

# Systemic sclerosis (scleroderma)

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## Abstract

*Systemic sclerosis (SSc) is an autoimmune systemic disease characterized by small vessel involvement that leads to tissue ischemia and fibroblast stimulation resulting in accumulation of collagen (fibrosis) in the skin and internal organs. The peak incidence of the disease is found between the third and fifth decade of life. The male to female ratio is 5:1. Annual incidence is 14.1 cases per million. Prevalence ranges from 19 to 75 cases per million. No well-defined treatment has been found. However several types of treatment exist and can be classified as such A) systemic therapies and B) organ - specific therapies. Systemic therapies are subdivided into vascular therapies, immunomodulating therapies and antifibrotic therapies. Organ-specific therapies are subdivided into therapy of pulmonary interstitial fibrosis, therapy of pulmonary hypertension, therapy of SSc renal crisis. Most of the above-mentioned therapies have been tested in open clinical trials. Systemic sclerosis is more common in coal and gold miners and miners exposed to vinyl-chloride, epoxyresins and aromatic hydrocarbons. However, these factors do not explain the spontaneously developed disease. Recently, CD34 stem cells of child origin were detected in women with SSc more commonly than in normal women. Furthermore, the SSc women display histocompatibility in most of the HLA loci with their children.*

## Keywords

Systemic scleroderma, fibrosing alveolitis, pulmonary hypertension, renal crisis, heart/lung transplantation therapy.

## Disease name and synonyms

Systemic sclerosis (SSc), Scleroderma, Progressive systemic sclerosis.

## Excluded diseases

The clinical manifestations of the disease are vascular and skin changes. Vascular changes include Raynaud's phenomenon, digital

ischemia, ulcers and gangrene. Raynaud's phenomenon is the episodic, reversible, sequential expression of pallor, cyanosis, redness of the digits, ears or nose, due to vasospasm/dilatation repeated attacks, in response to cold exposure or to emotion. Skin changes include puffy or tight and atrophic skin. Relying on the vascular changes in scleroderma, the following diseases should be then excluded: primary Raynaud's phenomenon, systemic lupus erythematosus (SLE), dermatomyositis/polymyositis (DM/PM), Sjögren's syndrome (SS), polyarteritis nodosa (PN), cryoglobulinemia. Relying on the skin changes in scleroderma, the following diseases should be then excluded: localized scleroderma, undifferentiated connective tissue disease (UCTD), SLE, DM/PM, overlap syndromes of SSc with other autoimmune diseases like SLE, SS, DM/PM, or rheumatoid arthritis (RA); chronic graft-versus-host disease (GVHD); POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes); eosinophilic fasciitis, eosinophilia myalgia syndrome and metabolic - genetic diseases as presented in "differential diagnosis".

#### Diagnostic criteria

In order to include patients into specific clinical trials or cohort studies, a person will be classified as having SSc if one major, two or more minor criteria are present (see Table 1). [1]

**Table 1: Criteria for the classification of systemic sclerosis**

A. Major criteria
Proximal scleroderma: symmetric thickening, tightening and induration of the skin of the fingers and the skin proximal to the metacarpophalangeal or metatarsophalangeal joints. The changes may affect the entire extremities, face, neck and trunk.
B. Minor criteria
1. Sclerodactyly: the above-mentioned skin changes are limited to the fingers.
2. Digital pitting scars or loss of substance from the finger pad. Depressed areas at tips of fingers or loss of digital pad tissue as a result of ischemia.
3. Basilar pulmonary fibrosis: bilateral reticular pattern of linear or lineonodular densities most pronounced in basilar portions of the lungs on standard chest roentgenogram, not attributable to primary lung disease.

#### Definition

SSc is a multisystemic, autoimmune disease affecting small arteries, microvessels and fibroblasts resulting in vascular obliteration, collagen accumulation and scarring (fibrosis) of skin and internal organs. This leads to hidebound skin and damage of gastrointestinal tract, lungs, heart and kidneys. The serological specificity of the disease is the presence of antinuclear antibodies (ANAs) which are directed

mainly against cell nuclear enzymes, like DNA topoisomerase -1 (anti -Topo I) and RNA polymerases, as well as centromeric proteins, (anticentromere antibodies, ACA).

#### Differential diagnosis

As shown in Table 2, differential diagnosis is based on the exclusion of diseases showing vascular, skin and visceral changes similar to SSc [2,3]. Physical trauma, chemical exposure, drugs and other autoimmune diseases are accompanied by Raynaud's phenomenon and should be excluded by history, physical and laboratory evaluation. Several forms of localized scleroderma (*i.e* without affecting internal organs), constitute a single circumscribed or linear area of tight skin without signs of visceral involvement, Raynaud's phenomenon or ANAs. Diseases resembling the early phase of scleroderma or overlapping with it should be recognized on the basis of additional clinical signs, the type of organ involvement, the autoantibody profile and biopsy findings. Renal biopsy, in particular, allows the distinction between SSc and SLE, vasculitis, cryoglobulinemia, and SS. The analysis of skin/subcutaneous tissue/fascia and muscle biopsies helps to distinguish between SSc and DM/PM or diffuse fasciitis with eosinophilia or eosinophilia - myalgia syndrome. Scleroderma-like changes in the skin or in the lung in a patient who underwent bone marrow transplantation are indicative of GVHD. Pulmonary fibrosis in scleroderma is associated with antibodies to Topo -I while idiopathic pulmonary fibrosis is not. Furthermore, idiopathic pulmonary fibrosis has a rapidly progressive course. Blood glucose level allows the exclusion of diabetes mellitus which is associated with scleroderma, sclerosis and arthropathy. Serum protein electrophoresis with or without immunofixation can rule out paraproteinemias, like amyloidosis and POEMS. Amyloidosis is diagnosed histologically after staining procedure with Congo red, birefringence characteristic is seen under polarizing microscopy. Amyloidosis diagnosis biopsy can be made on the following biopsies: gingiva, bone marrow, rectum, subcutaneous fat, kidney and liver [2,3].

**Table 2: Differential diagnosis of systemic sclerosis**

Based on the vascular changes

- Primary Raynaud's phenomenon
- Physical trauma (e.g. jackhammer operator)
- Chemical exposure (vinyl - chrolide, coal/silica/gold/heavy metal miners, organic solvents)
- Drugs/toxins [toxic oil syndrome (ingestion of adulterated, rapessed oil, Madrid, 1982), arsenic, bleomycin, cisplatin, ergotamine, beta-blockers (high dose), 5-hydroxytryptophan, carbidopa]
- Other autoimmune connective tissue diseases (SLE, DM/PM, vasculitis, RA, SS, cryoglobulinemia)

Based on skin changes

- Localized scleroderma (morphea, linear scleroderma with atrophy of the affected extremity, "en coup de sable" with and without facial hemiatrophy).
- Scleroderma - like skin changes
  - UCTD
  - Eosinophilic fasciitis with eosinophilia
  - Eosinophilia myalgia syndrome
  - Overlap syndromes (scleroderma, with SLE, or SS, or DM/PM, or RA)
  - Chronic form of GVHD
- Metabolic - genetic disorders
  - Scleredema/Scleremexedema
  - Insulin-dependent diabetes mellitus (scleredema, digital sclerosis)
  - POEMS and other paraproteinemias
  - Amyloidosis

Based on visceral involvement

- Aging and diabetes mellitus (esophageal hypomotility)
- Idiopathic pulmonary fibrosis
- Idiopathic (primary) pulmonary hypertension
- Sarcoidosis
- Amyloidosis
- Infiltrative cardiomyopathies
- Malignant hypertension
- Other autoimmune connective tissue diseases

### Prevalence

The disease has a worldwide distribution and affects all races. It is more frequent and severe in young black women. The peak incidence is found between the third and the fifth decade of life. The female to male ratio is approximately 5:1. Annual incidence is 14.1 cases per million. Prevalence ranges from 19 to 75 cases per 100,000 people. For reasons that have not been well understood, the highest prevalence has been reported in the Choctaw Native Americans in Oklahoma (472/100,000 persons) [3].

### Clinical description

Clinically, the condition may be divided into different subtypes [4].

- **Diffuse cutaneous SSc (dcSSc)**

The onset of symptoms is more abrupt. Raynaud's phenomenon is common but may follow other features. The earliest phenomenon is thickening on the trunk and acral skin edema, presence of tendon friction rubs, pulmonary fibrosis, oliguric renal crisis, diffuse gastrointestinal disease and heart failure or cardiac arrhythmia. Antibodies to Topo-I or to RNA-polymerases I, II, III are present while ACA [4] are absent.

- **Limited Cutaneous SSc (lcSSc)**

Raynaud's phenomenon occurring many years before the onset of skin changes. Skin induration is limited to hands, face and feet; pulmonary hypertension, skin calcification and telangiectasia occurring at a later date, ACA are highly prevalent. This subset also includes a subgroup of patients previously classified as patients with CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, telangiectasia) [4].

- **Systemic sclerosis sine scleroderma (ssSc)**

It is characterized by visceral disease without cutaneous involvement [4].

### Clinical findings

Raynaud's phenomenon affects almost all the patients. The skin is initially swollen and becomes tight later on. Musculoskeletal involvement is evident in 1/3 to 1/2 of the patients and is expressed as symmetric polyarthrits resembling rheumatoid arthritis and muscle weakness. Carpal tunnel syndrome and tendon friction rubs are due to the fibrotic thickening of the tendon sheaths. Muscle weakness occurs just in 5% of the lcSSc patients but in 50% of the dcSSc patients. It is due to:

- a) diffuse atrophy with arthralgia and morning stiffness in the majority of patients,
- b) scleroderma myopathy non associated with elevated muscle enzymes
- c) full-blown myositis (6%) with elevated muscle enzymes indistinguishable from PM/DM (overlap of SSc with PM/DM) [2,3,5].

Gastrointestinal manifestations are common in scleroderma (> 50% of patients); they include gastroesophageal reflux due to hypomotility of the distal part of the esophagus, dysphagia, odynophagia, burning pain in the epigastric and retrosternal regions and regurgitation of gastric contents, especially when the patient is lying flat or bending over [1-3,5]. Dysmotility of the small intestine may lead to abdominal pain and

malabsorption and muscular atrophy of the large bowel wall which may lead to wide-mouth diverticula. Pulmonary involvement occurs in 25% of the lcSSc and in more than 50% of the dcSSc patients. It has mainly three forms:

a) pulmonary interstitial fibrosis (PIF),  
 b) pulmonary hypertension and isolated reduction of diffusing capacity of the lung [expressed as isolated impairment of carbon monoxide transfer factor for whole lung (TLCO)]. Pulmonary alveolitis precedes PIF and can be detected by high-resolution computed tomography (HRCT) of the lung as increased lung density or patchy air-space opacification with reticular and nodular patterns (ground glass). It can also be seen by bronchoalveolar lavage (BAL), which recovers increased numbers of alveolar macrophages, neutrophils, eosinophils and CD8 positive T lymphocytes. PIF can be evident by chest X-ray or HRCT as linear and reticular densities, leading to honey-combing appearance affecting prominently the lower two thirds of the lung (reticular pattern). PIF is associated with the dcSSc and anti-Topo-I antibodies [5-7]. PH affects a small number of patients with lcSSc and ACA [5]. The most common symptom is exertional dyspnea and/or dry, non productive cough. On clinical examination bilateral basilar rales may be present. In the case of PIF, spirometric evaluation reveals decreased forced vital capacities (FVC) and decreased total lung capacities (TLC), while in case of PH, only the TLCO and the partial pressure of blood oxygen are decreased. PH leads to right-sided heart failure, which has very poor prognosis. Clinically evident cardiac involvement occurs in nearly 10% of the lcSSc patients and more than 20% of the dcSSc patients, it is mainly due either to abnormalities of the intra-myocardial circulation (common) or to cardiomyopathy resulting from myocardial fibrosis (rare). It is manifested as:

a) conduction system abnormalities (arrhythmias) [8],  
 b) left-sided heart failure,  
 c) pericardial effusion (usually silent).

However, ultrasound, electrophysiologic and thallium scanning studies revealed that arrhythmia, or reperfusion abnormalities of the intra-myocardial circulation occur in respectively 80% and 95% of patients [1-3,8]. Hypoxia/reperfusion injury due to vasospasm of distal coronary vessels («cardiac» Raynaud's phenomenon), leads to the areas of contraction band necrosis. Cardiac involvement has a poor prognosis. For reasons not fully understood, pericarditis is a precipitating manifestation of renal crisis. Renal involvement occurs in nearly 2% of the lcSSc and 6%-30% of the dcSSc

patients [1-3,5]. It affects mainly male patients with dcSSc who have antibodies to RNA polymerase III and who also suffer from cardiac involvement (especially pericarditis) or take prednisolone at levels of 25mg daily or higher. Renal involvement takes the form of scleroderma renal crisis, which is defined as follows: «a rise in diastolic blood pressure above 110 mmHg and decreasing clearance during the final week of observation associated with hematuria or proteinuria or retinal hemorrhages or microangiopathic hemolytic anemia or papilledema». Occasionally, renal crisis may occur with normal blood pressure. Creatinine levels above 3mg/dL, during the episode, male sex and older age at disease onset are associated with poor outcomes. Incidence and poor outcome of renal crisis have been reduced after the introduction of treatment with angiotensin converting enzyme (ACE) inhibitors [1-3].

### Management

It can be divided into two major parts:

- A) Systemic therapy,
- B) Organ-specific therapies.

Systemic therapy can be divided into: vascular therapy, immunomodulation and antifibrotic therapy.

Organ-specific therapies can be divided into the therapy of PIF; PH; peripheral vascular disease; cardiac disease; renal crisis; gastrointestinal involvement; skin involvement; musculoskeletal involvement [9].

### Systemic therapies

#### Vascular therapy

Smoking is completely prohibited. Drugs, such as  $\beta$ -blockers, which aggravate vasoconstriction and Raynaud's phenomenon should be avoided. Calcium channel blockers reduce cellular uptake of calcium and therefore inhibit the contraction of smooth muscle cells. Nifedipine at doses 10 mg tid (*ter in die*) or in the tablets retard (40-60 mg daily, divided into two doses) may reduce the frequency and the severity of the ischemic attacks. Frequent adverse affects include tachycardia, nausea, flushing, headaches, pretibial edema. The doses for the other drugs of the same category are diltiazem (60mg, tid), nifedipine (20mg, tid), amlodipine (5 mg per day) [10].

Prostaglandins and their analogues: prostaglandins are derived from arachidonic acid (AA), which is released primarily from the phospholipids phosphatidylinositol and phosphatidylcholine of the cell membrane, via the enzyme phospholipase A2. Once released,

AA can be converted into prostaglandins (PGs), thromboxanes (TXs) or leukotrienes (LTs), depending on tissue type, enzyme concentrations and cytokine milieu. Biologically active PGs are PGD<sub>2</sub>, PGI<sub>2</sub>, (prostacyclin), PGE<sub>2</sub>, and PGF<sub>2a</sub>. They act *via* cell - surface receptors and have important vasoactive properties. Stimulation of PGE<sub>2</sub>, PGI<sub>2</sub> and PGD<sub>2</sub> receptors leads to smooth muscle cell relaxation while stimulation of PGF<sub>2a</sub>, and TXA<sub>2</sub> receptor activates smooth muscle cell contraction [10]. The short half-life of PGs made their pharmacologic use difficult and led to the discovery of prostaglandin analogues with longer half-life.

Carboprostacyclin (iloprost), a synthetic analogue of prostacyclin, has proven to be useful in reducing severe ischemia which can lead to digit amputation. The drug should be used on an inpatient basis by slow intravenous infusion at doses ranging from 0.5 to 2 ng/kg/min for 6 hours per day for 4 weeks [11]. In addition to vasodilatation, the drug inhibits platelet aggregation, decreases blood viscosity and alters neutrophil function [9]. For the management of Raynaud's phenomenon [12], oral iloprost shows the same efficacy than placebo.

Antagonists of angiotensin II receptor, type 1; Losartan compared with nifedipine in a randomized, parallel group, controlled trial was shown to be effective as a short-term treatment of Raynaud's phenomenon [13].

#### *Immunomodulation*

Activation of the immune system plays a key-role at disease onset and on the disease-related organ damage.

Cyclosporine A suppresses cell-mediated immunity and collagen synthesis by activated SSc derived fibroblasts. The major response parameter evaluated in open studies was the severity and the extent of skin involvement, known as «skin score» [14]. Hypertension, hypertrichosis and deterioration of renal function are common side effects. Arteriolar hyalinization and interstitial fibrosis have been reported in the kidney of patients treated with cyclosporine. In addition, endothelial cell stimulation of endothelin production by cyclosporine was described. Relying on these findings, this drug should not be recommended for the treatment of SSc [9].

Methotrexate, 15mg per week, reduces the extent of skin involvement. However, its effect is not sufficient to consider the drug as significantly effective for the treatment of dcSSc [15]. In addition, methotrexate may induce pulmonary

morbidity such as cough, asthma, alveolitis and interstitial fibrosis.

Photophoresis is based on the inhibition of the activated T cells by extracorporeal photoactivated 8-methoxypsoralen. The patients receive the photosensitizing component 8-methoxypsoralen and then undergo leukophoresis. Peripheral blood in an extra corporeal flow system is exposed to ultraviolet A (UVA). T lymphocytes sensitized by 8-methoxypsoralen are sensitive to UVA and their function. The results of various studies are conflicting regarding the efficacy of photophoresis. Controlled studies are currently in progress [9].

Autologous stem cell transplantation aims at eliminating the active (including autoreactive) T lymphocytes and «reprogramming» the immune system by infusing their progenitor cells, known as CD34 positive stem cells. Improvement in skin score in 69% of the cases was reported. Lung function was not improved in a recent study while 17% of the patients died from the procedure [16]. This procedure still remains an experimental therapy.

#### **Antifibrotic therapy**

D-Penicillamine [17], interferons ( $\alpha$ - and  $\beta$ ) [9], recombinant human relaxin [18] have been tested in controlled trials which did not show any benefit.

#### **Organ specific therapies**

##### *Pulmonary Interstitial fibrosis (fibrosing alveolitis)*

Prednisolone, cyclophosphamide, either per os or in intravenous (IV) pulses, azathioprine and home oxygen have been used with limited success. Their efficacy has not been tested in controlled trials. Spirometry and PIF score on HRCT are response parameters.

Cyclophosphamide either as monthly IV injections at a dose of 0.750 g to 1 g/m<sup>2</sup> or as a 50mg to 125 mg oral daily dose has shown some benefit in open studies [19]. Controlled studies are in progress. Many experts add small doses of prednisolone, (20 mg daily or less) to the above-mentioned regimen.

Corticosteroids have been widely used for the treatment of interstitial lung disease with conflicting results [9].

Azathioprine at a daily dose of 2.4 mg/kg has been used following a 3-month induction phase with cyclophosphamide, especially in females who are at child bearing age [9].

Therapy is required for PH, especially when pulmonary artery pressure is above 50 mmHg and TLCO < 70%. Evidence for long-term

efficacy for the regimens described below is lacking.

Calcium channel blockers and ACE inhibitors. Short- and medium- term efficacy has been shown for nifedipine and captopril, as detected by a decrease in mean pulmonary vascular resistance [9].

Carboprostacyclin (Iloprost) has been used by direct infusion into the pulmonary artery, then by oral and inhaled delivery. One of the main problems is the need for sustained drug release for years and the decreasing of systemic vascular resistance which may precipitate a fall in cardiac output [9].

Prostacyclin (epoprostenol) in continuous, intravenous infusion improves the exercise capacity of the patients after 12 weeks of therapy compared to conventional therapy alone [20].

Warfarin increases survival in primary PH, but the drug has not been tested in PH secondary to SSc.

Oxygen was shown to reduce pulmonary vascular resistance for a short period of time. Single lung or heart/lung transplantation is still an experimental therapy, although there are encouraging results from a small number of transplanted patients [9].

#### *Renal disease*

Management of renal disease requires a high index of suspicion, especially the first 4 years [9]. Doses of prednisolone above 20mg daily should be avoided. Blood pressure should be controlled by ACE inhibitors. In case of renal crisis the patient should be hospitalized and high doses of captopril or endlapril should be prescribed with the aim to reduce both, systolic and diastolic blood pressure. Short-term hemodialysis should be considered if necessary. The degree of microangiopathic hemolytic anemia should be monitored carefully [9].

#### *Gastrointestinal manifestations*

H2-blockers and proton pump inhibitors are important therapeutic agents to eliminate dysphagia, odynophagia and gastroesophageal reflux symptoms. The hypomotility of the small intestine responds to long-acting somatostatin analogue octreotide and also to metoclopramide. Therapeutic measures for malabsorption include antibiotics, nutritional supplements, vitamins and low-residue diets. Pseudo-obstruction of the large bowel should be treated carefully, after hospitalizing the patient and giving fluids intravenously [9].

#### *Cardiac involvement*

It is treated on an empirical basis, depending upon its type.

#### **Etiology**

SSc is rather common in coal and gold miners and in workers exposed to vinyl-chloride, epoxyresins and aromatic hydrocarbons. Individuals taking pentazocin, bleomycin and products containing L-tryptophan develop SSc-like features [2,3,9]. However, all these factors do not explain the spontaneously developed disease. The activation of the immune system is an outstanding disease feature. Autoantibodies and perivascular lymphocytic (mainly CD4 positive T lymphocytes) infiltrates indicate activation of the immune system. The CD4 positive T cells can be activated by endothelial basement membrane components like laminine and type IV collagen. Consequently, these cells secrete an endothelial cytotoxic factor, named granzyme, as well as tumor necrosis factor (TNF) which activates endothelial cells and transforming growth factor -  $\beta$  (TGF- $\beta$ ) which activates fibroblasts to express TGF-  $\beta$  and platelet-derived growth factor (PDGF). PDGF activates fibroblasts to secrete increased amounts of collagen. The chronic form of GVHD (a T-cell dependent disease) shares clinical features with SSc. This observation supported the hypothesis that alloreactive T cells derived from the child survive for a long time in the mother's body and vice-versa. This phenomenon is called «microchimerism». Chimeras may survive longer if histocompatibility exists between mother and fetus [3,9]. Recently, CD34 stem cells of child origin were detected in women with SSc more commonly than in normal women. Furthermore the SSc women display histocompatibility on most of the HLA loci with their children [3].

#### **Diagnostic methods**

Only clinical examination allows the diagnosis of scleroderma.

#### **Genetic counseling**

Genetic counseling cannot be carried out.

#### **Antenatal diagnosis**

Antenatal diagnosis cannot be carried out.

#### **Unresolved questions**

Regarding etiology, pathogenesis and the therapeutic potential of various regimens.

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