Scleroderma

The term scleroderma is derived from the Greek words skleros (hard or indurated) and derma (skin) and it is used to describe a disease characterized by progressive skin hardening and induration. Hippocrates first described this condition as thickened skin

Definition

A systemic autoimmune disease of unknown origin characterized by excessive deposition of collagen and other connective tissue macromolecules in skin and multiple internal organs, prominent and often severe fibroproliferative alterations in the microvasculature, and numerous humoral and cellular immunologic abnormalities

Systemic sclerosis is a complex and heterogeneous disease with clinical forms ranging from limited skin involvement (limited cutaneous systemic sclerosis) to forms with diffuse skin sclerosis and severe and often progressive internal organ involvement (diffuse cutaneous systemic sclerosis), and occasionally a fulminant course (fulminant systemic sclerosis

Limited cutaneous systemic sclerosis involves areas distal to the elbows and knees but may involve the face and neck. CREST syndrome (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias—although not all are needed for the disorder to be called CREST) is an older term used to describe this subset of limited cutaneous systemic sclerosis.

Diffuse cutaneous systemic sclerosis refers to skin thickening affecting the trunk and the skin of the extremities proximal to the elbows and knees besides involvement of the face. There are rare cases of typical systemic sclerosis internal organ involvement in the absence of clinically apparent cutaneous involvement, a clinical subset known as “scleroderma sine scleroderma”.

Pathogenesis

The clinical and pathologic manifestations result from three distinct processes:

1) severe fibroproliferative vascular lesions of small arteries and arterioles

2) excessive and often progressive deposition of collagen and other extracellular matrix (ECM) macromolecules in skin and various internal organs

3) alterations of humoral and cellular immunity.

It is not clear which of these processes is of primary importance or how they are temporally related during the development and progression of the disease.

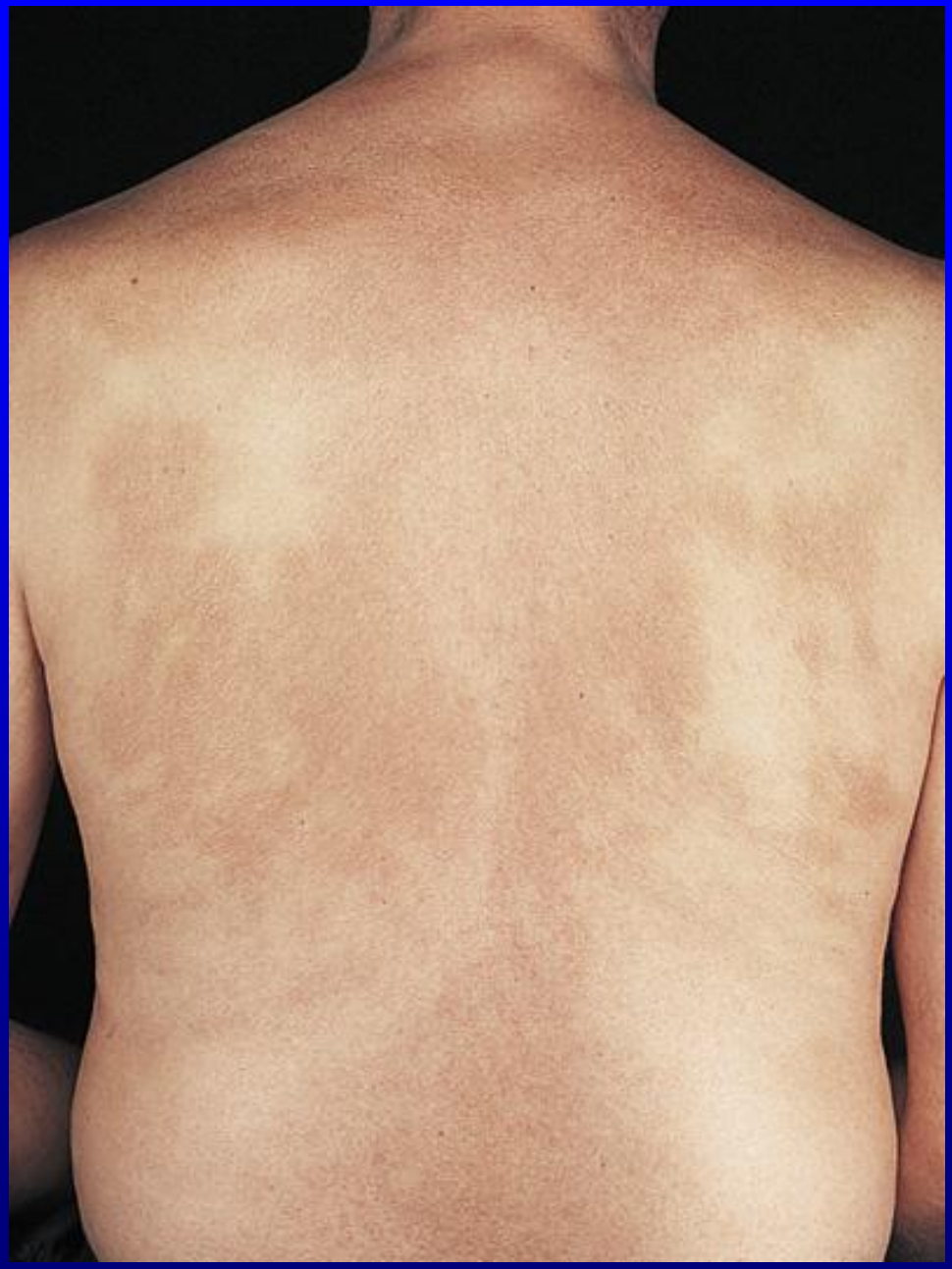
Etiology

The exact etiology of systemic sclerosis is not known.

- Genetic predisposition
- Environmental factors :
  - Silica exposure
  - Solvent exposure (vinyl chloride, trichloroethylene, epoxy resins, benzene, carbon tetrachloride)
  - Radiation exposure or radiotherapy
- Viral accelerating factors

Classification:

- Diffuse cutaneous scleroderma (progressive systemic sclerosisnak; PSS)
- Limited cutaneous scleroderma (acrosclerosis forms, e.g. CREST)
- Overlap syndromes, mixed connective tissue disease (MCTD) and undifferentiated connective tissue disease (UCTD)
- Localized scleroderma (morphea & linear scleroderma)



Morphea (generalized)

Epidemiology

Systemic sclerosis occurs worldwide, although its reported prevalence varies significantly in different countries

Systemic sclerosis affects individuals of all races,it appears that there is higher frequency among black individuals

The risk of systemic sclerosis is 4-9 times higher in women than in The peak onset occurs in individuals aged 30-50 years

Prognosis

Survival in patients with diffuse cutaneous disease has improved significantly; currently, the 5-year survival is estimated to be about 80%. Five-year survival in patients with limited cutaneous disease is approximately 90%.

Factors associated with a more severe prognosis are as follows:

- Younger age
- African descent
- Rapid progression of skin symptoms
- Greater extent of skin involvement
- Anemia
- Elevated erythrocyte sedimentation rate (ESR)
- Pulmonary, renal, and cardiac involvement

Complications

Complications of systemic sclerosis include the following:

Digital infarctions

Pulmonary hypertension

Myositis

Renal failure

Wound infections

Signs and symptoms :

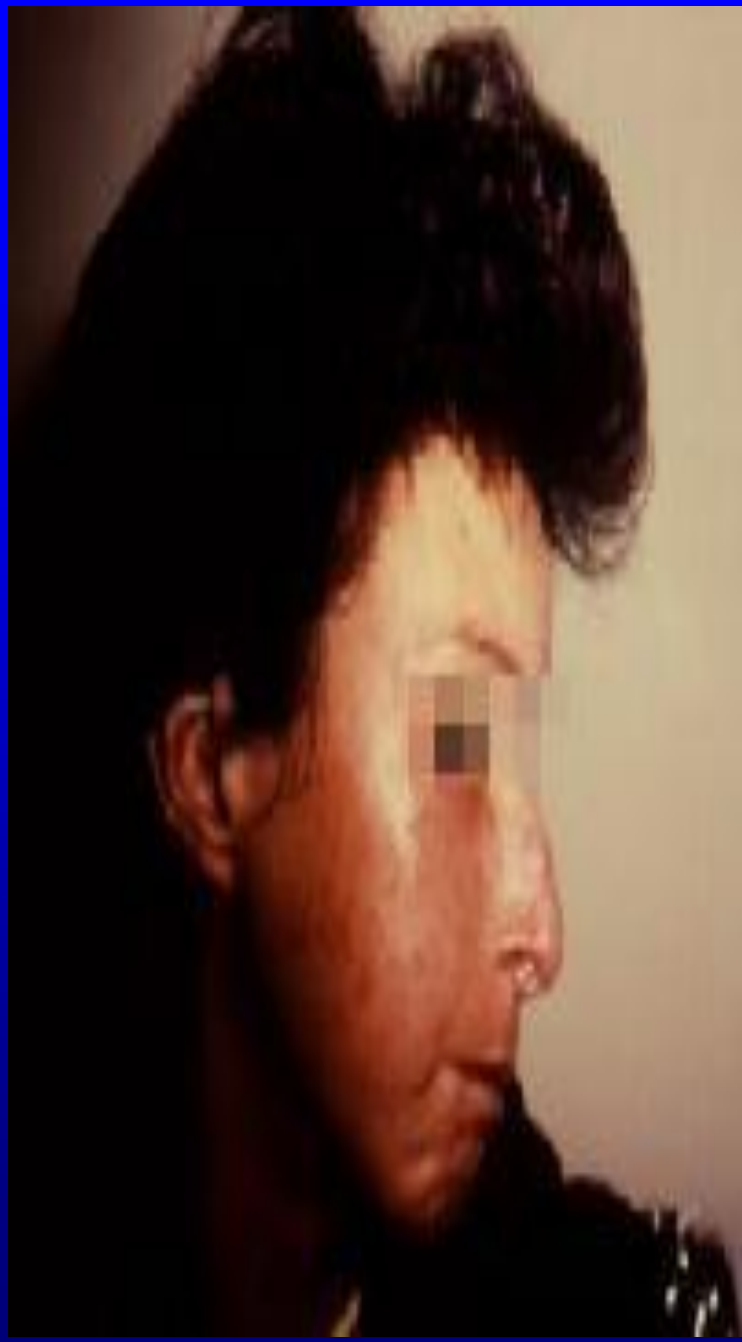
Skin
Vascular
Gastrointestinal (GI)
Respiratory
Musculoskeletal
Cardiac
Renal
Genitourinary
Eyes, ears, nose, and throat
EndocrineHypothyroidism
Neurologic/psychiatric
Constitutional

Skin manifestations

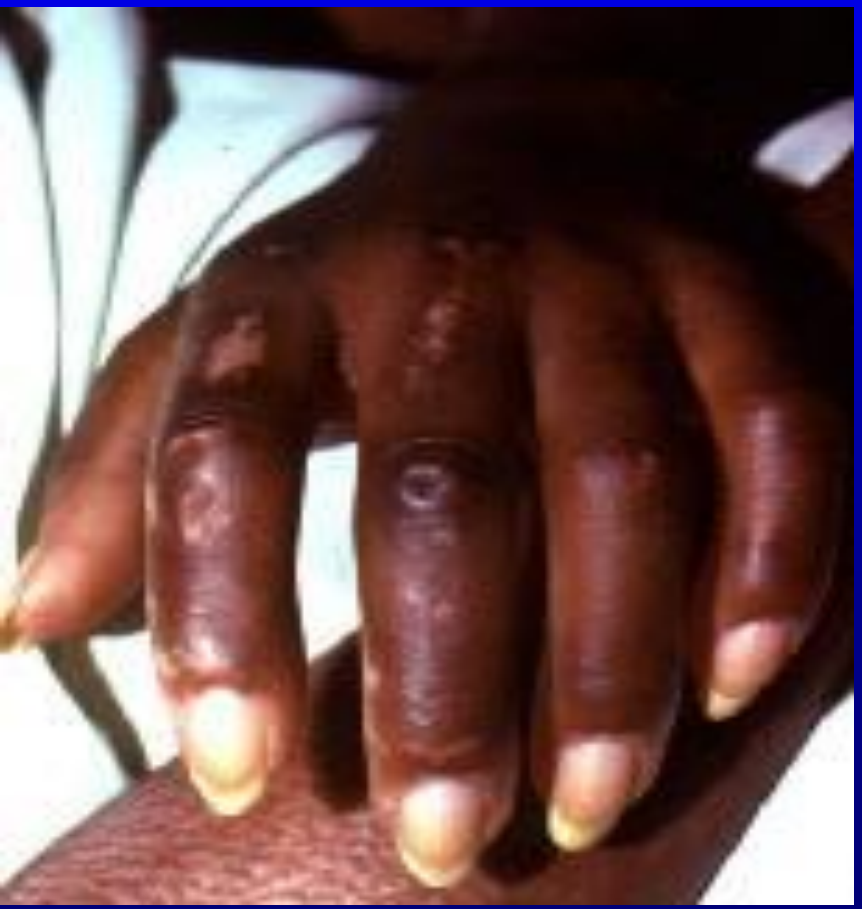
-Progressive skin tightness and induration, often preceded by swelling and puffiness (edematous stage)

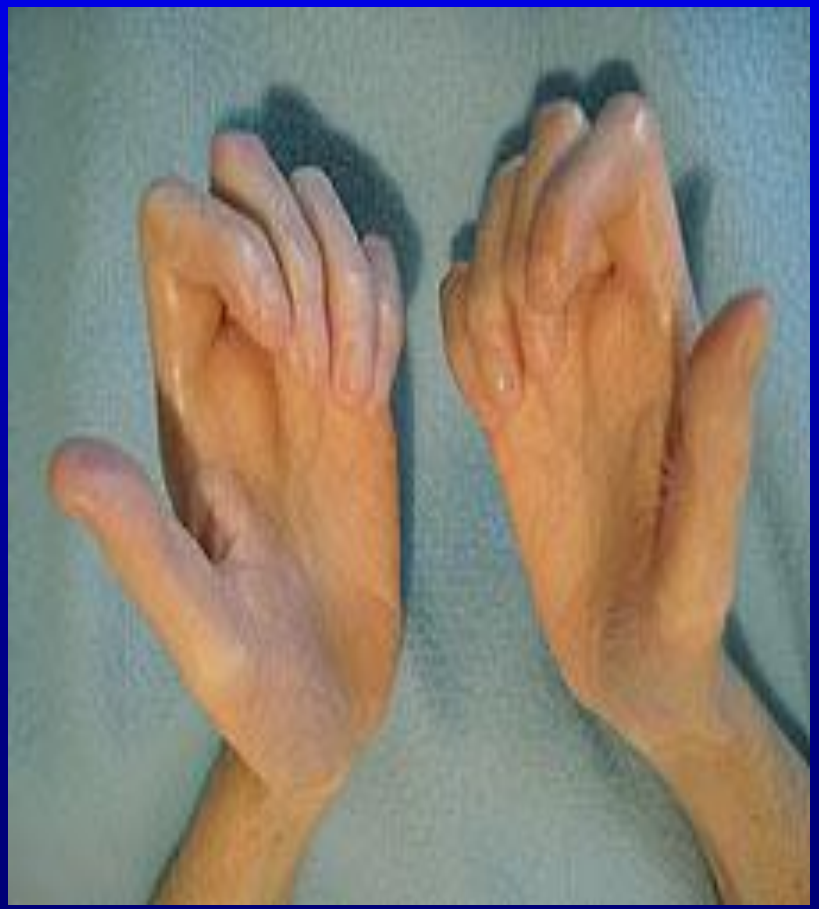
-Skin induration initially affects the fingers (sclerodactyly) and extends proximally

-Tightening of the skin in the face, with a characteristic beaklike facies and paucity of wrinkles.



Sclerodactyly with digital ulceration, loss of skin creases, joint contractures, and sparse hair



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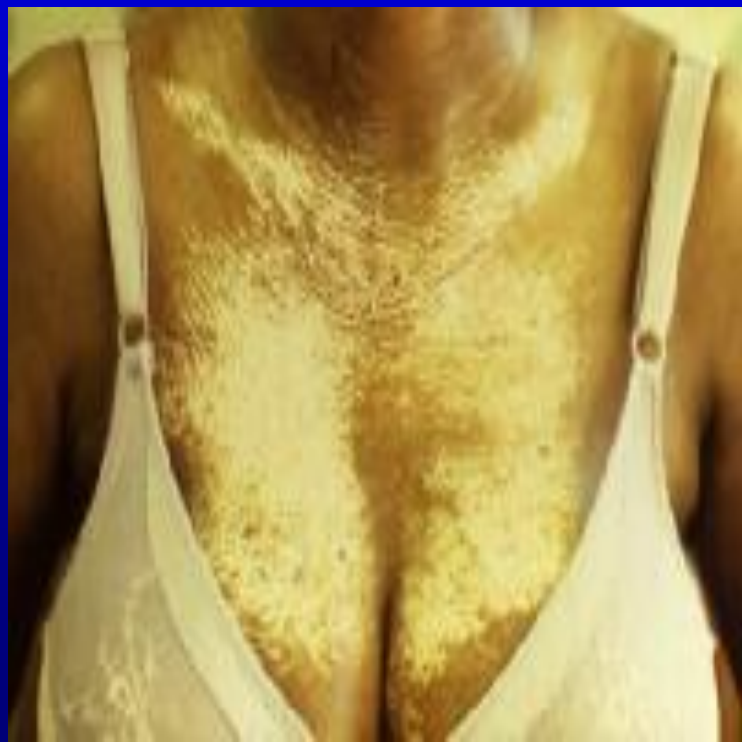
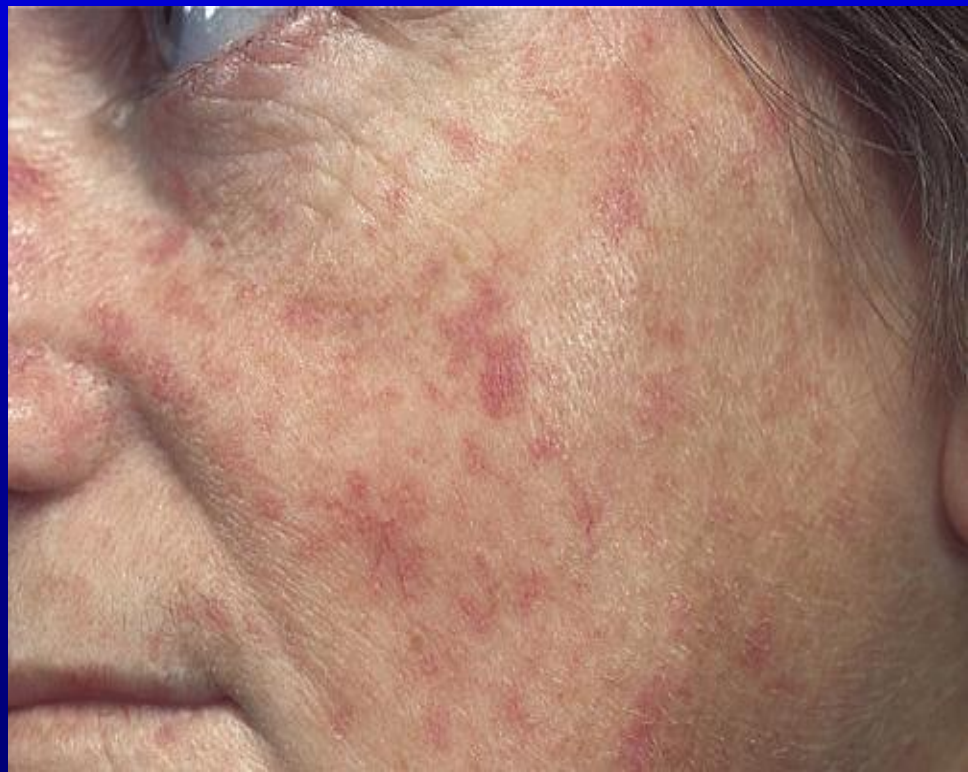
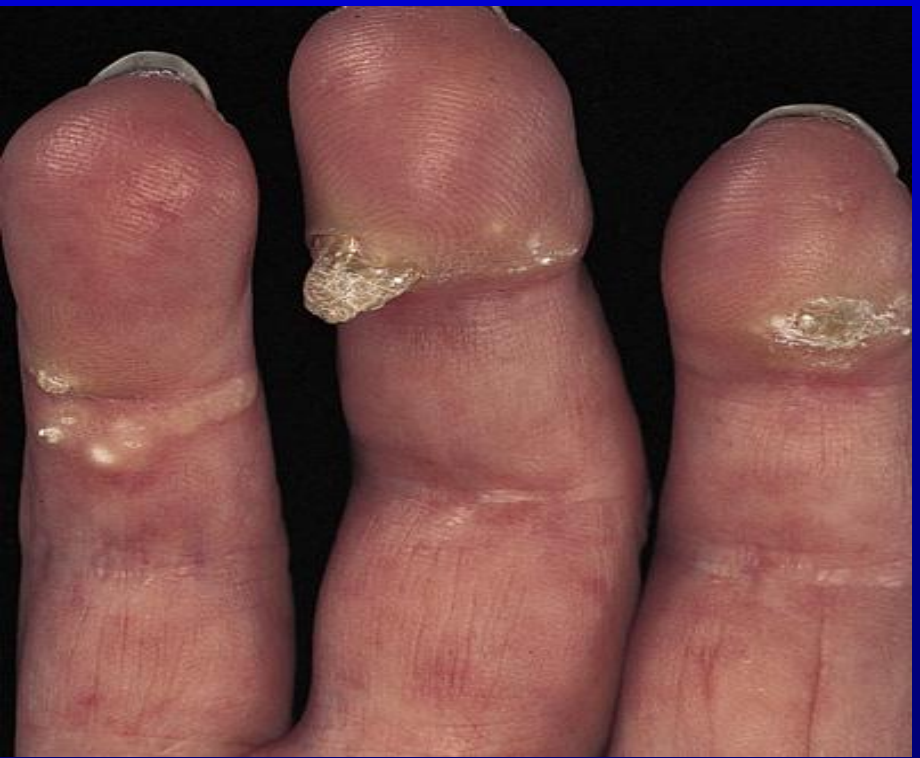
Prominent skin pigmentary changes both hyperpigmentation and hypopigmentation (see image below) Anterior chest demonstrating salt-and-pepper hypopigmentation and diffuse hyperpigmentation in a white woman.

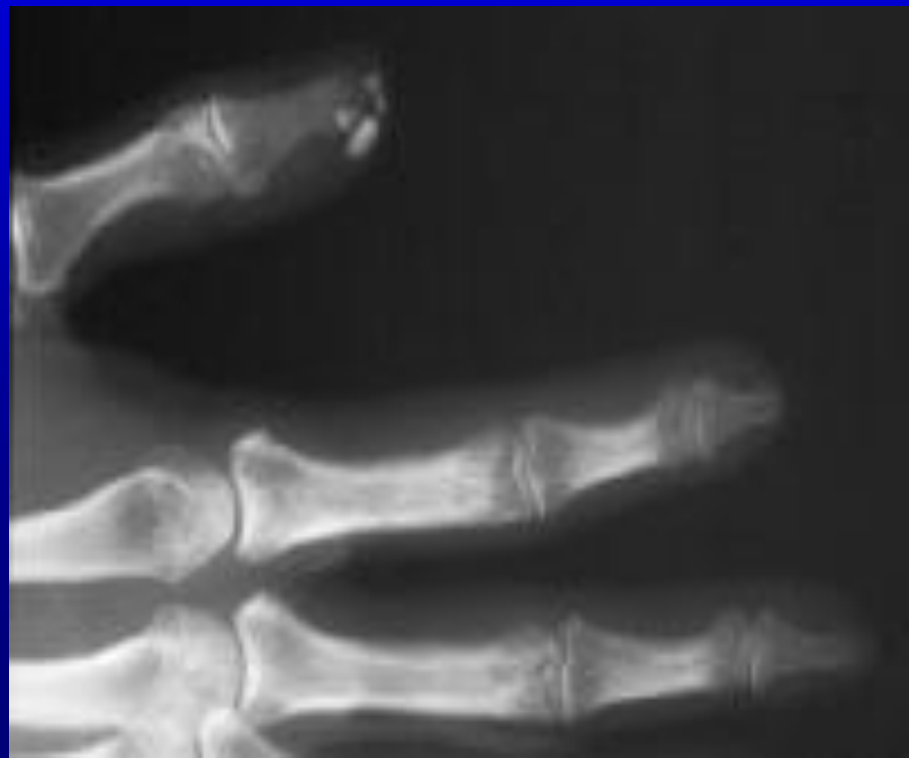


Telangiectasias are dilated vessels located just beneath the dermis on any skin area, but they are most obvious in the face, hands, and anterior chest; occasionally, telangiectasias may occur in mucosal surfaces and cause either obvious or occult bleeding



Calcinosis may develop in the fingers and extremities (see image below), most commonly in the finger tips, the extensor surface of the forearms and in the prepatellar regions; however, any area of the body can be affected.



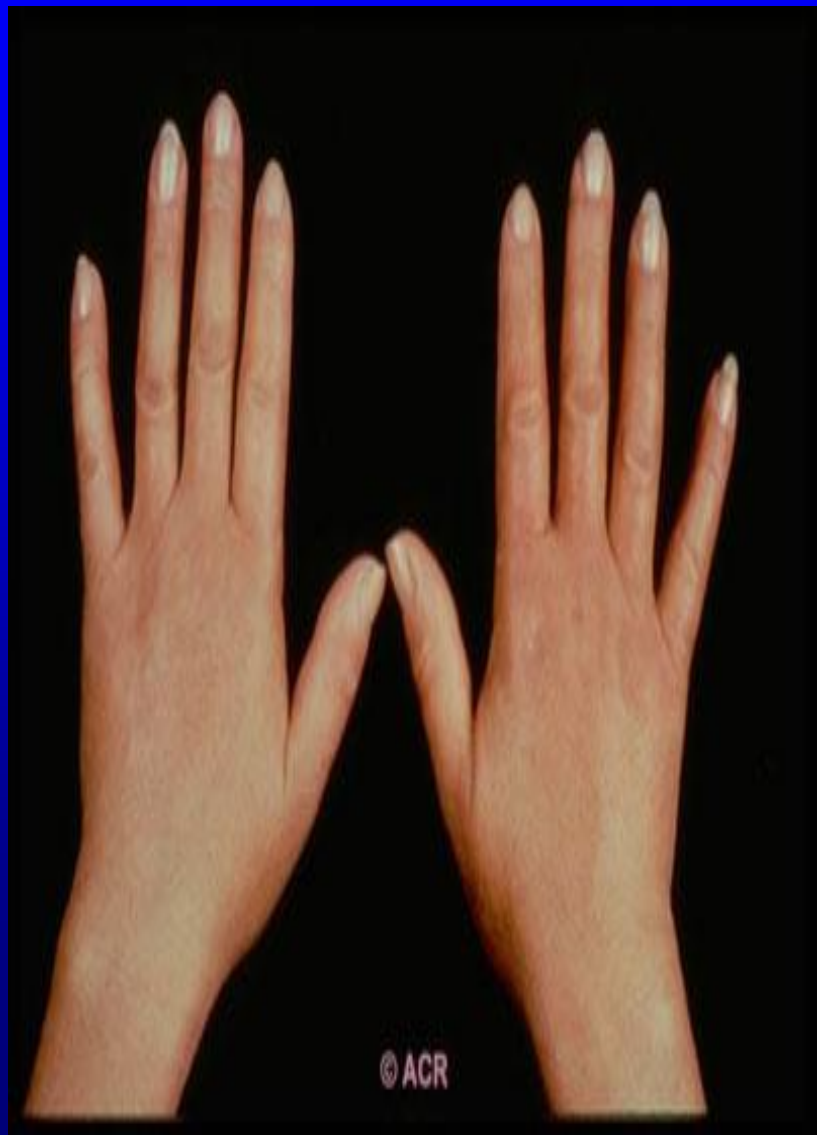


Diffuse pruritus

Vascular manifestations

Raynaud phenomenon
Healed pitting ulcers in fingertips
Large fingertip ulcers may lead to finger amputation
Cutaneous and mucosal telangiectasias
Evidence of macrovascular involvement including non-atherosclerotic myocardial infarction

Raynaud’s phenomenon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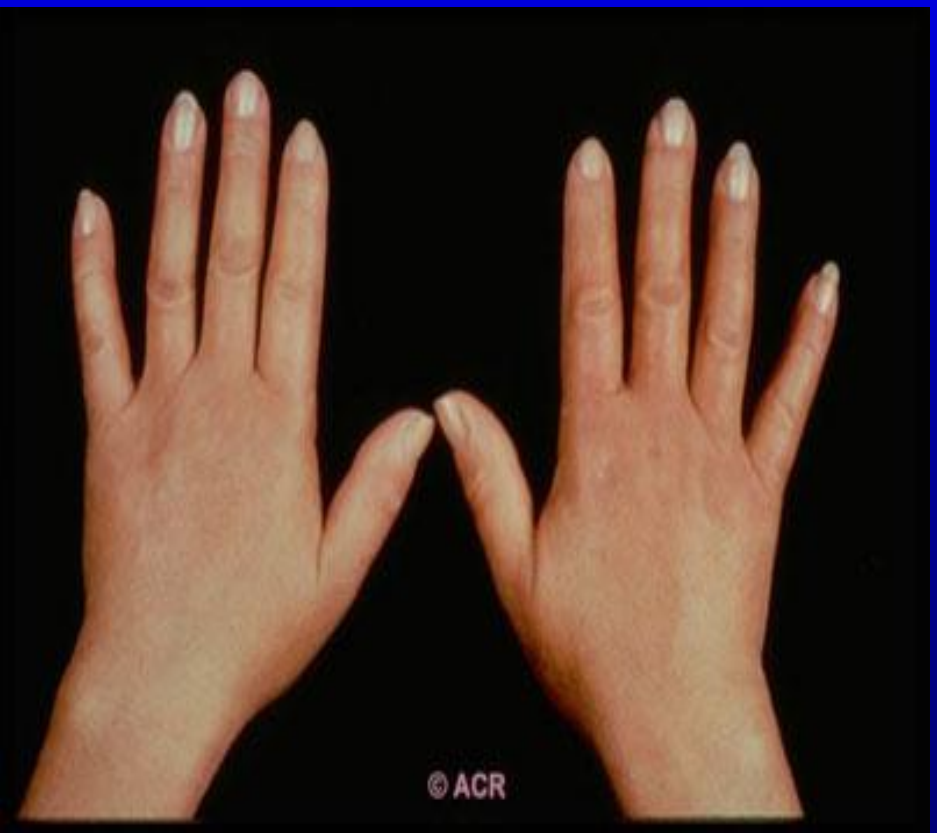
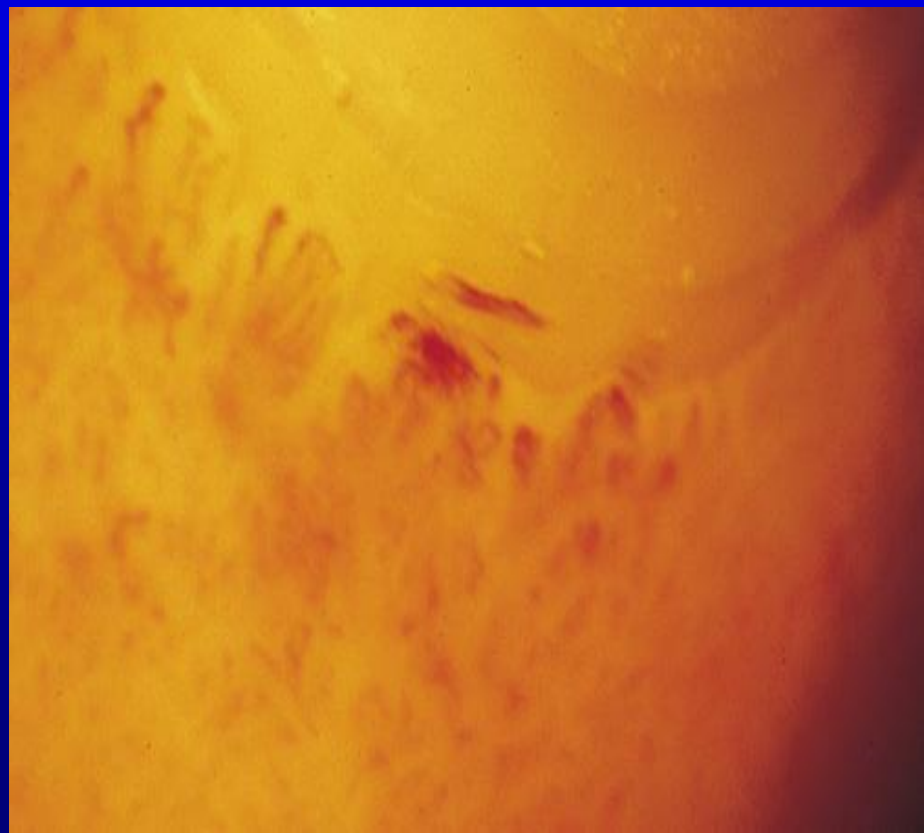
Nail-fold capillary microscopy demonstrates fewer capillaries than normal (ie, capillary loop drop; see image below) and numerous dilated and tortuous capillary loops Fingernail capillary bed demonstrating capillary dropout with large dilated vessels.





Gastrointestinal manifestations

Gastroesophageal reflux caused by lower esophageal sphincter (LES) incompetence and decreased or absent peristalsis in the lower two thirds of the esophagus (may lead to hoarseness, dysphagia and aspiration pneumonia)
Dyspepsia, bloating, and early satiety
Intestinal pseudo-obstruction
Constipation alternating with diarrhea from bacterial overgrowth (may lead to malabsorption)
Fecal incontinence
Malnutrition from inadequate caloric intake
Chronic iron deficiency anemia from occult blood loss

Respiratory manifestations

Progressive dyspnea
Chest pain (precordial) due to pulmonary artery hypertension
Dry persistent cough due to restrictive lung disease

Musculoskeletal manifestations

Arthralgia
Myalgia
Loss in joint range of motion and joint flexion contractures
Tendon friction rubs
Symptoms of carpal tunnel syndrome
Muscle weakness

Cardiac manifestations

Dyspnea due to congestive heart failure or myocardial fibrosis
Palpitations, irregular heart beats
syncope due to arrhythmias or conduction abnormalities
Symptoms of congestive heart failure or right sided heart failure
Systemic sclerosis is an independent risk factor for acute myocardial infarction

Renal manifestations

Hypertension
Renal crisis
Chronic renal insufficiency
History of high dose corticosteroid use.

Genitourinary manifestations

Erectile dysfunction
Bladder fibrosis
Dyspareunia (if introitus is affected)
Vaginal narrowing, dryness and pain caused by vaginal fibrosis

Eyes, ears, nose, and throat manifestations

Sicca syndrome
Poor dentition secondary to sicca syndrome
Loosening of dentition caused by alterations in the tooth suspensory ligament and thickening of the periodontal membrane
Hoarseness due to acid reflux with vocal cord inflammation or fibrosis
Increased risk for tongue cancer
Decreased oral aperture
Blindness caused by retinal artery occlusion

Neurologic/psychiatric manifestations

Facial pain and decreased sensation due to trigeminal neuralgia
Hand paresthesias and weakness due to carpal tunnel peripheral entrapment neuropathy
Headache and stroke during hypertensive renal crisis
Depression and anxiety

Constitutional manifestations

Fatigue
Weight loss
Loss of appetite

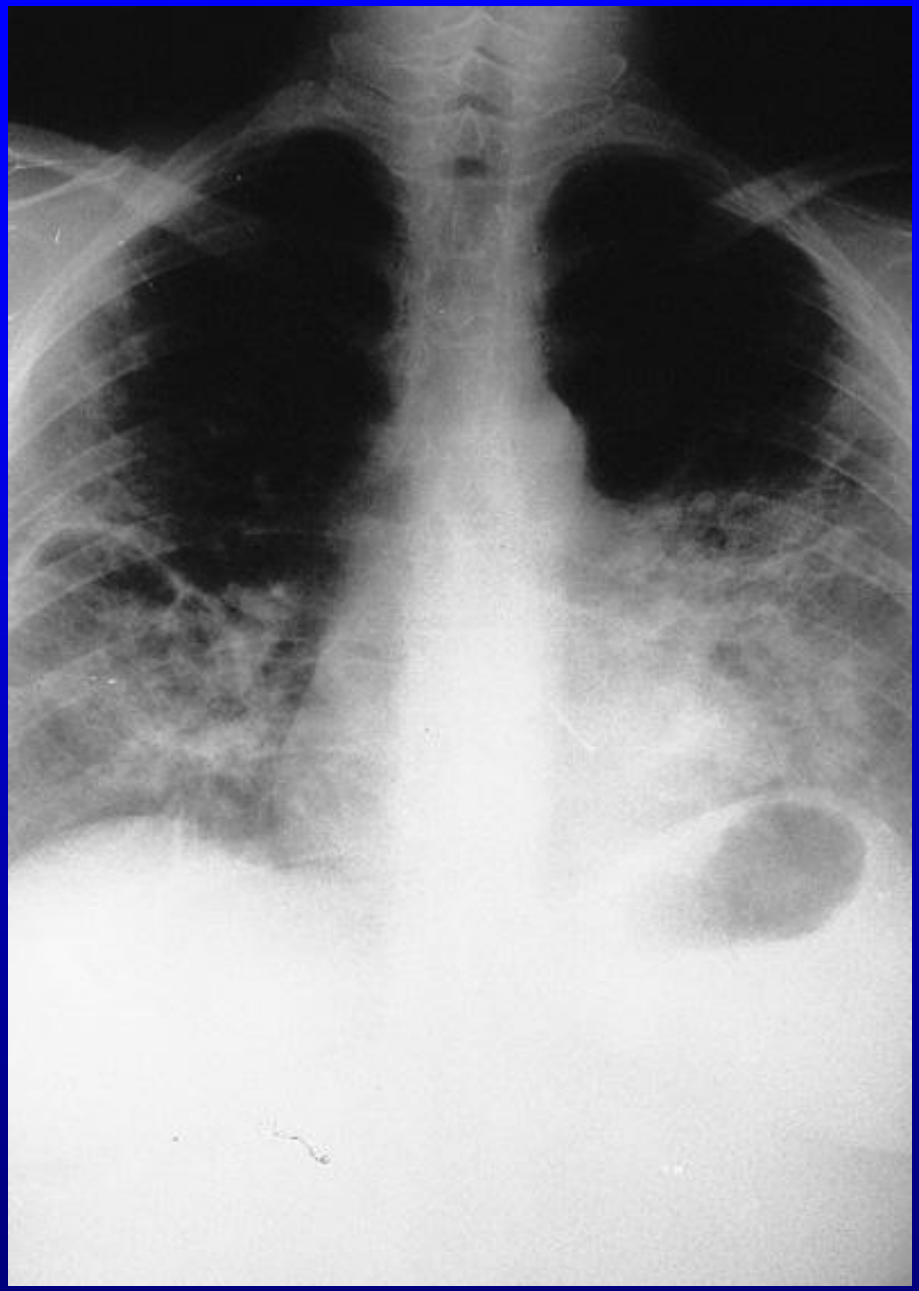
Eyes, ears, nose, and throat

Salivary production may be decreased and spontaneous sublingual pooling of saliva may be absent.
Xerostomia and xerophthalmia may be part of the examination findings.

Laboratory testing may include the following:
Complete blood cell count (CBC)
Serum muscle enzyme levels
Erythrocyte sedimentation rate
Serum CXCL4 level
N-terminal pro-brain natriuretic peptide
Autoantibody assays

Esophagogastroduodenoscopy with appropriate biopsies, esophageal manometry assessment, and pH monitoring studies

Chest radiography
HRCT
Pulmonary function testing (DLCO)



Bibasilar pulmonary fibrosis in PSS

Bronchoscopy with bronchoalveolar lavage is used to differentiate active infections from progressive interstitial lung disease

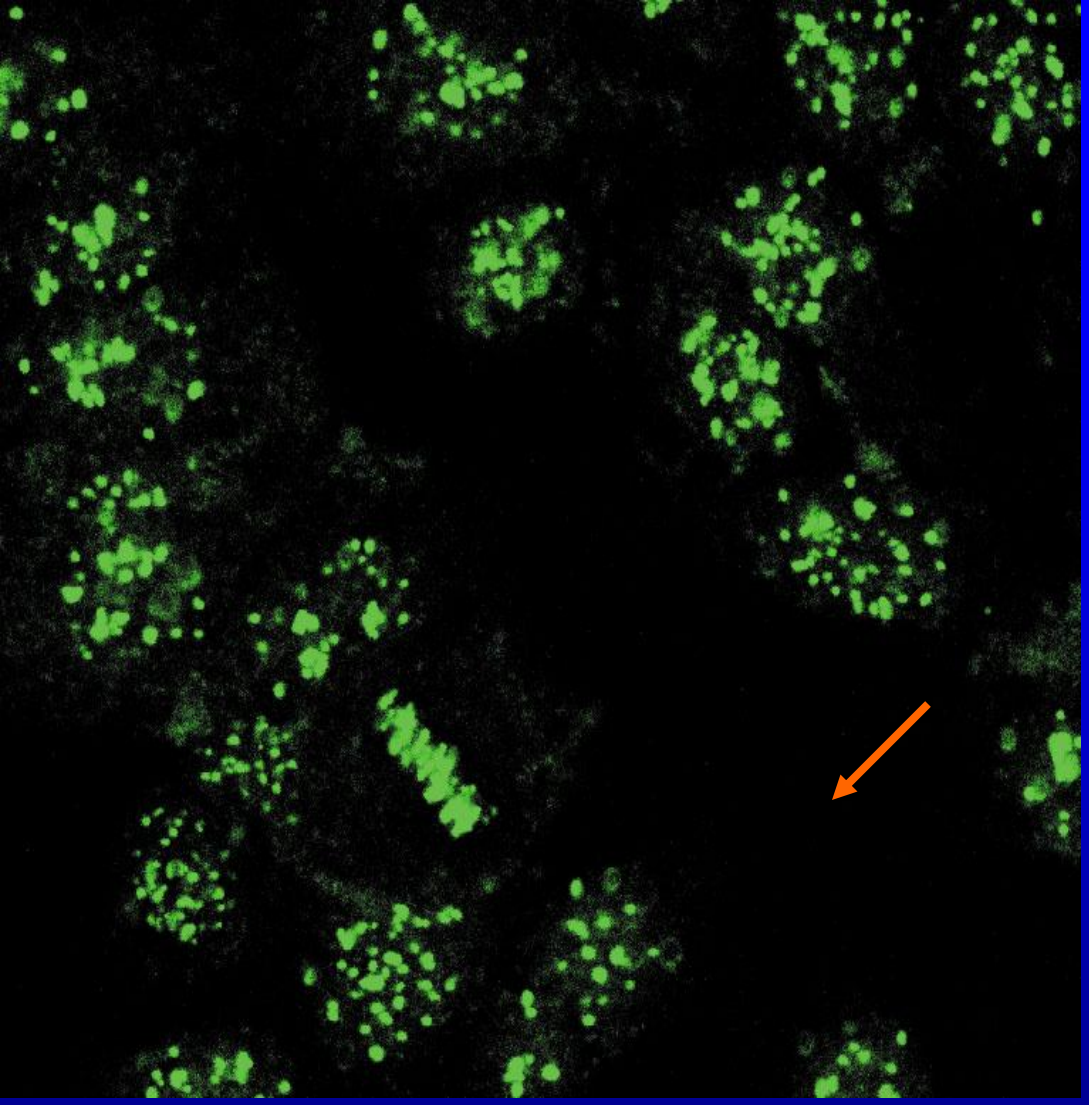
Electrocardiograms (ECGs) should be performed routinely to identify arrhythmias and conduction defects.

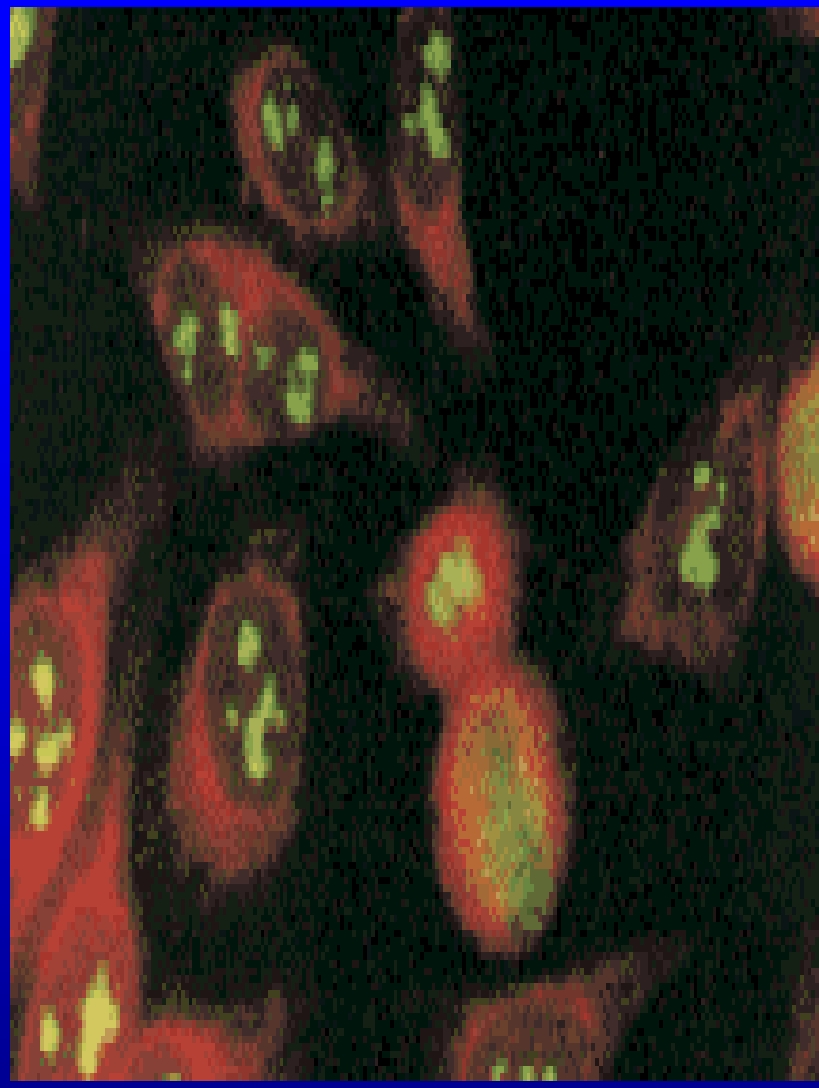
Autoantibodies

The value of serology testing is for initial diagnosis and assessment of associated conditions

-Antinuclear antibodies are present in about 90%-95% of affected patients, usually with a speckled or centromere pattern. A nucleolar pattern, although less common, is more specific for systemic sclerosis.

-Topoisomerase I antibodies (also known as Scl-70) are present in approximately 30% of patients with diffuse disease (absent in limited disease





Centromere antibodies
in acrosclerosis

Nucleolar antibodies
in scleroderma

-Anticentromere antibodies are present in about 45%-50% of patients with limited disease.

-Anti-RNA polymerase I and III antibodies

- Anti-ThRNP is present mostly in limited disease and is associated with more extensive visceral disease.

-Anti-PM-Scl is present in patients with overlap connective tissue disease or with mixed connective tissue disease (MCTD)

Scleroderma Renal Crisis

Patients with diffuse, rapidly progressive skin involvement have the highest risk of developing scleroderma renal crisis. Renal crisis occurs in about 10% of all patients with systemic sclerosis.

Renal crisis is observed within 4 years of diagnosis in about 75% of patients but may develop as late as 20 years after diagnosis. Renal crises are slightly more common in blacks than in whites, and men have a greater risk than women. The presence of RNA polymerase III antibodies increases the risk for renal crisis.

Scleroderma renal crisis that is not treated promptly and aggressively invariably leads to renal failure requiring dialysis or renal transplantation, or even death. Consequently, it is critical to check blood pressure, monitor serum creatinine, and start angiotensin-converting enzyme (ACE) inhibitors at the earliest signs of hypertension in at-risk patients. High doses of corticosteroids should be avoided in patients with systemic sclerosis owing to an increased risk of developing renal crisis.

treatment

Therapy of scleroderma:

1) **systemic: penicillamine (ineffective)**
2) **vasodilators (Ca-channel blockers, prostacyclin)**
3) **GI system: reflux - metoclopramide, slow motility – octreotid, antibiotics**
4) **pulmonary hypertension: ACE-inhibitors are ineffective, prostacyclin infusion(**Severe Raynaud syndrome can be treated
5) with intravenous iloprost.)

pneumonitis/fibrosis: corticosteroid/cytostatics

Cyclophosphamide improves dyspnea and pulmonary function test modestly in patients with severe interstitial lung disease

1) **kidney: ACE-inhibitors**

The hypertensive crises associated with scleroderma renal crisis must be treated early and aggressively (in the hospital) with angiotensin-converting enzyme inhibitors, eg, captopril, initiated at 25 mg orally every 6 hours and titrated up as tolerated to a maximum of 100 mg every 6 hours

Diet

There are no specific dietary recommendations
The following points may be considered:

Patients with esophageal involvement should avoid hard solid foods

Patients with intestinal hypomotility may benefit from high-fiber diets

Vitamin deficiencies and malabsorption should be addressed in patients with frequent or severe bacterial overgrowth

Large doses of vitamin C (>1000 mg/d) should be avoided because this stimulates collagen formation and may enhance fibrotic tissue deposition

Classification criteria of scleroderma *(ARA, 1980)*

A/ Major criterium:

1. Proximal scleroderma: symmetric thickening, tightening, and induration of the skin of the fingers and the skin proximal to the MCP or MTP joints. The changes may affect the entire extremity, face, neck, and trunk (thorax and abdomen).

B/ Minor kritériumok:

2. Sclerodactyly: as above limited to the fingers
3. Digital pitted scars or loss of substance from the fingerpad: depressed areas at tips of fingers or loss of digital pad tissue as a result of ischemia
4. Bibasilar pulmonary fibrosis: bilateral reticular pattern of linear or lineonodular densities most pronounced in basilar portions of the lungs on standard chest roentgenogram: may assume appearance of diffuse mottling or “honeycomb” lung. These changes should not be attributable to primary lung disease.

Definite diagnosis requires the major and 2 minor criteria.

SCLERODERMA-LIKE DISEASES

EOSINOPHILIC FASCIITIS: (Shulman's syndrome)
diffuse fasciitis with eosinophilia)

MIXED CONNESTIVE TISSUE DISEASE (MCTD) (Sharp's syndrome):
A mixture of SLE, scleroderma, PM, RA (SS).
Clinical picture: most prominent symptoms are:

- Raynaud's phenomenon,
- synovitis: arthritis/arthralgia,
- „sausage-like" fingers, hands and/or sclerodactyly,
- esophagus motility disorder (dysphagia),
- myositis (CPK elevation),
- pneumonitis, pulmonary fibrosis.

Laboratory: U1-RNP antibodies

***"OVERLAP"* SYNDROMES AND UCTD**
UCTD = in most cases, preceding SLE or scleroderma