytic anaemia
- ESR normal
- ANA
- Anti-Centromere (more common in I-SSC)
- anti-SCI-70 (more common in d-SSC)
Treatment

• no therapy can alter the natural history of SSc
• Treatment aimed at alleviating the symptoms and in slowing the progression of the cumulative organ damage
• Glucocorticoids may decrease stiffness and aching but do not influence the progression of skin or internal organ involvement.
Treatment

- cyclophosphamide reduced the progression of ILD in patients with early symptomatic disease
- Mycophenolate mofetil treatment may improve skin induration
Treatment of Raynaud’s

- dress warmly
- minimize cold exposure and stress
- Gloves
- Avoid drugs that could precipitate vasospasm
- Calcium channel blockers such as nifedipine
- phosphodiesterase inhibitors (e.g., sildenafil)
- serotonin reuptake inhibitors (e.g., fluoxetine),
- topical nitroglycerine
- intravenous prostaglandins.
Treatment of PAH

- Phosphodiesterase type 5 inhibitors (sildenafil)
- Endothelin-1 receptor antagonists (bosentan)
- Prostacyclin analogues (Epoprostenol, treprostinil)
- Oxygen therapy
- Lung transplantation
Case 2

• A 50-year-old woman was admitted to hospital with a 48-hour history of generalized headache and dyspnoea at rest.
• She had Raynaud’s disease that was controlled with nifedipine and had recently been referred to a gastroenterologist for investigation of difficulty in swallowing.
On examination

• The blood pressure was 220/130 mmHg
• Auscultation of the lungs revealed bibasal inspiratory crackles
• The ankles were mildly swollen
• Neurological examination was normal with the exception of the fundi, which revealed hard exudates, cotton wool spots and flame-shaped haemorrhages.
## Investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>11 g/dl</td>
</tr>
<tr>
<td>WCC</td>
<td>$11 \times 10^9/l$</td>
</tr>
<tr>
<td>Platelets</td>
<td>$100 \times 10^9/l$</td>
</tr>
<tr>
<td>Blood film</td>
<td>Shistocytes, Microspherocytes</td>
</tr>
<tr>
<td>Sodium</td>
<td>138 mmol/l</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.8 mmol/l</td>
</tr>
<tr>
<td>Urea</td>
<td>28 mmol/l</td>
</tr>
<tr>
<td>Creatinine</td>
<td>490 μmol/l</td>
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<tr>
<td>ECG</td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td>Chest X-ray</td>
<td>Bilateral basal alveolar shadows and small pleural effusions</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Protein ++, Blood 0</td>
</tr>
</tbody>
</table>
Diagnosis?
Any Questions?