Systemic sclerosis

A complex multisystem disease

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Systemic sclerosis is a rare disease characterised by vascular abnormalities and fibrosis of multiple organs. Proactive screening and follow up for organ-specific complications are important aspects of management.

Systemic sclerosis (SSc), also known as scleroderma, is a rare autoimmune condition with high morbidity and mortality caused by multisystem organ involvement secondary to vasculopathy, fibrosis and immune system alteration.[1] SSc is more common in women than men and has an estimated prevalence of 20 per 100,000 population in Australia.[1] Over the last few decades, however, there has been an improvement in outcomes and mortality, which has been attributed to better recognition of the disease and proactive screening for organ-specific complications.[2,3] This article will discuss the common manifestations of SSc and provide guidance about shared care with rheumatologists for patients with this condition.

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How do patients with systemic sclerosis present?

There is significant clinical variability in patient presentations of SSc, and clinicians should be aware of distinct manifestations and complications for early disease compared with late disease.[4] Patients can be classified according to the extent of their skin thickening or hardening with:

- limited cutaneous SSc (LcSSc), or
- diffuse cutaneous SSc (DcSSc).

There is a predominance of the limited subtype, which accounts for 70 to 80% of SSc presentations.[1]

SSc is characterised by vascular abnormalities and fibrosis of multiple organs; a summary of common manifestations is presented in Box 1.[4-6] Although there are clinical characteristics that are shared in both LcSSc and DcSSc, some features are associated with one subtype (Box 2). Patients with either LcSSc or DcSSc may have Raynaud's phenomenon, which occurs in 95% of all patients (Figure 1) – in patients with LcSSc this may

1. SYSTEMIC SCLEROSIS: COMMON MANIFESTATIONS

- Raynaud's phenomenon (occurs in 95% of patients) – often the initial symptom, may be associated with ischaemic digital ulcers[5]
- Skin and musculoskeletal symptoms – these include finger or hand 'puffiness', hand pain or swelling, skin thickening or hardening on the face or hands and inflammatory muscle or joint symptoms
- Gastrointestinal involvement – especially gastrointestinal reflux disease and other complications of dysmotility[6]
- Interstitial lung disease (occurs in up to 80% of patients) – can be detected earlier by screening with serial annual respiratory function tests[4]

2. SYSTEMIC SCLEROSIS: KEY SUBTYPE-SPECIFIC FEATURES*

Limited cutaneous systemic sclerosis (LcSSc)

- Long history (years) of Raynaud's phenomenon
- Skin thickening or hardening distal to elbows and knees
- Positivity for anticentromere antibody

Diffuse cutaneous systemic sclerosis (DcSSc)

- Short history (weeks to months) of Raynaud's phenomenon
- Skin thickening or hardening on proximal limbs and trunk
- Increased risk for scleroderma renal crisis
- Positivity for anti-Scl70 antibody

* Adapted from: Denton CP, Khanna D. Systemic sclerosis. Lancet 2017; 390: 1685-1699.[4]

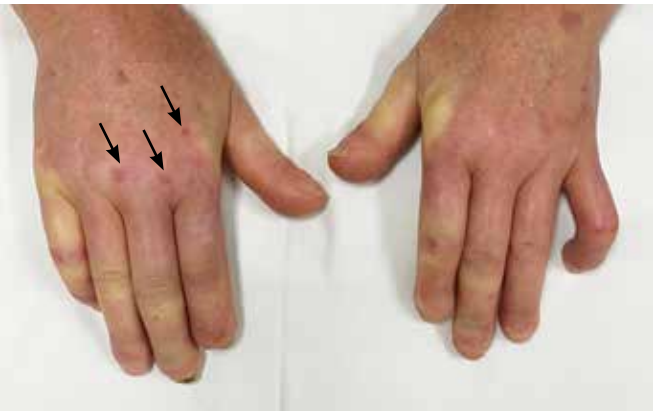

Figure 1. Raynaud's phenomenon, skin thickening affecting the digits with fixed flexion contraction and telangiectasia (arrows). There is callus from digital ulceration and trauma on a proximal interphalangeal joint.

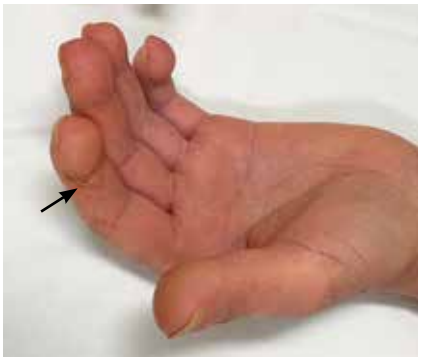

Figure 2. An inactive digital ulcer (digital pit) on a distal interphalangeal joint (arrow).

Figure 3. Skin thickening of the face, resulting in reduced oral aperture. Telangiectasia are visible on the cheeks (arrow).

have been present for many years before the development of other features. Ischaemic digital tip ulcers and chilblains are complications of Raynaud's phenomenon and are prone to developing infections as a result of poor wound healing (Figures 1 and 2).[4] Patients may have small pitting scars on the digital tips which are evidence of previous digital ulcers that have healed.

The complications of early skin thickening or fibrosis may become apparent at any stage of the disease and may involve the hands or face (Figures 1 to 3). Patients may develop joint contractures of the digits, with inability to flex or extend the digits or wrists causing significant functional impairment. This is more likely in patients with DcSSc and has been associated with anti-topoisomerase antibody (anti-Scl70 antibody).[5] Skin and musculoskeletal manifestations may be more pronounced in the early phases of DcSSc. Patients may present with generalised 'puffiness' of the fingers and hands, or with an inflammatory arthritis, myalgia or even mild myositis – these manifestations can occur in LcSSc but are often more florid and extensive in DcSSc.[4]

Patients with either LcSSc or DcSSc frequently have gastrointestinal involvement, which may be due to vascular or fibrotic complications. The most common gastrointestinal manifestation is gastro-oesophageal reflux disease, which can be present in 80% of all patients with SSc.[3] Patients may also present with iron deficiency anaemia secondary to upper gastrointestinal bleeding caused by gastric antral vascular ectasia. They may also have complications of gastrointestinal dysmotility due to fibrosis, such as small intestinal bacterial overgrowth or faecal incontinence.[6]

Up to 80% of all patients with SSc have interstitial lung disease (ILD), with most patients with ILD developing restrictive lung disease in the first five years after the onset of symptoms. Progressive lung disease occurs in 25 to 30% of patients.[4]

One of the major contributors to mortality in patients with SSc is the development of pulmonary arterial hypertension (PAH), which can occur at any time in patients with either LcSSc or DcSSc. Up to 10% of patients are affected by PAH.[1]

When can a diagnosis of systemic sclerosis be made?

A diagnosis of SSc can be considered when a patient meets the classification criteria for SSc defined by the American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) in 2013.[7] These criteria include a combination of clinical features and positive blood tests for SSc-associated autoantibodies: anticentromere antibody, anti-Scl70 antibody and/or anti-RNA

3. SYSTEMIC SCLEROSIS: IMPORTANT COMPLICATIONS

Cardiorespiratory complications

Pulmonary arterial hypertension (PAH)

- Can occur in up to 10% of all patients with SSc at any stage in the disease[3]
- Onset of symptoms is insidious, with exertional dyspnoea or angina before the development of symptoms of right heart failure
- Annual screening enables early diagnosis and is associated with improved survival – annual transthoracic echocardiography, respiratory function tests and serum NT-proBNP are currently recommended[3]

Cardiac involvement[4]

- An increasingly researched manifestation of SSc, previously under-recognised
- Suspicion of cardiac involvement requires multidisciplinary evaluation, such as assessment for arrhythmia and cardiac imaging (including MRI)

Interstitial lung disease (ILD)[10]

- Occurs in the majority of patients with SSc, typically develops early in a nonspecific interstitial pneumonia pattern
- Risk factors include DcSSc, older age at disease onset and anti-Scl70 antibody positivity
- Variable clinical course – some patients have stable lung function and radiology whereas others decline progressively
- Progression of ILD may be predicted by extent of fibrosis on high-resolution CT (>20% strong predictor of mortality)

Gastrointestinal complications

Dysmotility[11]

- Small and large intestines may be affected in 20 to 50% of patients with SSc
- Manifestations of gastrointestinal involvement are thought to be caused by motor impairment and dysmotility
- Patients presenting with obstructive symptoms without a mechanical aetiology may have pseudo-obstruction

Renal complications

Scleroderma renal crisis[4]

- Presence of a triad of accelerated or 'malignant' hypertension, acute kidney injury and thrombotic microangiopathy
- A rare complication (affecting up to 14% of patients with DcSSc), more common in patients with positive anti-RNA polymerase III antibody
- Risk factors include recent use of prednisolone (>15 mg daily) and presence of moderate to large pericardial effusion[1]
- Management includes nephrology support and immediate initiation of angiotensin converting enzyme (ACE) inhibition therapy
- Condition of scleroderma renal crisis has high mortality, particularly in patients who require dialysis for management of acute kidney injury

Vascular complications

Digital ischaemia[5]

- Raynaud's phenomenon can be complicated by digital ulceration as a result of ischaemia
- Ulcers may become infected or lead to gangrene requiring amputation
- Early recognition of infection is important, with referral to a rheumatologist for definitive management including vasodilator therapy and plastic surgical assessment if required
- Prevention of digital ulceration may be achieved using a combination of conservative measures (e.g. wearing gloves or using hand-warmers) and/or pharmacotherapy (including calcium channel blockers) for Raynaud's phenomenon

polymerase III antibody.[7] Classification criteria have been developed because of the hetergeneous presentation of SSc, primarily for use in clinical research to ensure a homogeneous selection of patients; however, these criteria can also serve to support a diagnosis of SSc.

A diagnosis of SSc should also be considered if a patient presents with Raynaud's phenomenon and additional clinical features (see Box 1) and has a positive antinuclear antibody (ANA) or positive anti-extractable nuclear antibody test result.

What causes systemic sclerosis?

Although the aetiology and pathogenesis of SSc remain poorly understood, epidemiological studies have shown strong evidence of familial clustering of cases, and increased risk in first-degree relatives of patients with SSc.[8] It is thought that susceptible individuals develop the disease after stimulation by initiating events.[8] There have been associations with occupational exposures, particularly exposure to vinyl chloride; more recently, development of a scleroderma-like disease has been observed in stonemasons exposed to dust from artificial stone.[8,9]

What are the complications of systemic sclerosis?

There are multiple complications of SSc that should not be missed. A summary of the important potential complications is provided in Box 3.[1,3-5,10,11]

What investigations should be ordered?

Initial investigations should aim to confirm a diagnosis of SSc and evaluate the presence of organ-specific complications.[4]

If SSc is suspected, blood tests for autoantibodies are required to confirm the diagnosis and help to predict the disease subtype, as patients with LcSSc have a better prognosis.[12] ANA is present in almost all patients with SSc (93 to 96%). Anticentromere antibody is associated with LcSSc whereas anti-Scl70 is associated with DcSSc.[1]

Baseline evaluation of organ involvement should include transthoracic echocardiography and respiratory function tests (RFTs) to investigate for ILD and PAH. In the setting of results from RFTs demonstrating reduced forced vital capacity (FVC) and/or reduced diffusing capacity for carbon monoxide (DLCO), the presence of ILD should be further investigated with high-resolution CT of the chest. It should be

noted, however, that a DLCO less than 70% with a relatively preserved FVC is associated with a diagnosis of PAH.[13,14] A thorough history and examination for symptoms and signs of gastrointestinal involvement should guide symptom-based investigations, such as iron studies or endoscopy, as required.

For patients with anti-RNA polymerase III antibody positivity or early DcSSc, blood pressure monitoring is recommended three times per week, with assessment of renal function and urinalysis at regular intervals to screen for scleroderma renal crisis.[4] International guidelines recommend annual transthoracic echocardiography, RFTs and serum NT-proBNP to screen for the development of ILD and PAH in all patients with SSc.[13]

What does shared care involve?

In recent decades, outcomes and survival for patients with SSc have improved, which has been attributed to improved recognition of organ-specific complications and proactive screening and follow-up.[4] Any patient with suspected SSc should be referred to a rheumatologist or specialised centre with appropriate expertise in SSc management for confirmation of the diagnosis and advice regarding organ-specific complications to be aware of during community follow-up.[15] Patients who develop progressive lung disease require the input of respiratory physicians or rheumatologists to guide use of immunosuppressive therapies.[4]

The approach to treatment of SSc is tailored to an individual patient's phenotype and based on international guidelines.[12] Involvement of other allied health specialists, including occupational therapists, physiotherapists, dietitians and speech pathologists, can improve care of patients with SSc.[15]

What about follow up and prevention?

Important aspects of management for patients with SSc in primary care are discussed in Box 4.[16]

4. SYSTEMIC SCLEROSIS: MANAGEMENT TIPS FOR GENERAL PRACTICE

Gastrointestinal manifestations – common and contributors to significant morbidity

- Patients with gastro-oesophageal reflux disease may require dual therapy to achieve adequate symptom control
- Early referral to a gastroenterologist, colorectal surgeon and/or speech pathologist should be considered for a patient who has symptoms of dysmotility or faecal incontinence

Vaccinations

- Annual assessment of vaccination status is recommended by international rheumatology guidelines and should be tailored to the patient according to the *Australian Immunisation Handbook*[16]
- Non-live vaccines may be given to patients taking immunosuppressive therapies

Dyspnoea – a red flag

- Development of dyspnoea in a patient with SSc should be investigated with cardiac and respiratory work-up

Blood pressure

- Blood pressure should be measured regularly in all patients with systemic sclerosis
- Patients at high risk of scleroderma renal crisis (i.e. patients with anti-RNA polymerase III antibody positivity or a diagnosis of DcSSc and patients taking corticosteroids) should be educated about measuring their blood pressure three times per week
- For patients with normotension at baseline, a rise in systolic blood pressure by 20 mmHg should trigger further investigation for the presence of scleroderma renal crisis

Smoking cessation

- Smoking cessation should be encouraged in all patients to prevent worsening of Raynaud's phenomenon, poor wound healing and pulmonary complications

Patients with SSc also have a higher prevalence of cancer, and age-appropriate malignancy screening is recommended as part of routine community follow up.[1]

Conclusion

It is important that all clinicians are aware of the common manifestations of SSc, which are often first seen in general practice. Regular communication and shared care with a rheumatologist will provide guidance for the risk, presence and severity of organ-specific complications relevant in the care of patients with SSc. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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