Early diagnosis and management of systemic sclerosis

MICHAEL HUGHES

Systemic sclerosis (SSc) is a rare but potentially life-threatening rheumatological condition with a wide range of signs and symptoms. This article describes the GP’s key role in the early diagnosis of SSc and discusses the current and emerging treatment options.

Systemic sclerosis (SSc) is a complex autoimmune connective tissue disease characterised by microvascular alterations and immune system activation, with fibrosis of the skin and other internal organs.\(^1,2\) SSc is a rare disease, with a reported prevalence in the UK of 8.2 per 100,000.\(^3\) Females are more commonly affected than males with a reported ratio of between 3:1 and 8:1,\(^4\) and a peak age of onset of disease of between 20 and 50 years.\(^5\)

The purpose of this review is to describe the clinical spectrum of disease seen in patients with SSc, the underlying mechanisms/causes of disease, an initial approach to management and assessment (including drug treatments), and the role of the GP, including in the early diagnosis of SSc.

Causes
Although great advancements have been made in understanding the aetiology of SSc, the underlying causes/mechanisms of the disease (including initiation) remain incompletely understood. Environmental factors are likely implicated in a genetically primed individual.\(^2\) Epigenetic modifications may hold the key to understanding the link between genetic and environmental factors.\(^6\)

Vascular disease (eg vascular injury and dysfunction) is believed to be a central and perhaps initiating event in the pathogenesis of SSc. A progressive obliterative vasculopathy is observed, including remodelling of the vasculature (eg intimal and smooth muscle hypertrophy), which promotes local hypoxia and fibrosis. Widespread aberrant tissue fibrosis is the clinical hallmark of SSc. The myofibroblast is believed to be central to the fibrotic disease process, mediated by the action of a number of potent profibrotic factors (in particular, transforming growth factor [TGF] beta).\(^2\) Immune system activation is clearly apparent, including the production of characteristic SSc-associated autoantibodies (discussed below) and a rich perivascular inflammatory cell infiltrate observed in the skin of patients with early diffuse disease.
Limited cutaneous systemic sclerosis | Diffuse cutaneous systemic sclerosis
---|---
Raynaud’s phenomenon for many years (even decades) before the onset of skin change | Recent onset of Raynaud’s phenomenon around (before or after) the onset of skin change
Distal skin involvement (hands, forearms, feet and below the level of the knees), can involve the face and neck | As for limited disease, but can affect the proximal upper and lower limbs, with possible truncal involvement
Late onset of pulmonary arterial hypertension | Early onset of major internal organ involvement: cardiac, lung fibrosis, myocardial and gastrointestinal disease
Telangiectases | Tendon friction rubs: associated with scleroderma renal crisis
Most are anticentromere positive: associated with the development of pulmonary arterial hypertension | Many are anti-Scl-70 (anti-topoisomerase) positive: associated with lung fibrosis
Anti-RNA polymerase III positive: associated with scleroderma renal crisis


### Signs and symptoms

SSc is a complex and heterogeneous disease and is therefore associated with a wide range of possible signs and symptoms. Whereas scleroderma (see Figure 1) refers to isolated thickening of the skin, in SSc there is also involvement of the internal organs, often in the presence of characteristic SSc-associated antibodies (discussed below). Scleroderma can be an isolated skin finding (e.g. morphea or linear scleroderma).

SSc is divided into limited and diffuse cutaneous disease (see Table 1). SSc may also occur in combination/overlap with other connective tissue diseases (e.g. lupus or myositis). The disease may also rarely occur in the absence of skin thickening with only internal organ involvement (‘SSc sine scleroderma’).

#### Raynaud’s phenomenon

Almost all (over 95%) of patients with SSc have Raynaud’s phenomenon, and this is often the earliest feature of the disease. Patients report a classical progression of triphasic colour change of white (deoxygenation), blue (cyanosis) and finally red (reactive hyperaemia) of the extremities (fingers and toes). Mono- and biphasic attacks are also recognised. Other vascular beds may be involved including the nose, lips and ears.

Attacks of Raynaud’s phenomenon may be associated with significant pain and discomfort, especially when the circulation is restored. A key feature is that attacks of Raynaud’s are transient, and are typically triggered by exposure to the cold and/or emotional stressors.

### Digital vascular disease

A spectrum of digital vascular disease is observed in SSc. Digital (finger) ulcers are common in patients with SSc and are associated with significant pain and disability.7 Around half of patients report a history of digital ulcers and these often occur early in the course of the disease.7 Patients should be educated to seek medical advice early if they develop new ulcers. Analgesia should be optimised as ulcerations may be exquisitely painful. Meticulous attention should be paid to appropriate wound care.7,8 Ulcers are often infected, in particular by *Staphylococcus aureus*, and therefore clinicians should have a low threshold for treatment with antibiotic therapy.7,8 Critical digital ischaemia (see Figure 2) is a medical emergency, as this may rapidly progress to irreversible gangrene, with possible loss of the digit.8

### Respiratory involvement

Lung fibrosis (interstitial lung disease) and pulmonary arterial hypertension (PAH) are now the two leading causes of mortality in SSc. Up to 80% of patients with SSc may develop lung fibrosis, and this is clinically significant in around one-third.9 Around 10% of patients with SSc may develop PAH,10 and this has a significant impact on survival. Three-year survival in SSc patients with PAH has been reported to be 56% compared to 94% in those without PAH.11

Patients with SSc undergo regular screening using pulmonary function tests, with or without transthoracic echocardiogram. In a study from France, survival was much higher in those patients who were enrolled in a systematic PAH ‘detection’ programme compared to ‘routine practice’ (eight-year survival of 64% vs 17% respectively).12

### Cardiovascular involvement

Primary cardiac (conduction system, myocardial and/or pericardial) involvement is increasingly recognised, and is often subclinical.13,14 Cardiac involvement can occur as part of the SSc disease process or due to other causes (e.g. secondary to PAH). Akin to many other rheumatological conditions, an
increased risk of cardiovascular disease has been reported by some authors, although this remains a controversial issue. An increased prevalence of large (proximal) vessel disease is also observed in patients with SSc.

**Gastrointestinal involvement**

The majority (up to 90%) of patients have gut involvement, which can affect the whole of the gastrointestinal tract from the mouth to the anus. Patients often have significant reflux disease including from oesophageal dysmotility. Patients may also develop symptoms related to gastroparesis. Gastric antral vascular ectasia, often referred to as a ‘watermelon stomach’, is an important and potentially treatable cause of blood loss.

Patients may develop malnutrition and this is often multifactorial, including secondary to poor oral intake (eg due to a limited oral aperture). Motility issues of the small and large bowel may result in pseudo-obstruction and promote the development of small-bowel bacterial overgrowth. Anorectal involvement may occur in around 40% of patients and this can result in potentially devastating faecal incontinence.

**Renal involvement**

The scleroderma renal crisis is reported to occur in between 5% to 10% of patients with SSc and was previously the leading cause of death. Patients may present with an acute hypertensive crisis including features of acute kidney injury, hypertensive retinopathy, fever, pulmonary oedema and encephalopathy. Early diagnosis and initiation of treatment with ACE inhibitors is crucial to maximise the chance of a good outcome. Renal replacement therapy is needed in almost all patients. Although renal recovery may occur up to several years after the onset of a renal crisis, around half of patients require lifelong renal replacement therapy.

**Musculoskeletal complications**

Non-specific musculoskeletal pain (eg arthralgias) are common, including from extensive skin thickening with stiffness of the joints. Significant hand contractures may develop, especially in patients with early diffuse disease. Patients may also develop overt inflammatory joint (similar to rheumatoid arthritis) and muscle (myositis) disease.

**Non-lethal morbidity**

SSc can be a significantly fatiguing disease. Depression is not uncommon in patients with SSc and is potentially multifactorial in origin, including from chronic pain and body image dissatisfaction. In a systematic review, which included two studies utilising the Beck Depression Inventory, the prevalence of clinically significant depressive symptoms was between 51% and 65%. Patients may develop sexual dysfunction and there is often a high level of body image dissatisfaction, including from cutaneous telangiectases (cutaneous dilated blood vessels).

Calcinosis (subcutaneous and/or intracutaneous calcium deposition) is common in patients with SSc and although this is often subclinical (eg only seen on radiographs), it can cause significant pain and ulcerate/become infected. Marked pruritus is often seen in patients with early diffuse cutaneous disease.

### Which patient groups are most susceptible?

This can be considered in relation to the proposed criteria for the ‘very early diagnosis of systemic sclerosis’ (VEDOSS). VEDOSS should be suspected in patients with one of three red flags: Raynaud’s phenomenon, puffy fingers or the presence of antinuclear antibodies (ANA). The diagnosis is then made by either the presence of SSc-associated autoantibodies and/or abnormal nailfold capillaries.

ANA are present in the majority (over 95%) of patients with SSc. Common SSc-associated autoantibodies are antitopo-isomerase I (Scl-70), anticentromere and anti-RNA polymerase III. The key importance of these antibodies is reflected through their inclusion in recent classification criteria for SSc (see Table 2).

Nailfold capillaroscopy is a non-invasive imaging method that allows the microcirculation to be examined *in situ*. The nailfold capillaries run parallel to the skin at the base of the nail and this allows them to be examined in their entirety. Normal nailfold capillaries are reassuring and have a regular and uniform (‘hairpin’

<table>
<thead>
<tr>
<th>Item</th>
<th>Sub-item(s)</th>
<th>Weight/score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)</td>
<td>Puffy fingers Sclerodactyly of the fingers</td>
<td>9</td>
</tr>
<tr>
<td>Skin thickening of the fingers (only count the higher score)</td>
<td>Digital tip ulcers Fingertip pitting scars</td>
<td>2</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)</td>
<td>Pulmonary arterial hypertension Interstitial lung disease</td>
<td>2</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Systemic sclerosis-related autoantibodies (maximum score is 3)</td>
<td>Anticentromere Anti-topo-isomerase I Anti-RNA polymerase III</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 2.** American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria for systemic sclerosis. Although these are intended for use as classification and not diagnostic criteria, they are a useful reference aid for clinicians in routine clinical practice. Patients with a total score of ≥9 are classified as having definite scleroderma. A key exclusion is that the criteria should not be applied to those patients who have a scleroderma-like disorder that better explains their manifestations (eg eosinophilic fasciitis and scleromyxedema)
like) appearance. For those clinicians who do not have access to a stereomicroscope or videocapillaroscopy (the latter of which is considered to be the ‘gold standard’), capillaroscopy can also be performed using lower magnification techniques including an ophthalmoscope, dermatoscope or USB microscope.\textsuperscript{25,26}

In a study that included 586 patients who were followed up for 3197 person-years, the presence of SSc-specific autoantibodies and SSc-type capillaroscopic abnormalities were independent predictors of the development of SSc (hazard ratios of 4.7 and 4.5 respectively).\textsuperscript{27} Patients with both abnormalities were 60 times more likely to develop SSc.

**First- and second-line treatment options**

Figure 3 presents an overview of the British Society of Rheumatology/British Health Professionals in Rheumatology (BSR/BHPR) guideline for the treatment of SSc,\textsuperscript{9} which is a useful reference tool for clinicians in both primary and secondary care alike. A key point to highlight is the importance of distinguishing between the limited and diffuse subsets of SSc, as this has an important impact on the likely disease course including prognosis, and in making treatment decisions.

Table 3 presents first- and second-line treatment options for SSc. Symptomatic treatment is indicated in all patients with SSc, including for vascular manifestations (e.g., Raynaud’s phenomenon). We have recently described in detail the assessment and management of Raynaud’s phenomenon.\textsuperscript{28} An approach to treatment of the condition is summarised in Table 4. Early diffuse cutaneous SSc is a management priority and often requires the introduction of immunosuppressive treatment (i.e., cyclophosphamide, methotrexate or mycophenolate mofetil). Regular follow-up is needed in all patients with SSc, including to observe for the development of organ-based complications.

**Emerging treatment options**

There has been a flurry of recent and ongoing international research into the treatment of SSc, including in patients with early diffuse disease. In a recent double-blind, placebo-controlled trial, treatment with tocilizumab (an interleukin 6 receptor-α inhibitor) was associated with a greater reduction of skin thickening at 24 weeks than placebo.\textsuperscript{29}

Several studies have supported autologous stem cell transplantation as a viable treatment option for patients with poor prognosis SSc.\textsuperscript{30,31} Compared with the existing gold standard of cyclophosphamide, treatment may stabilise/improve skin sclerosis and internal organ involvement, and is associated with a long-term survival benefit. However, it is also associated with an increased early treatment-related mortality, and should not be considered as a ‘cure’ for the disease.

**The GP’s role in management**

The GP’s role is two-fold. Firstly, GPs must be ever vigilant and consider the diagnosis of SSc, especially in patients presenting with Raynaud’s phenomenon. A suggested referral pathway in primary care for patients with possible SSc is presented in Figure 4. Secondly, GPs have an overall picture of SSc patients’ ongoing care, and are likely to be consulted by patients, in par-

---

**Figure 3.** Overview of the British Society for Rheumatology/British Health Professionals in Rheumatology (BSR/BHPR) treatment guideline for systemic sclerosis (SSc)\textsuperscript{9}

---

IcSSc = limited cutaneous systemic sclerosis; dcSSc = diffuse cutaneous systemic sclerosis
ticular between hospital attendances, about symptoms potentially related to disease-related complications. In addition, disease-modifying therapy is often prescribed and monitored in primary care. Strong links between primary and secondary care are needed in the care of patients with SSc.

**Conclusion**

SSc is a serious and potentially life-threatening rheumatological condition that has a significant impact on the patient’s quality of life. There is an increasing interest in facilitating the earlier diagnosis of SSc, and GPs have a key role in identifying those patients likely to develop SSc, including those presenting with Raynaud’s phenomenon. There are now a number of available treatments to manage the different organ-based complications associated with the disease. Immunosuppressive therapies are indicated in early diffuse cutaneous SSc. Emerging therapies including stem cell transplantation are now a treatment reality, and many new treatments are now being researched. GPs have an important role in the care of patients with SSc and therefore need to be aware of the many possible manifestations of the disease, and the different and emerging approaches to treatment.

**References**


---

**Table 3. First- and second-line treatment options for systemic sclerosis.** Some of these treatments can potentially be initiated in primary care (eg drug therapy for Raynaud’s phenomenon and proton-pump inhibitors for reflux disease). Scleroderma renal crisis is a medical emergency that requires immediate specialist input. Drugs for pulmonary arterial hypertension should be initiated under the supervision of a specialist centre.

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Clinical manifestation</th>
<th>Examples of treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and musculoskeletal</td>
<td>Scleroderma</td>
<td>Immunosuppressive therapy (eg cyclophosphamide, methotrexate and mycophenolate mofetil)</td>
</tr>
<tr>
<td></td>
<td>Inflammatory arthritis</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Heart failure</td>
<td>Appropriate drug therapies used in heart failure (eg ACE inhibitors and diuretics)</td>
</tr>
<tr>
<td></td>
<td>Inflammatory cardiac disease</td>
<td>Immunosuppressive therapy (eg steroid and/or cyclophosphamide)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pulmonary arterial hypertension</td>
<td>Endothelin-receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>Interstitial lung disease</td>
<td>Prostacyclin analogues</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phosphodiesterase type 5 (PDE5) inhibitors</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Gastro-oesophageal reflux disease</td>
<td>Proton-pump inhibitors</td>
</tr>
<tr>
<td>Peripheral vascular</td>
<td>Raynaud’s phenomenon and digital ulcers</td>
<td>Calcium-channel blockers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDE5 inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angiotensin II-receptor blockers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endothelin-receptor antagonists</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostacyclin analogues (eg intravenous iloprost)</td>
</tr>
<tr>
<td>Renal</td>
<td>Scleroderma renal crisis</td>
<td>ACE inhibitors</td>
</tr>
</tbody>
</table>

---

**Table 4. An approach to the treatment of Raynaud’s phenomenon**

- First distinguish between primary and secondary Raynaud’s phenomenon – including consideration of referral to rheumatology, in particular, if concern about a secondary cause, including systemic sclerosis
- Patient education is essential for all patients
- Scleroderma and Raynaud’s UK (SRUK) is a useful source of information about Raynaud’s phenomenon (and systemic sclerosis) for both patients and clinicians (www.sruk.co.uk)
- Lifestyle adaption and conservative measures (eg keeping warm and cold avoidance) is indicated in all patients with Raynaud’s phenomenon.
- Efforts should be made to support smoking cessation, if relevant
- Drug therapies are indicated if conservative measures are insufficient to control symptoms
- Calcium-channel blockers are often used as first-line treatment
- Phosphodiesterase type 5 (PDE5) inhibitors are increasingly being used after failure of calcium-channel blockers
- Other drug therapies used in Raynaud’s phenomenon include angiotensin II-receptor blockers and fluoxetine
- Digital ulcers and critical digital ischaemia represent persistent ischaemia/gangrene and can result in significant ischaemic tissue loss/need for amputation
- Persistent discolourisation/evolving gangrene is a medical emergency, which requires urgent evaluation


Declaration of interests
None to declare.

Dr Michael Hughes is a Consultant Rheumatologist in the Department of Rheumatology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield