Red flags in scleroderma

Background
Scleroderma (systemic sclerosis) is an uncommon connective tissue disease characterised by vascular, inflammatory and fibrotic dysfunction of multiple organ systems. Systemic sclerosis is often recognised late in the course of the disease.

Objective
This article outlines the clinical features of systemic sclerosis, in particular ‘red flags’ that indicate the presence of significant organ disease.

Discussion
Common clinical features include Raynaud phenomenon and skin thickening, often with calcinosis and telangiectasia. These features should alert the physician to look for red flag features. In the general practice setting, early recognition of scleroderma will enable timely referral to specialist centres for regular screening and effective management of its many serious visceral complications.

Scleroderma (SD), also known as systemic sclerosis, is an uncommon connective tissue disease characterised by vascular, inflammatory and fibrotic dysfunction of multiple organ systems. Systemic sclerosis may be recognised late in the course of the disease. Characteristic features suggesting its presence include Raynaud phenomenon, skin thickening, calcinosis and telangiectasia. Scleroderma may also be associated with serious visceral complications involving the pulmonary, gastrointestinal, cardiac and renal systems, resulting in significant morbidity and mortality. The presence of red flag symptoms and signs should alert the clinician to the presence of significant organ disease (Table 1). In the general practice setting, early recognition and identification of red flag features will enable timely referral to specialist centres for regular screening and effective management of serious visceral complications.

Early recognition and diagnosis
The diagnosis of SD is made clinically. Patients commonly present with classic Raynaud phenomenon (Table 2) and typical skin changes. Skin changes usually involve the hands (Figure 1) and can extend to variable degrees proximally to involve the forearms, arms, face, trunk and less commonly, the lower limbs (Figure 2). Early changes appear as skin thickening with puffy, swollen fingers (oedematous phase). Later, the skin becomes firm and tightly bound to the underlying subcutaneous tissue (indurative phase). This can lead to flexion contractures which limit hand function. Finally, in the atrophic phase, the skin thins and ulcerates easily, predisposing to infection (Figure 4). Involvement of the face may occur with thinning of the lips, reduced oral aperture, loss of skin wrinkles and facial expression lines. Other associated skin features are listed in Table 3.

Visceral involvement, particularly of the gastrointestinal system, may be evident at presentation.

Diffuse and limited scleroderma
Scleroderma is divided into diffuse and limited subtypes based mainly on the extent of skin involvement, but also on differences in organ involvement and prognosis (Table 4).

Patients with diffuse SD tend to present with rapidly progressive skin thickening, soon after the onset of Raynaud symptoms. These
patients are at greater risk of developing life threatening interstitial lung disease (ILD), renal and cardiac disease early in the course of disease. The diffuse form generally carries a worse prognosis.2,3

Limited SD is also known as CREST syndrome, an acronym for calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia (Figure 3). Patients with limited SD typically present with distal skin thickening, often many years after the onset of Raynaud symptoms. These patients rarely develop renal disease but disabling gastrointestinal disease and cardiopulmonary disease including ILD and pulmonary arterial hypertension (PAH) can occur. Patients with limited SD generally have a better prognosis than those with diffuse SD, except in the presence of PAH (Table 4).

Table 1. Red flag symptoms and signs

- **Skin**
  - rapidly progressive skin disease
  - severe Raynaud phenomenon
  - digital ulceration
  - digital ischaemia leading to infarction
- **Gastrointestinal**
  - anaemia
  - iron deficiency
  - other evidence of gastrointestinal bleeding
- **Lung**
  - dyspnoea
  - dry cough
  - declining exercise tolerance
  - signs of pulmonary hypertension and right heart failure
  - fine end expiratory crackles at base
  - pulmonary function tests (PFT) showing low or declining DLCO, FVC or both
- **Renal**
  - hypertension
  - worsening kidney function
  - MHA or active urinary sediment-glomerular haematuria, proteinuria
  - malignant hypertensive crisis

### Diagnostic tests

Antinuclear antibody (ANA) is often positive in scleroderma. An anticentromere pattern of ANA is common in limited disease.4 On extractable nuclear antigen (ENA) testing, anti-SCL 70 antibody

Figure 1. Sclerodactyly

Figure 2. Ischaemia due to severe Raynaud phenomenon

Table 3. Skin changes in systemic sclerosis

- Sclerodactyly
- Telangiectasia on the face, fingers and chest
- Digital pitting scars and ulcerations with secondary infection
- Tapering of fingers due to resorption of terminal phalanges
- Dropout or dilatation of nail fold capillary loops
- Calcific deposits in the skin and subcutaneous tissue (calcinosis), which may discharge of calcific material or become infected
- Thinning of the lips
- Reduced oral aperture
- Loss of facial skin wrinkles
- Loss of facial expression
Systemic complications

In patients with SD, visceral complications are the major cause of morbidity and mortality. Gastrointestinal disease is also common and includes:

- gastroesophageal reflux disease
- bleeding from gastric antral vascular ectasia (GAVE), and
- gastrointestinal hypomotility.

Gastrointestinal hypomotility may produce symptoms of dysphagia, bloating, constipation, diarrhoea, faecal incontinence and malabsorption from bacterial overgrowth. The most serious visceral complications of SD are:

- interstitial lung disease
- PAH
- pericarditis
- myocardial conduction defects, and
- renal crisis.

Significant interstitial lung disease occurs commonly in limited and diffuse SD, affecting 30–40% of patients and presenting with dry cough, exertional dyspnoea and falling forced vital capacity (FVC) and diffusing lung capacity output (DLCO). Progressive disease results in increased mortality if untreated.6

Pulmonary arterial hypertension may present with dyspnoea and fatigue, but also with a fall in DLCO, which is disproportionate to the fall in FVC.7 Pulmonary arterial hypertension occurs in about 12% of patients in studies that define PAH with a right heart catheter, and is more common in patients with limited SD. It is now the leading cause of SD related mortality with a 1 year survival of approximately 50% in untreated cases.6 It may coexist with ILD.

Scleroderma renal crisis is a rapidly progressive form of renal failure associated with hypertensive encephalopathy, severe headaches, seizures, retinopathy, microangiopathic haemolytic anaemia (MHA), and left ventricular failure. It is an uncommon (10% patients with diffuse SD) but serious complication of scleroderma, heralded by a rise in creatinine, blood pressure or development of MHA.8

Management

Although there is currently no single disease modifying therapy for SD, there are effective therapies available for its specific organ complications

Table 4. Subsets of scleroderma

<table>
<thead>
<tr>
<th>Diffuse disease</th>
<th>Limited disease</th>
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<tbody>
<tr>
<td>Skin changes</td>
<td>Proximal and distal to elbows and knees, truncal</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Uncommon (−10%)</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Common (30–40%)</td>
</tr>
<tr>
<td>Auto-antibodies</td>
<td>Anticientromere (&lt;5%)</td>
</tr>
<tr>
<td></td>
<td>Anti-Scl-70 (20–30%)</td>
</tr>
<tr>
<td>Survival</td>
<td>Markedly reduced if significant lung, cardiac or renal disease2,3</td>
</tr>
</tbody>
</table>
Table 5. Management summary for systemic sclerosis

<table>
<thead>
<tr>
<th></th>
<th>Absence of red flags</th>
<th>Presence of red flags</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin disease</td>
<td>• Proton pump inhibitors</td>
<td>• Individualised treatment with immunosuppression</td>
</tr>
<tr>
<td>Gastro-esophageal reflux</td>
<td>• Prokinetic agents</td>
<td>• Gastroscopy and laser photocoagulation for GAVE</td>
</tr>
<tr>
<td>Raynaud phenomenon</td>
<td>• Cease smoking</td>
<td>• Prostaglandin analogue (Iloprost) infusion</td>
</tr>
<tr>
<td></td>
<td>• Keep extremities warm</td>
<td>• Antibiotics if infected</td>
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<tr>
<td></td>
<td>• Avoid beta blockers</td>
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<tr>
<td></td>
<td>• Dihydropyridine Ca channel blockers (eg. nifedipine)</td>
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<tr>
<td></td>
<td>• GTN patch applied locally (eg. Minitan 5 mg)</td>
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<tr>
<td>Interstitial lung disease</td>
<td>• Screening with 6–12 monthly PFT (suspect if FVC&lt;85% or FVC falling &gt;10% per year)</td>
<td>• HRCT chest</td>
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<tr>
<td></td>
<td></td>
<td>• Individualised treatment with immunosuppression</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>• Screening with 6–12 monthly PFT (suspect if DLCO &lt;80% or DLCO falling disproportionately to FVC)</td>
<td>• Exercise stress echocardiogram</td>
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<tr>
<td></td>
<td>• Screening with annual transthoracic echocardiogram</td>
<td>• 6 minute walk test</td>
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<td></td>
<td>(systolic pulmonary arterial pressure &gt;35 mmHg requires further investigation)</td>
<td>• Right heart catheter</td>
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<td></td>
<td></td>
<td>• Treatment with endothelin receptor antagonents, PDE5 inhibitor, prostaglandin analogue</td>
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<tr>
<td>Renal disease</td>
<td>• Minimise steroid use</td>
<td>• ACEIs</td>
</tr>
<tr>
<td></td>
<td>• Regular monitoring of BP</td>
<td>• Inpatient management, liaising with renal physicians</td>
</tr>
</tbody>
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Involvement. Iloprost, a prostaglandin analogue, reduces the severity of Raynaud phenomenon and promotes ulcer healing. Intravenous or oral cyclophosphamide is used to slow the progression of ILD. Endothelin receptor antagonists (eg. bosentan, sitaxsentan), and prostaglandin analogues have been shown to improve exercise capacity, pulmonary haemodynamics and possibly survival in patients with PAH. Angiotensin converting enzyme inhibitors (ACEIs) are effective for associated renal disease if introduced early. Many of these therapies are only available through tertiary centres, and are more effective if introduced early. Table 5 summarises various management strategies for SD related organ diseases.

Important aspects of primary care

- Raising the index of suspicion: early recognition and prompt referral to tertiary centres or specialist rheumatologists for further investigation and treatment.
- Regular assessment for the presence of red flag symptoms and signs.

Conflict of interest: none declared.

References