

1. Scleroderma

Scleroderma

Elena M. Massarotti, MD

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2. A Patient with Scleroderma

A Patient with Scleroderma

- 45 year old woman
- Severe Raynaud's phenomenon
- Small joint arthritis affecting the upper extremities
- Severe reflux esophagitis
- Renal crisis manifest by accelerated hypertension

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3. Scleroderma-Definition

Scleroderma-Definition

Disorder characterized by **EXCESS** fibrosis in the skin and other organs: lungs, kidney, heart and GI tract

What causes this excess fibrosis?

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4. Major pathologic processes

Major pathologic processes

- **Excessive deposition of collagen** and other connective tissue components in the extracellular matrix
- **Chronic inflammation:** T cells and macrophages infiltrating affected tissues
- **Microvascular disease: intimal** proliferation of blood vessels

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5. Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

- **Vascular endothelial cell activation:** clinically manifest organ ischemia (eg. in digits)
- **Fibroblast activation:** excess collagen deposition leading to skin thickening
- **Immune mechanisms:** autoantibody formation

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6. Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

- **Vascular endothelial cell activation and Injury**
- **Activation of fibroblasts**
- **Immune mechanisms**

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7. Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

- **Major trigger** for the fibrotic process
- Initial event is endothelial injury but what causes this is not known
 - a) Cytotoxic factor –Granzyme I (collagenase) degrades the basal lamina & is found in cytolytic T cells
 - b) Anti-endothelial antibodies found in PSS may also cause the initial endothelial injury

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8. Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

- Platelets are activated **secondary** to disrupted endothelium
- Activated platelets release granule contents especially
 - PDGF** : Mitogenic and chemoattractant for fibroblasts and smooth muscle cells
 - TGF- β** : **Most potent inducer** of collagen and fibronectin synthesis by fibroblasts and increases extracellular matrix formation

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9. Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

Fibroblast Activation

- As evident, these growth factors (**PDGF & TGF- β**) attract fibroblasts to the interstitium

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10. Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

Activated Fibroblasts

- Release Type I and III collagen in the ECM of dermis
- Deposition of other connective tissue molecules like fibronectin and glycosaminoglycans
- Excess collagen deposition in dermis leads to marked skin thickening with a leathery feel; skin pliability is reduced with physiologic and cosmetic disturbances
- Glands in dermis affected – dryness of skin

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Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

- Vascular endothelial cell activation and injury
- Activation of fibroblasts
- Immune mechanisms

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Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

- Immune dysregulation
- Both **Humoral** and **Cell Mediated** Immune dysfunction noted

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13. Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

Humoral

Evidence for this is based on fact that these patients have numerous antibodies in the serum:

- 1) Elevated levels of Rheumatoid Factor
- 2) Elevated levels of cryoglobulins
- 3) Elevated polyclonal gammaglobulins
- 4) Autoantibody formation

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14. Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

- Autoantibody formation
- 95 % patients have a positive ANA:
- **Antibody to Topoisomerase I (Scl-70)** seen in Diffuse form of the disease
 - **Antibody to Centromere** seen in Limited form of the disease

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15. Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

Cell Mediated Immune Dysregulation

- Lymphopenia
- Increased Ratio of T Helper to T suppressor cells
- Elevated levels of IL-2 and IL-2 receptors found and co-relate with disease activity

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16. Scleroderma-Pathogenesis

Scleroderma-Pathogenesis

Other contributory factors

- **Mast Cells:** Release substances affecting function of endothelial cells and fibroblasts found in affected microvasculature of these patients
- **Fibronectin:** Found in increased amounts in these patients. This is a component of ECM and is secreted by macrophages
- **Endothelin-** peptide synthesized by endothelial cells
 - Most potent vasoconstrictor known
 - Increased levels of plasma endothelin found in patients with Raynaud's

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17. Scleroderma- Summary of Pathogenesis

Scleroderma- Summary of Pathogenesis

- Unidentified etiologic trigger
- Endothelial Cell Injury and activation
- Platelet Activation
- Release of PDGF and TGF- β
- Fibroblast Activation
- Overproduction of Collagen and Fibronectin in dermis
- Fibrosis in skin and organs
- Immune System Activation

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18. Scleroderma-Clinical Features

Scleroderma-Clinical Features

- **Rare disease (0.2 and 0.4 per 100,000 people)**
- **F>>M ; 2:1 – 20:1**
- **Age of onset : 35 – 55 years**
- **Genetic influence not very strong but may be present**
 - familial aggregation rare
 - disease not seen with higher frequency in twins
- **Etiology unknown**
 - Environmental triggers
 - Bleomycin, Vinyl chloride, L-Tryptophan, Adulterated Rapeseed cooking oil in Spain

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19. Scleroderma-Classification

Scleroderma-Classification

Localized

Morphea
Linear Scleroderma

Generalized

Progressive Systemic Sclerosis (PSS)
Limited Scleroderma (CREST Syndrome)

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20. Scleroderma-Classification

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Limited Scleroderma (CREST Syndrome)

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21. Scleroderma-Clinical Features

Scleroderma-Clinical Features

- LOCALIZED and GENERALIZED forms
- Major distinguishing features are
 - EXTENT of skin involvement
 - Presence/Absence of organ involvement

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22. Localized Scleroderma-Clinical features

Localized Scleroderma-Clinical features

LOCALIZED FORMS

Morphea

Linear Scleroderma

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23. Localized Scleroderma-Clinical features

Localized Scleroderma-Clinical features

Involvement of skin- Focal or circumscribed

- More benign
- No visceral organ involvement

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24. Localized Scleroderma-Clinical features

Localized Scleroderma-Clinical features

Morphea

- Occurs on any part of the body
- Either presents as large patches or small spots (guttate morphea)
- Involutional atrophy occurs , cosmetic deformity results

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25. Localized Scleroderma-Clinical features

Localized Scleroderma-Clinical features

Linear Scleroderma

- Usually single extremity or face (Coup de Saber)
- Disease is active for 2-3 years, then involutes

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26. Generalized Scleroderma

Generalized Scleroderma

GENERALIZED SCLERODERMA

Progressive Systemic Sclerosis(PSS)

Limited Scleroderma (CREST Syndrome)

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27.

PSS-Clinical Features

PSS-Clinical Features

- Diffuse, progressive, uncontrolled fibrosis of skin & major organs: heart, lungs and kidneys
- Skin thickening starts acraly and progresses proximal to the face and trunk
- Raynaud's phenomenon

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Raynaud's Phenomenon

Raynaud's Phenomenon

Clinical manifestation of microvascular injury leading to digital ischemia

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29. Raynaud's Phenomenon

Raynaud's Phenomenon

- **EPISODIC** – pallor/blanching and cyanosis of fingers, toes, ears and nose on exposure to cold
- Digital arteries of fingers contract in response to cold even in normal people but in scleroderma this response is accentuated
- Due to intense vasospasm of digital arteries, patients are at risk for ischemic necrosis and digital gangrene

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30. Raynaud's Phenomenon

Raynaud's Phenomenon

Mechanism:

Endothelial cell injury
Platelet activation
Release of TXA₂
Platelet aggregation
Endothelin release
Vasospasm

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31. Raynaud's Phenomenon

Raynaud's Phenomenon

- Primary
 - No associated disease states
- Secondary
 - Associated with connective tissue diseases

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32. Primary Raynaud's Phenomenon

Primary Raynaud's Phenomenon

- Seen in normal people
- 10% of healthy females
- Starts during the teenage years

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33. Raynaud's Phenomenon

Raynaud's Phenomenon

	Primary	Secondary
<i>Sex</i>	Female	Male and Female
<i>Age of Onset</i>	Menarche	Mid 20's or later
<i>Frequency of Attacks</i>	>10 day	0-5 a day
<i>Finger Edema</i>	No	Frequent
<i>Periungual erythema</i>	Rare	Frequent
<i>Arthritis</i>	No	Frequent
<i>Nail fold capillaroscopy</i>	Normal	Dilated tortuous capillaries
<i>Autoantibodies</i>	Absent	Present

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34. PSS-Clinical features

PSS-Clinical features

Skin

- Starts distally
- Progresses proximally to trunk and face
- Skin is hard, tethered, leathery feel
- Fibrosis leads to joint contractures
- Skin ulceration, infection
- Raynaud's can cause digital gangrene, autoamputation and secondary osteomyelitis

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PSS-Clinical features

PSS-Clinical features

Lung

- Interstitial fibrosis
 - Thickened alveolar interstitial space due to excess collagen deposition
 - Alveolar space volume decreases
 - A-a gradient widens
- Pulmonary Hypertension
 - Due to fibrosis and intimal proliferation of pulmonary vessels
 - Can lead to right heart failure
- Lung involvement is leading cause of death in Scleroderma

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PSS-Clinical features

PSS-Clinical features

Heart

- Pericarditis/Pericardial effusions
- Myocardial fibrosis
- Arrhythmias, conduction blocks

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PSS-Clinical features

PSS-Clinical features

- Predictors of Renal Crises
 - Early disease < 4 years
 - Rapid progression of skin thickening
 - New onset anemia
 - High doses steroids
- Note:
 - Scl-70 antibody NOT a predictor

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PSS-Pathology

PSS-Pathology

Renal Crises:

- Pathology: Intimal proliferation, medial thickening and luminal narrowing in renal arterioles leading to ischemia and fibrosis

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39. PSS–Renal Crises

PSS–Renal Crises

- Rx:
 - ACE-inhibitors
 - Dialysis
 - Renal Transplant

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40. PSS-Clinical features

PSS-Clinical features

GI

- Esophageal dysmotility due to fibrosis in submucosa, muscularis and lamina propria leads to:
 - Reflux esophagitis
 - Barrett’s esophagus
- Colon
 - “Pseudodiverticula”

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PSS-Clinical features

PSS-Clinical features

Musculoskeletal System

- Myositis – elevated CPK
- Joint contractures
- Synovitis- not severe like in RA

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42.

PSS-Diagnosis

PSS-Diagnosis

- Combination of clinical features and supportive antibody tests
- Antibodies:
 - 95 % ANA- nucleolar and speckled
 - 30 % Anti-Scl 70 (Topoisomerase I) antibody
 - Antibodies may be an epiphenomenon/ pathogenic

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PSS-Treatment

PSS-Treatment

- No effective treatment
- Death can occur within 3 – 5 years of onset due to major organ involvement
- Truncal skin involvement associated with greater mortality than digital or proximal skin involvement

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PSS-Treatment

PSS-Treatment

- Low doses prednisone for **synovitis/myositis**
- **Raynaud's**- Vasodilators like Ca-channel blockers; sildenafil
- **Acid- Reflux disease**-antacids, H2 blockers and Proton pump inhibitors
- **Renal Crises**- ACE-inhibitors; Transplantation
- **Pulmonary Hypertension**: Bosentan -receptor antagonist of endothelin 1- potent vasoconstrictor; resulting in inhibition of vasoconstriction

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PSS-Treatment

PSS-Treatment

- Lung Fibrosis- Cytoxan
- Relaxin- thought initially to be useful but studies did not show benefit
- Bone marrow Transplant
- Lung/Kidney Transplant for organ involvement

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46.

Limited Scleroderma

Limited Scleroderma

CREST Syndrome

- C- Calcinosis
- R- Raynaud's
- E- Esophageal dysmotility
- S- Sclerodactyly
- T- Telangiectasias

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Limited Scleroderma

Limited Scleroderma

Organ involvement

- Lung- Pulmonary Hypertension
- Esophagus – Reflux disease

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Limited Scleroderma

Limited Scleroderma

Autoantibody

70 % - Anti-Centromere Antibody

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49. PSS v/s Limited Scleroderma

PSS v/s Limited Scleroderma

	Diffuse (PSS)	Limited
<i>Onset of Raynaud's</i>	< 1 year	Years to decade
<i>Skin</i>	Truncal and acral	Acral to none
<i>Tendon friction rubs</i>	Present	Absent
<i>Visceral disease</i>	Early, frequent	Rare and late
<i>Autoantibodies</i>	Anti-topoisomerase (30-40%)	Anti-centromere (70-80%)

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50. Scleroderma-like syndromes

Scleroderma-like syndromes

Toxic Oil

- Rapeseed oil adulterated with aniline used in cooking in Spain
- Myalgias, skin rash, pulmonary edema and peripheral neuropathy
- Oil has free radicals which caused endothelial injury

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51. Scleroderma-like syndromes

Scleroderma-like syndromes

Drug induced

- Bleomycin-Raynaud's, IPF
- L-Tryptophan- Sleeping pill
 - caused an eosinophilic fasciitis syndrome with myalgias, fasciitis, fibrosis, peripheral neuropathy

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52. Pop Quiz

Pop Quiz

Which of the following contributes to the excessive fibrosis seen in scleroderma?

- TNF- α
- TGF- β
- Il-1
- HLA-DR β 1 0401

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Pop Quiz

Pop Quiz

Which of the following is not seen with limited scleroderma?

- Interstitial lung disease
- Pulmonary hypertension
- Raynaud's phenomenon
- Autoantibody formation

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