The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Systemic sclerosis

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1 Introduction

The first description of Systemic Sclerosis (SSc) was made by Carlo Curzio and dates back to 1753, but the name *scleroderma* was ascribed only in 1847 by Gintrac. SSc is a clinically heterogeneous, multisystemic, autoimmune connective tissue disorder typically involving the skin (Raynaud's phenomenon (RP), digital ulcers, skin thickening, telangiectasias, calcinosis Fig. 1), lung (pulmonary fibrosis, pulmonary hypertension), heart (arrhythmias, myocardial fibrosis, congestive heart failure), musculoskeletal apparatus (arthritis, arthralgias, tendon friction rubs, joint contractures, myopathy), gastrointestinal tract (oesophageal and small intestine hypomotility) and kidney (scleroderma renal crisis).

SSc can be further subcategorised into 4 principal subsets:

- limited SSc (skin sclerosis restricted to the hands and the distal forearms, and to a lesser extent the face and the neck),
- diffuse SSc (sclerotic skin also on the chest, abdomen, upper arms and shoulders),
- SSc sine scleroderma (internal organ involvement only) and
- overlap syndromes (criteria fulfilling SSc occurring concomitantly with features of systemic lupus erythematosus [SLE], rheumatoid arthritis [RA] or inflammatory myopathy).

Limited SSc was formerly identified with CREST syndrome (**C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dismotility, **S**clerodactyly, **T**elangiectasias), a clinical entity described long ago. However, patients with limited SSc do not necessarily have all the features of CREST syndrome, although many of them do. Table 1 summarizes the clinical features of limited and diffuse SSc.

The disease occurs worldwide, and the incidence and the prevalence rates show wide variation, with the higher prevalence being approximately 230 cases per million in the USA and South Australia. The disease is predominant in females, with a 3–5 : 1 ratio; SSc onset is most commonly between 30 and 50 years of age.

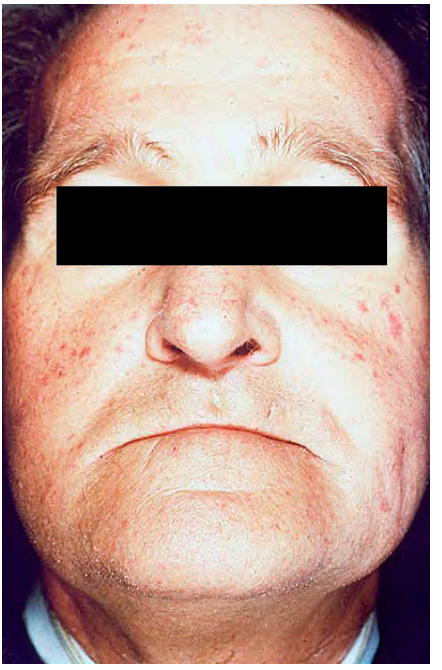

Figure 1. A patient suffering from limited SSc with a typical *scleroderma facies*: the skin is thickened, the wrinkles are smoothed but the ones around lips are furrowed, there is a remarkable reduction in the maximum oral aperture ("microstomia"), the nose becomes pinched, many telangiectasias can appear, the face can appear expressionless because of a reduced capacity to smile or to move eyelids or cheeks.

Pathophysiologically, the two leading mechanisms involved in SSc are a massive accumulation of extracellular matrix components leading to fibrosis and a vascular disease characterised by arterial vasospasm, smooth muscle hyperactivity, intimal proliferation and eventual vascular occlusion leading to tissue ischaemia [1].

2 Diagnostic measurements for experts

Skin involvement

Regarding the extent of cutaneous involvement, the most widely scoring system, named "modified Rodnan thickness skin score", evaluates skin sclerosis at 17 sites, with scores at each site being 0 (normal), 1 (equivocal sclerosis), 2 (definite sclerosis), or 3 (hide bound); the skin score reflects disease severity.

In SSc patients, nailfold capillaroscopy shows a typical scleroderma pattern, with enlarged capillary loops and/or the loss of capillaries or avascular areas.

Gastrointestinal involvement

In cases with symptoms of oesophageal dysfunction, a barium swallow, endoscopic and/or manometric investigation are warranted.

Lung involvement

The most sensitive method for detecting early lung disease in scleroderma is to perform pulmonary function testing: mild changes in function can be detected

Table 1. Signs and symptoms of the disease.

	Limited SSc	**%**	**Diffuse SSc**	**%**
Constitutional symptoms	Rare		Severe	
Skin	RP alone for years	95	Delayed RP	85
	Digital ulcerations on fingertips or distal toes	15	Digital ulcerations on fingertips or distal toes	30
	Skin thickening limited to hands (sclerodactyly) and face (Fig. 1)	95	Skin thickening progressing from fingers to trunk rapidly	100
	Subcutaneous calcinosis at sites of trauma	50	Subcutaneous calcinosis at sites of trauma	10
	Telangiectasias on the face, upper chest, palms, fingertips, and mucous membrane in early stages	80	Telangiectasias on the face, arms and trunk in the later stages	30
Musculoskeletal apparatus	Minimal arthralgias	60	Arthritis, carpal tunnel syndrome	80
	Tendon friction rubs	3	Tendon friction rubs	65
	Myopathy	10	Myopathy	20
Lung	Inflammatory alveolitis leading to pulmonary interstitial fibrosis	35	Inflammatory alveolitis leading to pulmonary interstitial fibrosis	45
	Pulmonary hypertension	10	Pulmonary hypertension	<1
Heart	Pericarditis	15	Pericarditis	15
	Congestive heart failure	5	Congestive heart failure	15
	Arrythmias	20	Arrythmias	15
	Pericarditis	20	Patchy myocardial fibrosis (at autopsy)	50

Table 1. *(continued)* Signs and symptoms of the disease.

	Limited SSc	%	Diffuse SSc	%
Gastrointestinal tract	Oesophageal hypomotility (dysphagia, dyspepsia, reflux symptoms)	75	Oesophageal hypomotility (dysphagia, dyspepsia, reflux symptoms)	75
	Small intestine hypomotility (intermittent pseudo-obstruction)	25	Small intestine hypomotility (intermittent pseudo-obstruction)	25
	Association with PBC and AIH	17		
Kidneys	Scleroderma renal crisis (malignant hypertension, rapidly progressive renal failure)	1	Scleroderma renal crisis (malignant hypertension, rapidly progressive renal failure)	20

RP, Raynaud's Phenomenon **AIH**, Autoimmune Hepatitis **PBC**, Primary Biliary Cirrhosis

before any symptoms develop. The most common changes of pulmonary function testing are either a reduced diffusion capacity (D_LCO) or a reduction in lung volumes typical of a restrictive ventilatory defect associated with a reduction in gas exchange. A high-resolution computed tomography scan of the chest is a very sensitive technique for detecting changes in the lung parenchyma, showing, in cases of active alveolitis, a ground-glass opacity of the lung and a honeycombing lung parenchyma in cases of interstitial fibrosis.

Bronchoalveolar lavage is used to detect inflammation and active alveolitis.

Pulmonary hypertension can be detected early and non-invasively by measuring the pulmonary artery pressure with two-dimensional Doppler echocardiography; patients with a pathologic or borderline tricuspid regurgitant jet velocity should undergo a right-heart *catheterisation.*

Laboratory investigations

A positive antinuclear antibodies (ANA) with a centromere (Fig. 2), a speckled and/or nucleolar staining pattern is frequently noted; specific autoantibodies include anti-centromere antibodies (ACA, usually associated with limited SSc) and anti-DNA topoisomerase I (anti-Scl-70, usually associated with diffuse SSc) [1].

3 Requirements for family practitioners

Most commonly, SSc patients present to family practitioners complaining of Raynaud's phenomenon, that may have been present alone for years before any other manifestations occur. It is important to distinguish between patients with primary or uncomplicated Raynaud's phenomenon and those with a secondary one.

A secondary cause of Raynaud's phenomenon is suggested by the following findings:

- age at onset of more than 30 years;
- episodes that are intense, painful, asymmetric, or associated with ischaemic skin lesions;
- clinical features suggestive of a connective tissue disease;
- positivity of ANA and antibodies against extractable nuclear antigens (ENA);
- evidence of microvascular disease on microscopy of nail-fold capillaries.

The family practitioner should exclude potential causative or aggravating factors (carpal tunnel syndrome, environmental agents and injury, use of particular drugs such as sympathomimetic agents, cocaine, nicotine, ergotamines etc). Patients should undergo a nailfold capillaroscopy and a superior limb arterial Doppler ultrasonography plus laboratory tests (complete blood count, active phase reactants, serum protein electrophoresis, thyroid function test, cryoglobulins, rheumatoid factor, ANA, anti-ENA, C3 and C4) to rule out diseases such as hypothyroidism, cancer, cold agglutinin syndrome, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), cryoglobulinaemia, atherosclerosis, embolic disease, thoracic outlet syndrome.

The presence of ANA displays relatively low positive predictive value for an associated connective tissue disease (30 %), whereas the presence of antibodies against a specific autoantigen is more highly suggestive of secondary disease: scleroderma is more likely in patients with ACA or anti-topoisomerase antibodies.

Skin thickening is another feature commonly present at disease onset; apart from SSc, it may be a manifestation of many other diseases and can result from exposure to drugs (e. g., bleomycin, pentazocine, vitamin K and B12) or harmful environmental factors (petroleum distillates, organic solvents, vibrating tools). Some endocrine disorders (diabetes mellitus and hypothyroidism), renal disease, and infiltrative disorders (amyloidosis, eosinophilic fasciitis, chronic GVH disease) can cause scleroderma-like skin changes [2].

4 Follow up

Patients suffering from non complicated limited SSc should undergo a rheumatologic visit once a year, while limited SSc patients with pulmonary involvement and diffuse SSc patients need a tighter follow-up, three times a year.

Patients must be questioned about the appearance of symptoms such as dysphagia, dyspepsia, constipation, diarrhoea, breathlessness on exertion, non-productive cough. At clinical examination, particular attention should be paid to heart and lung auscultation revealing arrhythmias and velcro rales; fingertip ulcers and skin thickening (modified Rodnan thickness skin score) should be strictly monitored. Blood pressure measurement is recommended on a monthly basis.

Periodical routine laboratory tests should be performed, including complete blood count, acute phase reactants, muscular enzymes, hepatic and renal functions, with urine analysis and measurements of the glomerular filtration rate.

A complete assessment to evaluate the internal organ involvement (electrocardiogram, two-dimensional Doppler echocardiography with pulmonary artery pressure measurement, chest X-ray, pulmonary function tests with D_LCO evaluation, barium swallow, nailfold capillaroscopy) is necessary at diagnosis and yearly thereafter; high-resolution computed tomography scan of the chest, gastroenteric tract endoscopic study, a manometric investigation of the oesophagus and a 24-hour pH monitoring are required every two years or if new symptoms appear [1].

5 Management (therapeutic principles)

In consideration of the multifaceted nature of the disease, therapeutic management of SSc patients consists of a combination of agents acting upon different clinical aspects. The management of Raynaud's phenomenon should first consider non-pharmacologic strategies such as avoidance of cold, stress, nicotine, caffeine and sympathomimetic decongestant medications. Low-dose acetylsalicylic acid and calcium-channel blockers are first-line options.

In severe Raynaud's phenomenon, it has been demonstrated that iloprost (a prostacyclin analogue given parenterally) reduces the number of weekly attacks and the global Raynaud severity score; moreover, it is effective in healing at least 50 % of digital cutaneous lesions, helping to avoid amputation of the distal tip of a digit. More recently, bosentan (a non selective endothelin antagonist already registered for treatment of pulmonary hypertension) has shown a beneficial effect upon digital ischaemia, reducing the appearance of new ulcers.

In patients with abnormal oesophageal motility, the empiric use of acid reducing agents, particularly proton pump inhibitors, is generally recommended; prokinetic agents may be valuable.

In cases of active inflammatory alveolitis — that is presumed to precede the development of interstitial fibrosis — treatment is recommended. The combination of glucocorticoids (prednisone 10 mg/kg) and cyclophosphamide (administered both orally at a dose of 1 mg/kg increased to 2 mg/kg if tolerated and intravenously at a dose of 600 mg/m^2 per month) is the only therapeutic regimen that has shown

a modest clinical efficacy at preventing deterioration of lung function in patients with active alveolitis.

Pulmonary hypertension in SSc may be due to lung interstitial fibrosis, increased pulmonary arterial vasoreactivity or obliterative vasculopathy. Among the therapeutic options for pulmonary hypertension, there is evidence for the efficacy of bosentan, the phosphodiesterase-5-inhibitor sildenafil and various prostacyclin analogs, that may be administered by inhalation, subcutaneous infusion or intravenously.

A mild myopathy with little biochemical or histological change is a common feature of SSc; glucocorticoids alone or in combination with methotrexate or azathioprine are generally employed [3].

6 Diagnostic tests and testing methods

The presence of characteristic autoantibodies is supportive of the diagnosis of SSc [4, 5].

ACA are seen mostly in patients with limited SSc and with a greater frequency in women. They are associated with calcinosis, tuft resorption and digital ulcers. ACA are typically detected by the indirect immunofluorescence on HEp-2 cells giving a discrete speckled appearance on interphase nuclei and chromatin of mitotic cells (Fig. 2). Three main centromere/kinetochore-associated proteins (CENP-A of 29 kDa, CENP-B of 80 kDa and CENP-C of 140 KDa, altogether known as "CENPs") are recognised by autoimmune sera. To characterise the reactivity to individual CENP antigens, Elisa or Line immunoassays are necessary. ACA display a sensitivity of 3–12 and 57–82 % for diagnosing diffuse and limited SSc respectively.

Anti-Scl-70 are associated with diffuse SSc with a sensitivity of 34–65 % among patients with diffuse SSc even if 25 % of patients do not have extensive skin, heart or kidney problems, with a clinical course similar to that of limited SSc. Moreover, they are associated with prominent pulmonary interstitial fibrosis and vascular problems, although Scl-70 positive patients are protected from vasculopathy type of pulmonary hypertension. Anti-Scl-70 are directed against an acid nuclear enzyme, DNA topoisomerase I, which catalyzes the conversion of DNA topologic forms mediated through transient single-strand DNA breaks and relegation. Historically, the usual method for detection anti-Scl-70 was immunodiffusion and immunoblotting, but nowadays most laboratories detect them by Elisa or Line immunoassays. The disappearance of anti-Scl-70 is associated with favourable outcomes, and serum levels of anti-Scl-70 may correlate positively with the severity of skin involvement and with global disease activity.

A nucleolar pattern of ANA at high titres is very specific to scleroderma, and several specific antibodies have been identified; they are not very common and commercial assays are still not available for all of them:

- anti-U_3-RNP or antifibrillarin antibodies are associated with diffuse cutaneous disease, pulmonary fibrosis and isolated pulmonary hypertension,
- anti-Th/To and anti-Pm/Scl antibodies are more frequent in white patients with limited scleroderma. Pulmonary hypertension and myositis are respectively common features in these patients,
- anti-RNA-polymerase I antibodies are associated with severe, diffuse forms of systemic sclerosis; higher frequency of cardiac, hepatic and renal involvement,
- anti-RNA-polymerase III antibodies are detected in 12–23 % of patients with systemic sclerosis. They are associated with diffuse or extensive skin manifestation and have been detected during a renal crisis in the absence of skin manifestations, i. e., sclerosis sine scleroderma.
- Anti-U_1-RNP antibodies are associated with overlap syndromes, mostly with mixed connective tissue disease.

7 Diagnostic criteria

There are no universally accepted classification and/or diagnostic criteria for SSc. In 1980, the ACR classification criteria (Table 2) were designed to differentiate SSc from other diseases; unfortunately, they do not include specific tests for ANA and nailfold capillaroscopy (Fig. 2). It has been shown they lack sensitivity, particularly in identifying patients with limited SSc. More recently, Nadashkevich proposed an updated classification set that included the presence of ANA but did not include nailfold capillaroscopy. The validity of these criteria has been tested preliminarily on a population of 99 SSc patients, yielding a 99 % sensitivity and 100 % specificity. However, these criteria have not been widely adopted [6].

Table 2. Clinical and laboratory diagnostic criteria.

Major Criterion	Minor Criteria
Proximal scleroderma (Skin involvement extending proximally to metacarpophalangeal joints)	1. Sclerodactyly 2. Digital pitting scars of fingertips or loss of substance of the distal fingerpad 3. Bibasilar pulmonary fibrosis

To make a diagnosis of Systemic Sclerosis, at least the major criterion or two or more minor criteria must be fulfilled.

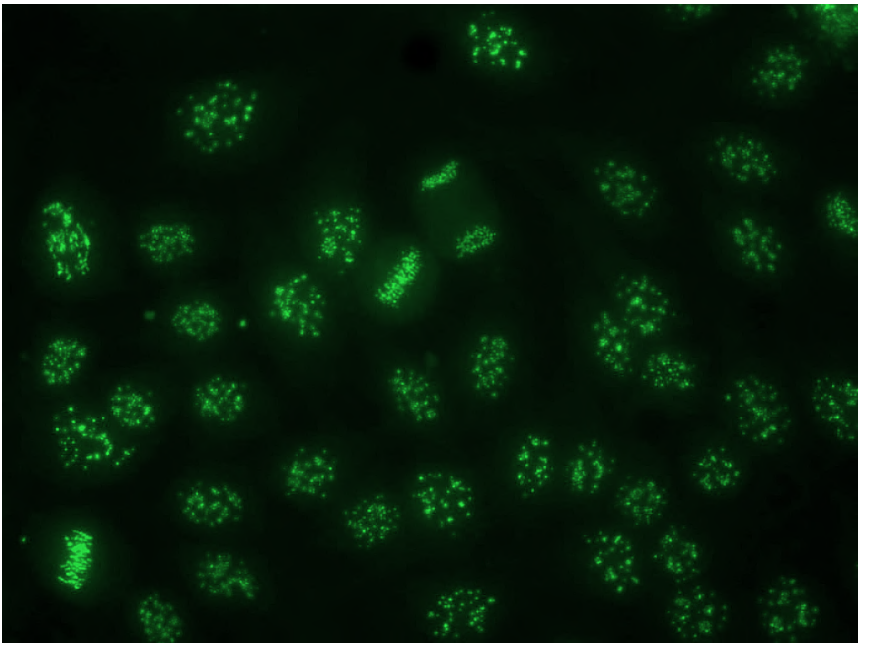

Figure 2. Indirect Immunofluorescence test on Hep-2 cells showing a discrete speckled appearance on interphase nuclei and chromatin of mitotic cells, typical of anti-centromere antibodies(ACA).

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