Scleroderma
systemic scleroderma

M.H. Jokar
Dept. Rheumatology
Emam Reza Hospital
Overview

• Basics
• Epidemiology
• Pathogenesis
• Pathology
• Clinical features
• Laboratory evaluation
Basics

• **Definition**: A systemic disorder characterized by accumulation of connective tissue in the skin and visceral organs, causing structural and functional abnormalities

• **Etiology**: Unknown

• **Clinical characteristics**:
  – vascular damage
  – immune activation
  – excessive synthesis and deposition of extracellular matrix (fibrosis)
Uncontrolled and irreversible proliferation of normal connective tissue along with striking vascular changes

- Collagen
- Proteoglycans
- Fibronectin
- Laminin
<table>
<thead>
<tr>
<th>Epidemiology of Systemic Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak age (years)</td>
</tr>
<tr>
<td>Sex distribution (F:M)</td>
</tr>
<tr>
<td>Prevalence rate (/100,000)</td>
</tr>
<tr>
<td>Annual incidence (/100,000)</td>
</tr>
<tr>
<td>Geography</td>
</tr>
<tr>
<td>Genetic associations</td>
</tr>
<tr>
<td>Relative risk</td>
</tr>
</tbody>
</table>
Initiating factors are not known

- Numerous environmental agents (PVC)
- Drugs (Bleomycin, Pentezocine)
- Viruses
- Defective immunoregulation
  - Autoantibodies
  - Cellular autoimmunity
  - Genetics and viruses
Pathogenesis
Genetic Risk

- The relative risk among first-degree: 13
- HLA DRB1*1104, DQA1*0501, DQB1*0301
Environmental Agents and Drugs Implicated in Scleroderma-like Syndromes

<table>
<thead>
<tr>
<th>Chemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silica</td>
</tr>
<tr>
<td>Heavy metals</td>
</tr>
<tr>
<td>Mercury</td>
</tr>
<tr>
<td>Organic chemicals</td>
</tr>
<tr>
<td>- Vinyl chloride</td>
</tr>
<tr>
<td>- Benzene</td>
</tr>
<tr>
<td>- Toluene</td>
</tr>
<tr>
<td>- Trichloroethylene</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
</tr>
<tr>
<td>Pentazocine</td>
</tr>
<tr>
<td>Taxol</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dietary Supplement/Appetite Suppressants</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-tryptophan (contamination)</td>
</tr>
<tr>
<td>Mazindol</td>
</tr>
<tr>
<td>Fenfluramine</td>
</tr>
<tr>
<td>Diethylpropion</td>
</tr>
</tbody>
</table>
INFECTIOUS AGENTS: VIRUSES

• Human cytomegalovirus (hCMV)

• Parvovirus B19
Vasculopathy

Endothelial damage

Vasoconstriction

Tissue ischemia

Decreased production of prostacyclin

Platelet aggregation

TXA

PDGF

TGF-beta

More vasoconstriction

Mitogenesis

Stimulates collagen synthesis

chemotaxis

CTGF
Fibrosis

Host
- Genetic susceptibility
- Infection
- Environmental factors
- Microchimerism

Vascular
- Endothelial cell injury
- Vasoconstriction
- Vascular occlusion
- Tissue hypoxia

Immune
- T cell activation
- Macrophage activation
- Autoantibodies
- Cytokines

Fibroblast activation and growth

FIBROSIS
Cause of excess production of connective tissue matrix:

PDGF
TGF beta
IL1
MICROCHIMERISM
PATHOLOGY

• In early-stage:
  inflammatory cell infiltrates

• Noninflammatory proliferative/obliterative vasculopathy
  Fibrosis
Vascular Pathology

- Intimal proliferation
- Medial hypertrophy
Tissue Fibrosis

- Excessive accumulation of:
  - Fibrillar collagens
  - Fibronectin
  - Elastin
  - Proteoglycans,
  - Cartilage oligomeric matrix protein (COMP)
Classification

- Diffuse
- Limited
- Localized (morphea, linear)
Fibrous thickening affects:

- Skin
- Muscles
- Joints
- Tendons
- Certain internal organs especially esophagus, intestinal tract, lungs and kidneys
Raynaud’s phenomenon

- An episodic self-limited and reversible vasomotor disturbance manifested as color changes bilaterally in the fingers, toes, and sometimes ears, nose, and lips.

- Color changes: pallor, cyanosis, erythema

- Numbness, tingling, pain on recovery
Scleroderma and Raynaud’s

- **Frequency:**
  - Diffuse: 85%
  - Limited: 95%

- In 70% first presentation
Skin

- Edematous
- Hardening
- Softening
Gastrointestinal Tract

**Esophagus**
- Esophageal dysmotility
- Dysphagia
- GER

**Small bowel**
- Diarrhea
- Malabsorption
- Deficient peristalsis

**Large bowel**
- Diarrhea
- Constipation
- Obstruction
- Perforation
Pulmonary Features

- At least two-thirds of SSc patients and is now the leading cause of death
- Pulmonary fibrosis
- Vascular lesions: Pulmonary hypertension
Renal Features

- Renal failure was the leading cause of death in SSc until the advent of effective treatment

- Mostly in diffuse cutaneous scleroderma

- Renal crisis characterized by malignant hypertension, which can progress rapidly to renal failure
Sicca Syndrome
Scleroderma

**Joints**
- Polyarthralgia
- Polyarthritis
- Stiff painful muscles

**Heart**
- Arrhythmias
- Conduction defects
- Pericarditis
- Congestive Cardiac failure
Immunological tests

• Scleroderma 70 antibody \((SC1-70)\)
  Associated with diffuse disease

• Anticentromere antibodies \((ACA)\)
  Associated with limited disease
<table>
<thead>
<tr>
<th>Classification criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
</tr>
<tr>
<td>• skin change in any location proximal to the metacarpophalangeal joints</td>
</tr>
<tr>
<td><strong>Minor criteria:</strong></td>
</tr>
<tr>
<td>1. sclerodactyly,</td>
</tr>
<tr>
<td>2. digital pitting scars of fingertips or loss of digital finger pad substance,</td>
</tr>
<tr>
<td>3. bibasilar pulmonary fibrosis</td>
</tr>
</tbody>
</table>
Differential Diagnosis

- Digital sclerosis of diabetes mellitus
- Amyloidosis
- Scleroderma
- Scleromyxedema
- Human graft-versus-host disease
Differential Diagnosis

- Eosinophilic fasciitis
- Porphyria cutanea tarda
- Pentazocine-induced scleroderma

Disorders characterized by similar internal organ involvement
- Primary pulmonary hypertension
- Primary biliary cirrhosis
- Idiopathic pulmonary fibros
THE NATURAL HISTORY OF SYSTEMIC SCLEROSIS BY CLASSIFICATION OF DISEASE

- diffuse
- limited
- accrual of visceral involvement

Total skin score vs. Duration of disease (years) from first non-Raynaud Manifestation

- GI
- lung
- kidney
- heart
Linear scleroderma
Morpheo