Qiang Li
MBBS, FRACP, is Scleroderma Fellow, Rheumatology Department, Monash Medical Centre, Melbourne, Victoria. drqiang@hotmail.com

Joanne Sahhar
MBBS, FRACP, is Head, Monash Scleroderma Clinic, Monash Medical Centre, Melbourne, Victoria.

Geoffrey Littlejohn
MBBS, MD, MPH, FRACP, is Director of Rheumatology, Monash Medical Centre, Melbourne, Victoria.

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 telangectasia. 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*).[1]

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 telangectasia (*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

Table 2. Raynaud phenomenon

- Episodic vasoconstriction resulting in:
  - pallor and/or cyanosis of fingers and/or toes followed by
  - rubor on rewarming
- Pallor and/or cyanosis are usually associated with coldness and numbness of digits, and rubor with pain and tingling
- Episodes may be precipitated by:
  - cold exposure
  - vibration, or
  - emotional stress

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

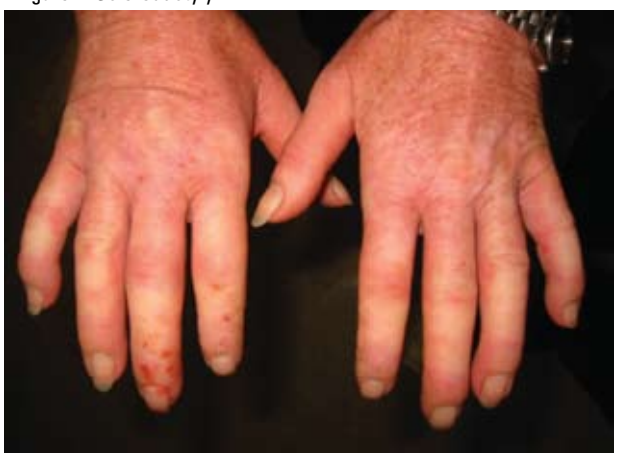


Figure 2. Ischaemia due to severe Raynaud phenomenon

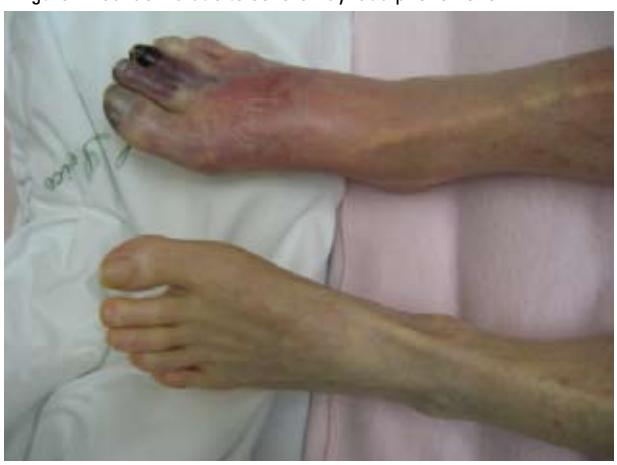


Table 3. Skin changes in systemic sclerosis

- 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

may be positive; indicative of an increased risk of interstitial lung disease.[5] Other ENAs (eg. Ro/La/RNP) may be present in an overlap syndrome. Specialised nail fold capillaroscopy of digits may assist diagnosis in early disease.

Figure 3. Telangiectasia

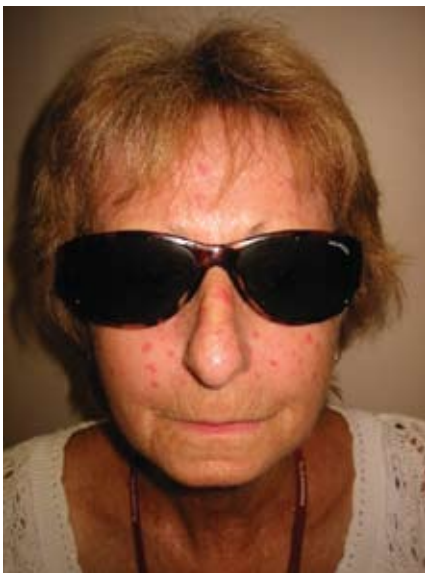
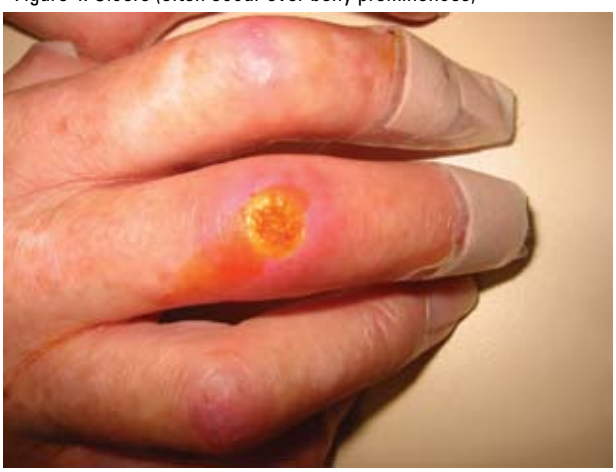


Figure 4. Ulcers (often occur over bony prominences)



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

Table 4. Subsets of scleroderma[1]

	Diffuse disease	Limited disease
Skin changes	Proximal and distal to elbows and knees, truncal	Distal to elbows and knees, ± face and neck
Renal disease	Uncommon (~10%)[8]	Rare (~1%)
Pulmonary arterial hypertension	Uncommon	More common (12%; up to 26% in some studies)[15]
Interstitial lung disease	Common (30–40%)[10,16]	Common (30%)
Auto-antibodies	Anticentromere (<5%) Anti-Scl-70 (20–30%)[4,5]	Anticentromere (90%) Anti-Scl-70 (10–15%)
Survival	Markedly reduced if significant lung, cardiac or renal disease[2, 3]	Prognosis usually good, but reduced if untreated PAH[6]

Table 5. Management summary for systemic sclerosis

	Absence of red flags	Presence of red flags
Skin disease		• Individualised treatment with immunosuppression
Gastro-esophageal reflux	• Proton pump inhibitors • Prokinetic agents	• Gastroscopy and laser photocoagulation for GAVE
Raynaud phenomenon	• Cease smoking • Keep extremities warm • Avoid beta blockers • Dihydropyridine Ca channel blockers (eg. nifedipine) • GTN patch applied locally (eg. Minitran 5 mg)	• Prostaglandin analogue (Iloprost) infusion • Antibiotics if infected
Interstitial lung disease	• Screening with 6–12 monthly PFT (suspect if FVC<85% or FVC falling >10% per year)	• HRCT chest • Individualised treatment with immunosuppression
Pulmonary arterial hypertension	• Screening with 6–12 monthly PFT (suspect if DLCO <80% or DLCO falling disproportionately to FVC) • Screening with annual transthoracic echocardiogram (systolic pulmonary arterial pressure >35 mmHg requires further investigation[17])	• Exercise stress echocardiogram • 6 minute walk test • Right heart catheter • Treatment with endothelin receptor antagonists, PDE5 inhibitor, prostaglandin analogue
Renal disease	• Minimise steroid use • Regular monitoring of BP	• ACEIs • Inpatient management, liaising with renal physicians

involvement. Iloprost, a prostaglandin analogue, reduces the severity of Raynaud phenomenon and promotes ulcer healing.[9] Intravenous or oral cyclophosphamide is used to slow the progression of ILD.[10] 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.[11–13] Angiotensin converting enzyme inhibitors (ACEIs) are effective for associated renal disease if introduced early.[14] 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

1. Le Roy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): Classification subsets and pathogenesis. J Rheumatol 1988;15:202–5.
2. Silman AJ. Scleroderma and survival. Ann Rheum Dis 1991:50:267–9.
3. Altman RD, Medsger TA, Jr, Bloch DA. Predictors of survival in systemic sclerosis (scleroderma). Arthritis Rheum 1991;34:403–13.
4. Steen VD, Powell DL, Medsger TA Jr. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. Arthritis Rheum 1988;31:196–203.
5. Steen VD, Conte C, Owens GR, et al. Severe restrictive lung disease in systemic sclerosis. Arthritis Rheum 1994:37;1283–9.
6. Koh ET, Lee P, Gladman D, et al. Pulmonary Hypertension in Systemic Sclerosis: An analysis of 17 patients. Br J Rheumatol 1996;35:989–93.
7. MacGregor AJ, Canavan R, Knight C. Pulmonary hypertension in systemic sclerosis: risk factors for progression and consequences for survival. Rheumatology 2001;40:453–9.
8. Steen VD, MedsgerTA, Osial TA. Factors predicting the development of renal involvement in progressive systemic sclerosis. Am J Med 1989;76:779–86.
9. Pope J, Fenlon D, Thompson A, et al. Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev 1998; Issue 2. Art. No.: CD000953.
10. Sahhar JS, Littlejohn G, Conron M. Fibrosing alveolitis in systemic sclerosis: the need for early treatment and screening. Intern Med J 2004;34:626–38.
11. Channick R N, Simmonneau G, Sitbon O, et al. Effects of a dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomized placebo controlled study. Lancet 2001;358:1119–23.
12. Lewis J R, Badesch DB, Robyn J, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002;346:896–903.
13. Williams MH, Das C, Handler CE, et al. Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. Heart 2006;92:926–32.
14. Steen VD, Constantino JP, Shapiro AP, et al. Outcomes of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. Ann Int Med 1990:113:352–7.
15. Murderer D, St George D, Knight C, et al. Prevalence and outcome in Systemic Sclerosis associated pulmonary arterial hypertension. Application of a registry approach. Ann Rheum Dis 2003;62:1088–93.
16. Steen VD, Medsger TA, Jr. Severe organ involvement in systemic sclerosis with diffuse scleroderma. Arthritis Rheum 2000;43:2437–44.
17. Proudman SM, Stevens WM, Sahhar J, et al. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. Int Med J 2007;37:485.

AFP CORRESPONDENCE afp@racgp.org.au