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Management of systemic sclerosis

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Pathogenesis

The pathogenesis of systemic sclerosis (SSc) remains incompletely understood. The earliest events occur in the microcirculation with endothelial cell activation, followed by perivascular inflammation with monocytes and later lymphocytes. Subsequently, fibroblasts become activated and deposit increased extracellular matrix in lesional tissues including the skin and internal organs.[1] The resulting architectural disruption leads to the morbidity, and ultimately mortality, associated with SSc. There is evidence to support genetic factors in the development of SSc but few candidate susceptibility or severity genes have yet been identified.

Classification

This article focuses mainly on SSc (scleroderma with systemic involvement), but the spectrum of scleroderma encompasses Raynaud's phenomenon and localised subtypes of skin fibrosis such as morphoea (Table 1). The extent of skin involvement defines the disease subset in cutaneous SSc (Fig 1):[2]

- diffuse cutaneous SSc (dcSSc): skin involvement proximal to the elbows and knees, and
- limited cutaneous SSc (lcSSc): skin involvement distal to these joints.

A subset of patients has the clinical features of isolated Raynaud's phenomenon, with evidence of microvasculopathy based upon nailfold capillaroscopy and/or serum autoantibodies against nuclear antigens (autoimmune Raynaud's phenomenon). They have a 10–15% likelihood of developing a defined connective tissue disease (including SSc) during long-term follow-up.

The term limited SSc has recently been applied to another group of patients who lack definite skin involvement but who harbour specific antibodies against hallmark antigens or have scleroderma-associated capillaroscopic changes.[3]

In addition, a small number of patients with vascular symptoms and SSc-specific antibodies develop major organ-based complications in the

Key Points

Appropriate management of systemic sclerosis (SSc) requires accurate disease subsetting, staging of the disease within each subset and risk stratification for major organ-based complications, based upon clinical features and serology

All patients with SSc should be screened for major complications to facilitate early intervention

Hypertensive renal crisis can occur in any patients with SSc; angiotensin-converting enzyme inhibitors should be instituted as early as possible in these cases

Significant reduction in transfer factor on lung function tests may reflect either interstitial lung disease or pulmonary hypertension (PAH). Doppler echocardiography and high-resolution computed tomography of the chest are indicated

PAH should be confirmed by right heart catheterisation before considering advanced therapy for symptomatic cases

KEY WORDS: pulmonary fibrosis, pulmonary hypertension, Raynaud's phenomenon, renal crisis, scleroderma, systemic sclerosis

Table 1. Scleroderma spectrum of disorders.

Raynaud's phenomenon	Primary Autoimmune
Systemic sclerosis	Limited Limited cutaneous Diffuse cutaneous *sine* scleroderma Scleroderma overlap syndromes
Localised	Morphoea: localised generalised Linear scleroderma *En coup de sabre*

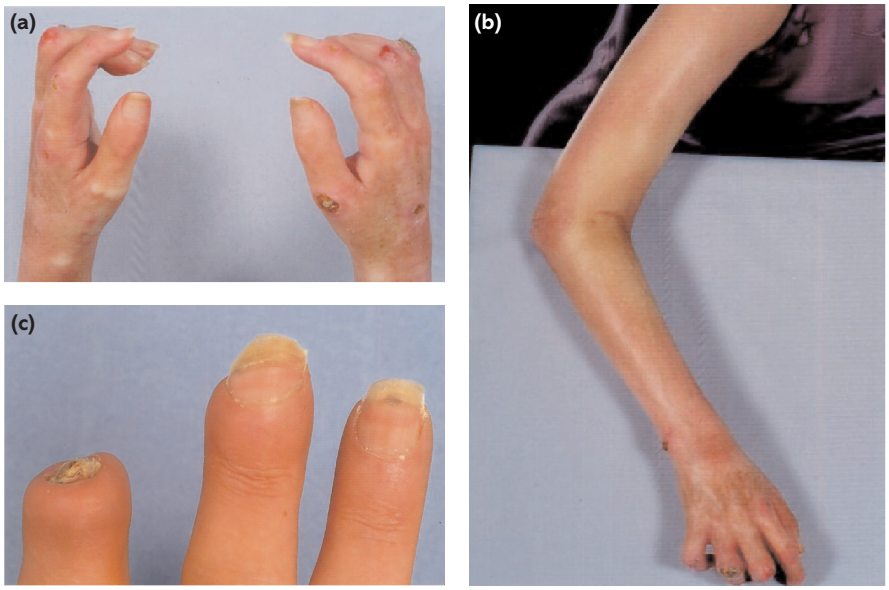

Fig 1. Cutaneous manifestations of systemic sclerosis. Diffuse cutaneous SSc (dcSSc) is characterised in the early stages by skin induration which may ulcerate. Biopsies initially may show perivascular inflammatory cell infiltrates but later involved skin has reduced blood vessel density and is prone to ischaemic and trophic ulceration. Panels show **(a)** dcSSc with severe contractures, **(b)** dcSSc with proximal skin sclerosis, and **(c)** limited cutaneous SSc in which digital pulp loss and severe vasculopathy has led to autoamputation of affected digits.

absence of significant skin sclerosis; these cases are designated SSc *sine* scleroderma.[4]

The reported incidence of SSc varies from 3.7–22.8 cases per million per year[5] with women more likely to be affected (female:male ratio c. 5:1).

Raynaud's phenomenon

Raynaud's phenomenon affects virtually all patients, with variable severity. In lcSSc, it typically precedes the development of other features of the disease, often by many years. In contrast, the onset of vascular symptoms in patients with dcSSc is more likely to be contemporary with other manifestations. Persistent vasospasm, together with structural changes in blood vessels, may lead to painful ischaemia, digital ulceration and even digital infarction. Several pathological mechanisms (structural vasculopathy, infection, trauma and calcinosis) may contribute.

Treatment

A range of vasodilators (particularly calcium-channel blockers) is used for Raynaud's phenomenon. Treatment of established ulcers includes:

- appropriate use of antibiotics
- parenteral prostacyclin analogues
- occasionally selective digital sympathectomy (radical microarteriolysis).

Recently, the endothelin receptor antagonist bosentan has been shown in a clinical trial to prevent new digital ulceration in severe secondary Raynaud's. Other agents reported to be helpful include phosphodiesterase inhibitors (eg PDEI 5) such as sildenafil.

Managing organ-based problems in scleroderma

Skin

Cyclophosphamide, mycophenolate mofetil (MMF) and methotrexate (MXT) are all currently used in the management of skin disease[6] but only MXT has shown benefit in controlled trials – although statistical benefit rather than clinical.[7] Alternative strategies used in pilot studies include antithymocyte globulin followed first by MMF and high-dose cyclophosphamide and then by autologous peripheral stem cell transplant.

The apparent effectiveness of these treatments needs to be considered in the context of the natural history of skin diseases in diffuse scleroderma which can sometimes show striking improvement by three years of disease duration even without therapy. Ultimately, early stage diffuse SSc may benefit from more targeted cytokine- or chemokine-directed therapies.

Renal complications in systemic sclerosis

The most important manifestation of renal involvement is the scleroderma renal crisis (SRC), the major cause of mortality in SSc before the introduction of angiotensin-converting enzyme inhibitors (ACEIs) about 25 years ago. Their use has led to a significant improvement in survival from 10% at one year to 65% at five years.[8] The development of SRC occurs most often in patients with early diffuse SSc in the context of rapid skin progression.

Other associations include:

- new anaemia
- new cardiac events (heart failure or pericardial effusion)
- presence of anti-RNA polymerase I and III antibody
- antecedent use of drugs, including high-dose steroids, non-steroidal anti-inflammatory drugs and ciclosporin.[9]

Patients typically present with an abrupt onset of severe systemic hypertension with new onset headache, visual alterations and accelerated oliguric renal failure. In addition, they may develop seizures, flash pulmonary oedema or hypertensive congestive heart failure. Fundoscopy typically reveals retinopathy of at least grade II. Urine microscopy will usually show haematuria and proteinuria and occasionally red cell casts. Microangiopathic haemolytic anaemia or thrombocytopenia may be evident. Renal biopsy will show characteristic changes in the small interlobular and arcuate arteries with intimal proliferation and deposition of mucinous ground substance. Fibrinoid necrosis may occasionally be seen but true vasculitis is rare.

Treatment

Treatment of SRC patients is with ACEIs. The dose is titrated to achieve a blood pressure reduction of 10–20 mmHg systolic pressure over 24 hours with daily monitoring of creatinine clearance or calculated glomerular filtration rate. ACEIs should be continued even if the patient is on dialysis. Patients are routinely given continuous low-dose prostacyclin to improve blood pressure control and renal blood flow. Plasma exchange may be useful in the presence of thrombotic microangiopathy. There is a potential for renal function recovery and subsequent discontinuation of dialysis, so plans for renal transplant should be delayed until at least 18 months have passed without return of renal function.[10] The newer angiotensin receptor blockers may have an additive effect to ACEIs in refractory cases, but are believed to be somewhat less effective as single agent therapy. Additional treatment with alpha-blocking agents or calcium-channel blockers may be required for refractory hypertension.

Pulmonary complications

Pulmonary fibrosis

Interstitial lung disease (SSc-ILD) and pulmonary hypertension (PAH) are major causes of mortality and morbidity in SSc. Symptoms of pulmonary fibrosis usually occur late and include dyspnoea, fatigue and dry cough.[11] Other causes of dyspnoea such as anaemia, chest wall restriction and concomitant conditions such as reflux, infection and drug exposure (eg MXT) may be contributory. The following are relevant investigations:[12]

- *Pulmonary function tests* (PFTs): diffusion capacity of the lung for carbon monoxide (DLCO) is the best predictor of survival and its reduction frequently precedes the fall in forced vital capacity (FVC).
- *Chest X-ray*: although insensitive, baseline chest X-ray is useful to exclude other pathologies.
- *High-resolution computed tomography* (HRCT): extent of disease correlates well with DLCO. HRCT should be combined with PFT to determine disease severity. Disease pattern such as ground-glass attenuation indicative of fine intralobular fibrosis does not always denote reversible disease.[13]
- *Thorascopic biopsy* allows histological assessment but adds little to prognostic evaluation unless there are unusual HRCT appearances.

Additional investigations include bronchoalveolar lavage (BAL) and clearance of diethylene triamine pentacetate (DTPA) lung scanning. BAL neutrophilia is associated with extensive disease, whereas eosinophilia may be more predictive of future loss of pulmonary function.[14] The pulmonary clearance of inhaled ^{99m}Tc-DTPA denotes increased pulmonary epithelial permeability. Rapid clearance is linked with an increased risk of progressive disease. In patients with isolated reduction of DLCO it can be useful to differentiate between those with PAH and those with early interstitial lung disease. However, this test is not widely available.

There are few prospective or placebo-controlled trials on the treatment of SSc-ILD.[15] The agent for which most evidence of efficacy is available is cyclophosphamide. Results from two current trials will soon be available:

- The UK Fibrosing Alveolitis in Scleroderma Trial comparing intravenous cyclophosphamide and azathioprine.
- The North American scleroderma lung study which compares oral cyclophosphamide with placebo.

Pulmonary hypertension

The reported prevalence of PAH in SSc is estimated to be 7–15% with a five-year cumulative survival of 10% compared with 80% in those without PAH.[16] It is defined as a mean pulmonary arterial pressure (PAP) above 25 mmHg at rest or above 30 mmHg during exercise, with normal pulmonary artery wedge pressure. PAH may occur in the context of both classical limited SSc with anticentromere antibody and diffuse SSc with antifibrillarin antibodies (U3RNP). Early diagnosis is essential to optimise treatment and improve prognosis as one-year survival in late stage disease is less than 50% despite treatment. However, diagnosis is often delayed due to non-specific symptoms and may be mistaken for lack of fitness. Exertional dyspnoea is the major symptom, with disease progression characterised by impaired exercise capacity and fatigue. Signs of right heart failure with venous pressure elevation, oedema and syncope may develop.

Investigations. All patients should be monitored by annual Doppler echocardiography and PFTs.[17] Doppler echo allows both qualitative and haemodynamic assessment, in particular estimation of the peak (systolic) PAP by Doppler assessment of the regurgitant blood jet velocity through the tricuspid valve. A reduced TLCO (<60% of predicted) with normal FVC above 75% of predicted may indicate subsequent development of PAH.

Echocardiography and PFT changes are confirmed with right heart catheterisation; this may also reveal any cardiac consequences of disease activity. There is reasonable correlation between right heart catheterisation and Doppler studies at high pressures but in the range of 30–50 mmHg up to 30% of Doppler readings are either false-positive or

false-negative. It is important to be aware of the limitations of non-invasive screening methods in assessing early PAH. If PAH is confirmed, other causes must be excluded and V/Q scanning and CT pulmonary angiogram are important. The severity of disease is serially assessed with Doppler echo every three or six months. The six-minute walk test (6MWT) is often used as a clinical measure of exercise capacity in PAH.

Treatment. The development of effective treatment for PAH is a major milestone for SSc management.[18] The benefits are clear for long-term oxygen therapy for the associated hypoxia, diuretics and digoxin for symptomatic relief, and anticoagulation. Licensed therapy for PAH now includes parenteral prostacyclin analogues and the oral endothelin receptor antagonist bosentan. The effect of intravenous prostacyclin (epoprostenol) is rapid and improves exercise capacity, cardiac output and survival but, apart from its cost, its use is limited by catheterisation/pump problems and side effects such as neuropathy, jaw pain and diarrhoea. Other modes of prostacylin administration include inhaled and subcutaneous preparations, but these have less established efficacy. Bosentan has demonstrated efficacy in improving 6MWT, increased time to clinical worsening and may improve survival.

Ongoing work includes studies with PDEIs and selective endothelin receptor A antagonists. Atrial septostomy to create a right-to-left shunt and heart-lung or lung transplantation remain treatment options in late stage, severe PAH.

Gastrointestinal manifestations

Gastrointestinal involvement is the commonest visceral complication in SSc. Oesophageal dysmotility occurs in a majority of patients and proton pump inhibitors remain the mainstay of treatment for this complication. Additional prokinetic agents may be required. Vascular lesions of the gut mucosa may lead to transfusion-dependent chronic anaemia or acute blood loss. These vascular lesions are typically localised around the cardia but may occur throughout the gut and are amenable to local laser therapy.[19]

Midgut disease

Midgut disease, with altered motility and bacterial overgrowth, responds to broad-spectrum antibiotics. There is occasionally recurrent pseudo-obstruction and malabsorption. Management is primarily focused on symptom control and nutritional support. Prokinetic agents, subcutaneous octreotide, pancreatic enzyme supplementation and long-term parenteral support can all be useful.

Large bowel disease

Treatment to improve stool frequency and consistency with alternating aperients and antidiarrhoeal agents is required in large bowel disease. Many patients find frequent small meals with a low-fibre diet useful. Surgery should be avoided if possible as it is poorly tolerated; if it is necessary, surgery should involve a gastrointestinal surgeon with an interest in scleroderma. Implantation of a sacral nerve stimulator may be effective in difficult cases.

Table 2. Principles for management of systemic sclerosis.

- Accurate diagnosis
- Appropriate subsetting
- Staging disease within subset disease-modifying therapy?
- Risk stratification for major organ-based complications based upon serological, genetic and clinical features
- Screening and early intervention when complications develop
  - organ-based therapy

Conclusions

The primary goal in the management of patients with SSc is to treat the inflammatory and vascular aspects of the disease with an organ-based approach (Table 2). Patients with aggressive skin disease should be enrolled into controlled

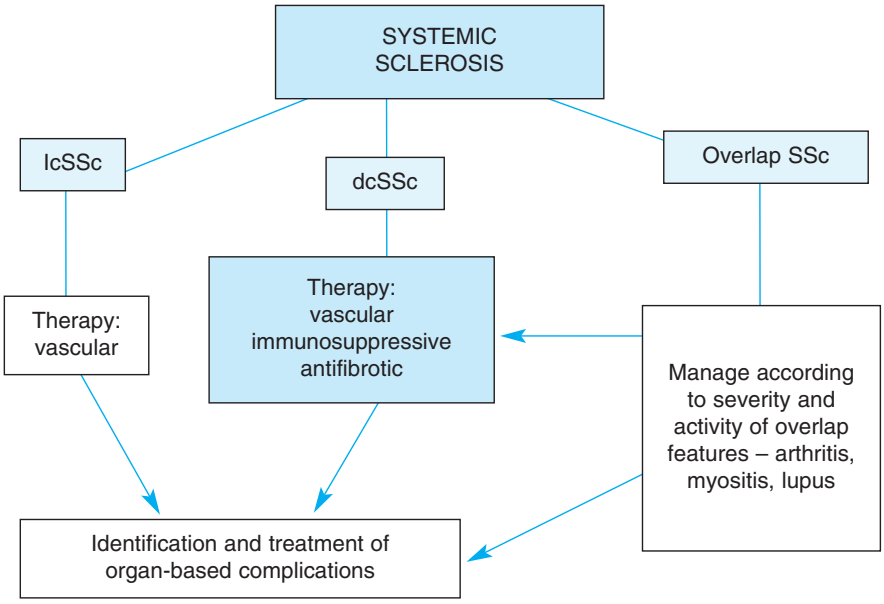

Fig 2. Overview of management of systemic sclerosis. Most systemic sclerosis (SSc) cases may be classified as either limited cutaneous (lcSSc) or diffuse cutaneous (dcSSc) based upon the extent of skin involvement. A small proportion of patients have features of one or more additional connective tissue diseases such as arthritis, polymyositis or systemic lupus erythematosus. Clinical features are often associated with typical autoantibodies (rheumatoid factor or anti-dsDNA). Anti-U1RNP, anti-U3RNP or anti-PM-Scl are more often seen in overlap SSc than other hallmark SSc reactivities. The different approaches to therapy for each subgroup are shown.

trials of treatment. There is also an established nationwide central registry of SSc patients. These sources should give more information about the natural progression of the disease and the potential benefits of treatments using current organ-based therapies.

A standard approach to management of individuals in the major subgroups of SSc is shown in Fig 2 and the current approaches for treatment of organ-based manifestations of SSc are summarised in Table 3. The aim of disease-modifying strategies is to attenuate the vascular, immunological and fibrotic components of SSc (Table 4), but these approaches are much less developed than those for internal organ complications.

SSc serves as a paradigm for a broader range of fibrotic diseases such as cirrhosis and glomerulosclerosis. Future therapeutic advances may therefore have a much broader application.

Table 3. Organ-directed treatments for systemic sclerosis.

Respiratory:	
Interstitial lung disease	● Cyclophosphamide, azathioprine, prednisolone, ?bosentan, ?alefacept ● Oxygen, transplantation ● Warfarin, spironolactone
Pulmonary hypertension	● Bosentan, iloprost, flolan, triprostenil, ?sildenafil ● Oxygen, atrial septostomy, transplantation ● Warfarin, antiarrhythmics
Cardiac	● Cyclophosphamide, prednisolone ● Implantable pacemaker
Renal	● ACEIs, iloprost in renal crisis ● ARBs, α blockers, CCBs ● Renal support
Gut	● Proton pump inhibitors, prokinetic agents ● Antibiotics, aperients/anti-diarrhoeal agents ● Nutritional supplementation (including enteral/parenteral tube feeding) ● Sacral nerve stimulator
Skin	● Emulsifying cream, paraffin wax ● Antihistamine and low-dose prednisolone for pruritus ● Minocycline, CCBs, warfarin, ?anti-TNFα agents for calcinosis ● Tacrolimus ointment, heparinoid cream
Dental problems	● Oral hygiene, dentistry, saliva supplements
Sexual dysfunction	● Urological assessment

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; TNF = tumour necrosis factor.

Table 4. Disease-modifying treatments for systemic sclerosis.

Vascular	● Vasodilators (CCBs, β-blockers, sildenafil) ● Vascular remodelling (ACEIs, ARBs, selective serotonin reuptake antagonists, ?bosentan) ● Prostacyclin analogues (iloprost, flolan, beraprost) ● Antioxidants (probucol, vitamin supplements)
Immunological	● Methotrexate ● Cyclophosphamide ● Antithymocyte globulin ● Mycophenolate mofetil ● Azathioprine ● Stem cell transplant ● Low-dose corticosteroids (<10 mg/day prednisolone) ● Anti-TNF agents
Antifibrotic	● No proven effective antifibrotic Candidates include: – anti-TGFα antibody – halofuginone – endothelin receptor antagonists

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; TGF = transforming growth factor; TNF = tumour necrosis factor.

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Anti-tumour necrosis factor therapy in seronegative spondyloarthritis

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Background

The seronegative spondyloarthritides are a group of chronic inflammatory disorders that include ankylosing spondylitis (AS), reactive arthritis and the axial forms of psoriatic and enteropathic arthritis. Standard therapy for AS to date has comprised non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy, focused on reducing pain and maintaining mobility. There is however no substantial evidence that 'as required' NSAIDs alter the radiological or clinical progression of the disease and the risks associated with long-term therapy are legion.

Interest has therefore turned to the use of the so-called 'biologics', particularly the tumour necrosis factor (TNF)-α blocking agents which have a proven record in rheumatoid arthritis (RA) (see accompanying article on biologic therapy in RA). Open-label and randomised controlled trials (RCTs) have demonstrated the efficacy of these agents in spondyloarthropathy, prompting both the Assessment in Ankylosing Spondylitis (ASAS) Working Group and the British Society of Rheumatology (BSR) to produce guidelines for their use.

This review summarises the clinical features of AS, current methods of its diagnosis and assessment, focusing on the role of TNF-α blockade in treatment of AS. Although benefit from anti-TNF therapy has also been shown for psoriatic arthritis, the bulk of clinical research and guidelines have focused on AS.

Clinical features, diagnosis and activity assessment

The prevalence of AS is up to 1.1%.[1] Onset of symptoms typically occurs in the third decade, with men affected 3–4 times more frequently than women, both morbidity and mortality are increased, and the socioeconomic costs are substantial. Susceptibility to AS has a major genetic component, with HLA-B27 the biggest single contributor,[2] with over 90% of AS patients HLA-B27 positive. AS primarily affects the axial skeleton. Peripheral arthropathy (frequently asymmetrical), enthesitis (inflammation at the site of tendon or ligament attachment to bone) and anterior uveitis are common. Fibrotic lung disease, aortic incompetence and amyloidosis are less frequent.

Diagnosis

The diagnosis of AS is made according to the modified New York criteria and relies upon one radiological criterion and at least one clinical criterion.[3]

Table 1. New York radiological scoring method for sacroiliac joints.

Grade		
0	No abnormalities	
1	Suspicious changes:	no specific abnormalities
2	Minimal sacroiliitis:	loss of definition of the joint, some sclerosis, minimal erosions, some joint space narrowing
3	Moderate sacroiliitis:	definite sclerosis on both sides of the joint, blurring and indistinct margins, erosive changes, loss of joint space
4	Ankylosis	