MedicineToday 2012; 13(6): 35-42

PEER REVIEWED FEATURE
POINTS: 2 CPD/2 PDP

Managing scleroderma

Challenges in primary care

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Scleroderma is a complex and challenging connective tissue disease that may affect multiple organ systems. Most patients have a slowly progressive course and can be managed with vigilant screening, monitoring and timely intervention.

Key points

- Scleroderma is a multisystem disease affecting the skin and a number of internal organs.
- Close surveillance and timely intervention for end-organ involvement is vital.
- Lung complications are the leading cause of mortality in patients with scleroderma, and annual screening with doppler echocardiography and pulmonary function tests are recommended.
- Early referral of patients with the triad of puffy fingers, Raynaud's phenomenon and positive antinuclear antibodies should be considered.

Scleroderma, also known as systemic sclerosis, is a multisystem connective tissue disease of unknown aetiology, characterised by vasculopathy and fibrosis.[1] Although best known for its characteristic skin involvement, systemic sclerosis can affect a number of internal organs, making the prompt recognition and treatment of these manifestations vital.

EPIDEMIOLOGY

In Australia the estimated incidence rate of scleroderma is 22.8 new cases per million per year, with a prevalence of 233 cases per million.[2,3] This equates to approximately 520 new cases of scleroderma each year, with over 5300 patients with scleroderma co-managed in primary care centres across Australia.

Despite the female to male preponderance of 7:1, no convincing hormonal- or pregnancy-related factors have been identified. Although scleroderma can occur at all ages, the peak incidence occurs between the third and fifth decades.

A higher prevalence of scleroderma has been noted among non-Europeans (Africans, Asians and Caribbeans), with these patients having a higher frequency of diffuse disease and interstitial lung disease (ILD).[4] Although having a first-degree relative with scleroderma remains the strongest known risk factor for developing the condition, the relative risk of developing scleroderma is still low at 1.6% in affected families versus 0.026% in the general population.[5]

PATHOGENESIS

The pathophysiology of scleroderma is complex and incompletely understood. Scleroderma is best regarded as a complex process of microvascular damage, autoimmune dysregulation and fibrosis, triggered by as yet unidentified genetic and environmental factors.[6]

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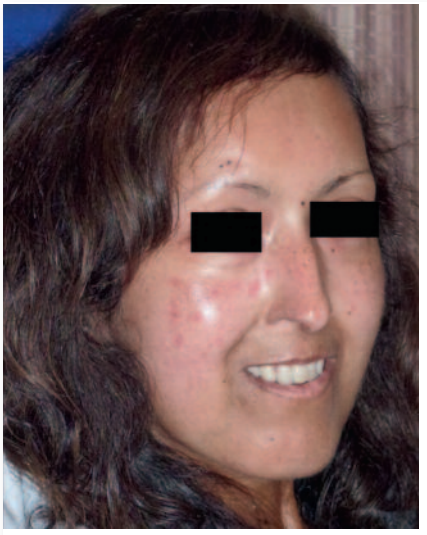
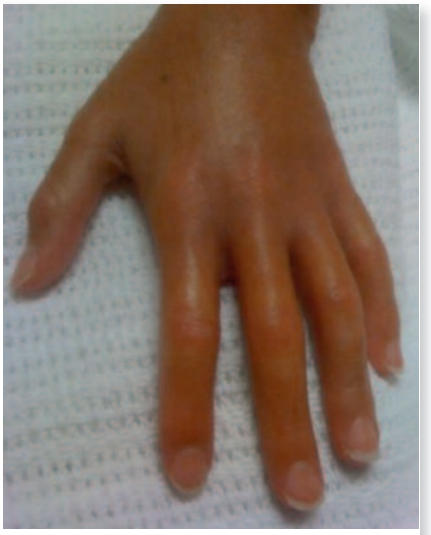
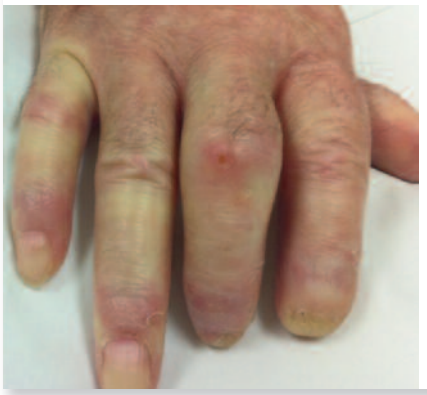






Figures 1a to c. a (top left). Typical scleroderma facies with tight and shiny skin, facial telangiectasias, 'beak'-like nose, and microstomia. b (top right). Scleroderma with puffy fingers, hyperpigmentation and waxy skin. c (left). Chronic scleroderma changes with sclerodactyly, contracture, digital ulceration and auto-amputation.

DISEASE SUBSETS

The two main subsets of scleroderma, limited cutaneous scleroderma, and diffuse cutaneous scleroderma, are classified according to the extent and distribution of skin 'sclerosis' or thickening (see Figures 1a to c). Each of these subsets has a different propensity for the type and extent of internal organ involvement.

Limited cutaneous scleroderma

Patients with limited cutaneous scleroderma have skin sclerosis distal to the elbows and knees (with or without facial involvement). These patients often have a long history of Raynaud's phenomenon before diagnosis and a late peak in mortality from pulmonary arterial hypertension (PAH), which occurs in about 10 to 15% of those affected. Patients with limited cutaneous scleroderma may develop ILD (severe in approximately 15% of patients) and usually have minimal cardiac and kidney involvement.

Diffuse cutaneous scleroderma

In patients with diffuse cutaneous scleroderma, the skin involvement extends more proximally to involve the upper arms, thighs and/or trunk. Patients with diffuse cutaneous scleroderma tend to have worsening of their skin thickening in the first one to three years of disease, with the skin manifestations often improving to varying degrees following this early phase. Patients with diffuse cutaneous scleroderma have a higher incidence of ILD, renal crisis, cardiac disease and large joint contractures, and tend to have a worse survival overall. PAH develops in 5 to 10% of patients with diffuse cutaneous scleroderma.

DIAGNOSIS

Various classification criteria for scleroderma have progressively evolved to include patients with very early disease (see Table).[7-9] These criteria rely on clinical findings in association with the presence of scleroderma-specific antibodies.

A recent consensus statement from leading international experts identified Raynaud's phenomenon, puffy fingers and positive antinuclear antibodies as indicators of a diagnosis of very early systemic sclerosis, and this triad should prompt referral of patients to a rheumatologist for assessment.[9] Approximately 80% of patients with Raynaud's phenomenon, abnormal nailfold capillaroscopy and scleroderma-specific autoantibodies developed scleroderma when followed over a nine-year period.[10]

Scleroderma-specific antibodies tend to be associated with certain disease manifestations; however, the absence of specific antibodies does not rule out a diagnosis of scleroderma. For example, although the presence of anticentromere antibodies is highly specific for limited cutaneous scleroderma, fewer than half of all patients with limited cutaneous scleroderma will have this antibody.[11] The presence of anticentromere antibody has been associated with more calcinosis, telangectasias and digital ischaemia. Similarly, when we look at the antitopoisomerase antibody (also known as anti-Scl-70), only one-third of all patients with diffuse cutaneous scleroderma have this antibody. Patients with Scl-70 antibodies have an increased risk of developing ILD. Anti-RNA polymerase (I, II, III) antibodies, which are present in about 15% of patients with scleroderma in Australia, are associated with the diffuse cutaneous scleroderma subtype and joint contractures; approximately one in five

TABLE. COMPARISON OF CLASSIFICATION CRITERIA FOR ESTABLISHED, EARLY AND VERY EARLY SCLERODERMA

	American College of Rheumatology criteria for established scleroderma*[7]	Early scleroderma†[8]	Very early scleroderma‡[9]
Major criterion	Scleroderma proximal to metacarpophalangeal joints	Raynaud's phenomenon	Raynaud's phenomenon Puffy swollen digits turning into sclerodactly Abnormal capillaroscopy with scleroderma pattern Positive anticentromere antibodies Positive antitopoisomerase-1 antibodies
Minor criterion	Sclerodactyly Digital pitting or pulp atrophy Bibasilar pulmonary fibrosis	Abnormal capillaroscopy with scleroderma pattern Scleroderma-selective autoantibodies§	N/A

* Presence of one major criterion or two of the three minor criteria indicates scleroderma.
† Objective documentation of Raynaud's phenomenon and one minor criterion, or subjective evidence of Raynaud's phenomenon and both minor criteria indicates early scleroderma.
‡ Criteria considered as having a high clinical relevance for a very early diagnosis of scleroderma.
§ Anticentromere, antitopoisomerase I, antifibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNA polymerase I or III in a titre of 1:100 or higher.

patients with this antibody will develop renal crisis.[12]

DIFFERENTIAL DIAGNOSES

There are a number of conditions that mimic scleroderma with skin thickening as a common feature (see the box on this page). These diseases are rare and differentiated from scleroderma by the pattern of skin thickening, extradermal organ involvement and other associated features. Raynaud's phenomenon and positive antinuclear antibodies are not features of these rare disorders.[13]

SPECIFIC DISEASE MANIFESTATIONS AND MANAGEMENT

Skin

The extent and pattern of skin disease determines the subset of scleroderma. In patients with early diffuse disease, especially if the rate of progression of skin thickening is rapid, survival is worse and internal organs are more frequently affected. In this group, international guidelines recommend use of methotrexate therapy.[14] Other treatments that have been used in patients with progressive diffuse skin disease include mycophenolate mofetil and cyclophosphamide, particularly in those with coexisting internal organ involvement. In patients with diffuse disease in whom the skin is softening or in those with limited disease who are unlikely to develop progressive skin involvement, therapy for skin disease may not be indicated.

Telangiectasiae are commonly seen in patients with scleroderma and are due to macroscopically dilated cutaneous capillaries or venules (see Figure 1c). Facial telangiectasiae may have cosmetic and psychological consequences. The management of these is centred on topical concealment and laser treatment.

Musculoskeletal

Involvement of the musculoskeletal system is common in patients with scleroderma and causes much of the functional disability of the condition. Musculoskeletal symptoms are estimated to occur in up to 97% of patients at some point during the disease course.

Arthritis

Joint involvement is often associated with skin thickening and tightening in patients with scleroderma. Joint contractures are common. Arthralgia is also common, although it can vary from mild, intermittent arthralgia to a symmetrical, inflammatory polyarthropathy similar to that of rheumatoid arthritis. Methotrexate and other immunosuppressives may be used in patients with significant inflammatory arthritis.

Tendinopathy

Tendon disease may occur in patients with scleroderma with the presence of palpable tendon friction rubs, particularly around the ankles and wrists. It is associated with poorer survival, more extensive skin disease and an increased risk of renal crisis and cardiac disease. Treatment is similar to that prescribed under the skin and arthritis sections.

DIFFERENTIAL DIAGNOSES OF SCLERODERMA

- Morphea
- Eosinophilic fasciitis
- Nephrogenic systemic fibrosis
- Scleroedema
- Scleromyxoedema
- Diabetic cheiroarthropathy

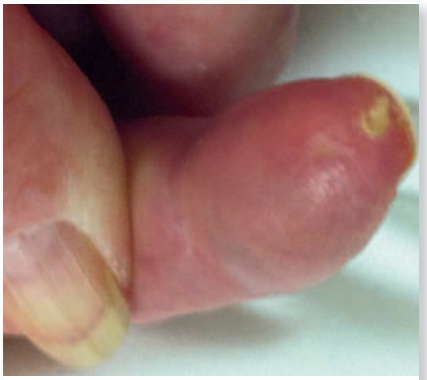


Figure 2. Ulcerating digital calcinosis.

Myopathy

Muscle involvement is common in patients with scleroderma, and myositis may occasionally occur. The myopathy of scleroderma may also be due to use of medications, such as corticosteroids, or secondary to physical deconditioning.

Assessment of a patient with scleroderma and muscle weakness should include measurement of muscle enzymes and consideration of further testing with electromyography or muscle MRI. In some patients, muscle biopsy may be indicated.

Inflammatory muscle disease may be managed with use of methotrexate, azathioprine and/or intravenous immunoglobulin. General measures include the correction of vitamin D deficiency and physical therapies to prevent deconditioning.

Raynaud's phenomenon, digital ulceration and calcinosis

Raynaud's phenomenon, peripheral cyanosis or pallor and pain due to digital vasospasm often predates scleroderma by many years.

Raynaud's phenomenon occurs in 90% of patients with scleroderma. Treatment involves the avoidance of precipitants such as cold exposure and minimising heat loss (from the head and ears, chest, hands and feet) by staying warm and using warmers. In more persistent or severe cases, treatment with oral vasodilators is indicated. The most commonly used drugs are calcium channel blockers, such as nifedipine, felodipine and diltiazem. If these are ineffective or not tolerated, other drugs that can be trialled include transdermal nitrates, phosphodiesterase type 5 inhibitors (tadalafil or sildenafil) and selective serotonin reuptake inhibitors (fluoxetine). Occasionally, intravenous iloprost (a prostacyclin analogue) is used for more severe episodes.

Digital ulceration is one of the complications of scleroderma and may cause significant morbidity due to pain and poor hand function. It is estimated that up to 30% of patients with scleroderma will develop a digital ulcer each year. The cause is generally a combination of poor vascular supply and trauma. General management involves pain relief and treatment of infection, as well as use of oral vasodilators to improve blood flow. Intravenous iloprost is often used as a rescue remedy to aid the healing of persistent ulceration. Other treatments used in severe digital ulceration include botulinum toxin injections around the affected digital vessel and digital sympathectomy. Infrequently, gangrene complicates severe Raynaud's phenomenon and digital ulceration, and digital amputation may be required (in 1.6% and 0.4% of patients, respectively, in a large scleroderma cohort over 18 months).[15]

Calcinosis, the deposition of insoluble calcium salts in the tissues, occurs in about 25 to 40% of patients with scleroderma (Figure 2). Commonly affected sites include the forearms, elbows, volar aspects of the fingertips, metacarpophalangeal joints and interphalangeal joints. Surgical removal of symptomatic deposits is the mainstay of current treatment.

Lung disease

Pulmonary disease, inclusive of PAH and ILD, is the leading cause of mortality in patients with scleroderma, accounting for over 60% of scleroderma-related deaths.

Pulmonary arterial hypertension

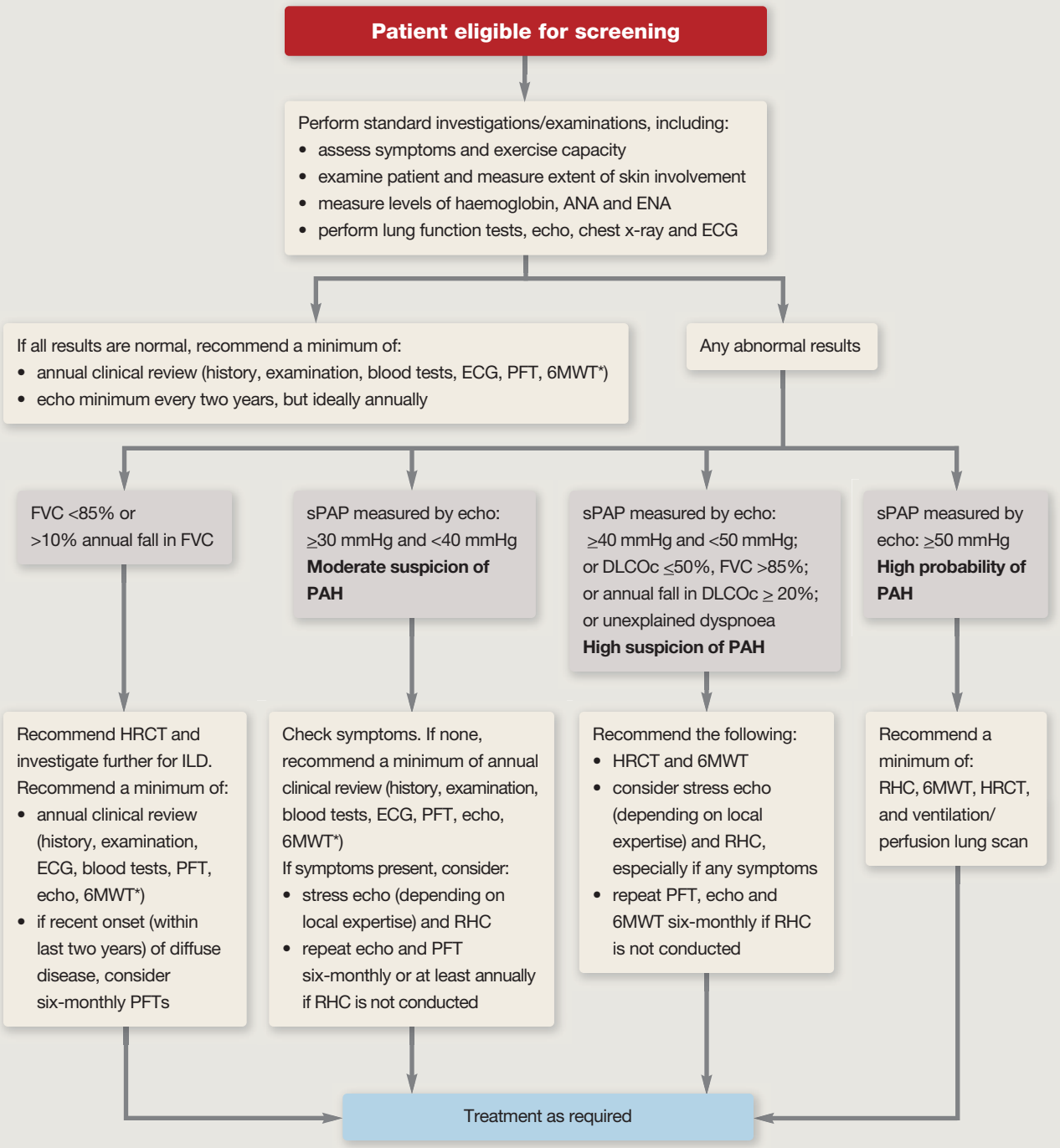
PAH affects 10 to 15% of patients with scleroderma. It is often clinically silent in the early stages with minimal symptoms. However, exertional breathlessness, fatigue and syncope often develop as the disease progresses. Current international guidelines recommend annual echocardiography and pulmonary function testing. A screening algorithm has been developed by the Australian Scleroderma Interest Group to guide clinicians in the early detection of PAH (see the flowchart on page 40).[16,17] Right heart catherisation is essential for the definitive diagnosis of PAH; the latter is defined as mean pulmonary artery pressure of more than 25 mmHg at rest, with a normal pulmonary capillary wedge pressure.

PBS guidelines enable designated pulmonary hypertension centres across Australia to prescribe PAH-specific agents to patients with PAH (see the full schedule for details). These agents include endothelin receptor antagonists (bosentan and ambrisentan), phosphodiesterase inhibitors (sildenafil and tadalafil) and prostanoids (intravenous epoprostenol and inhaled iloprost). There is a growing body of evidence suggesting that screening results in the early detection and treatment of PAH and improves the quality of life and survival of affected patients.[18,19] However, despite best current practice, PAH still has a 50% mortality at three years. This highlights the need for an active research agenda to investigate the role of combination therapies as well as more novel therapies.

Interstitial lung disease

Common symptoms of ILD include exertional dyspnoea and cough. Clinically, there may be signs of reduced breath sounds and basal inspiratory crepitations. Diagnosis is based on characteristic changes on high-resolution CT scans of the lungs (Figure 3). The appropriate screening test for ILD is lung function tests. The finding of reduced forced vital

SUGGESTED ALGORITHM FOR SCREENING PATIENTS WITH SCLERODERMA FOR PAH AND ILD



* Perform 6MWT if resources permit.

ABBREVIATIONS: 6MWT = six-minute walk test; ANA = antinuclear antibodies; DLCOc = diffusing capacity corrected for haemoglobin; echo = echocardiogram; ECG = electrocardiogram; ENA = nucleolar autoantibodies; FVC = forced vital capacity; HRCT = high resolution CT scan of the chest; ILD = interstitial lung disease; PAH = pulmonary arterial hypertension; PFT = pulmonary function tests; RHC = right heart catheterisation; sPAP = systolic pulmonary artery pressure.

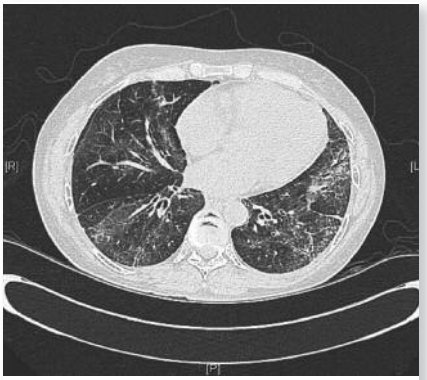


Figure 3. High-resolution CT scan showing interstitial lung disease with interstitial thickening, ground glass change, honeycombing and traction brochiectasis.

capacity (FVC) or a reduced diffusing capacity is an indication for further investigation with high-resolution CT.

We have shown that a simple assessment of the extent of lung disease on high-resolution CT (where limited is less than 20% disease, extensive is more than 20% and an FVC of more than 70% denotes extensive in indeterminate scans) is predictive of poor outcome on follow up.[20] This may allow the selection of patients who require treatment, as only a proportion of those with scleroderma ILD will experience progression of their disease. In scleroderma ILD, the only therapeutic agent with proven efficacy from double-blind, randomised trials is cyclophospha - mide.[21] Treatment with cyclophosphamide has been shown to slow the progression of ILD and improve health-related quality of life. Symptomatic treatment is available with supplemental oxygen. Rarely, lung transplantation is an option.

Renal disease

The major manifestation of scleroderma in the kidneys is renal crisis. This condition, characterised by new-onset, accelerated hypertension or rapidly progressive oligouric renal failure, used to be the main cause of scleroderma-related deaths, with a 90% mortality at one year. However, with the earlier recognition of this complication and the aggressive use of angiotensin converting enzyme (ACE) inhibitors, renal crisis is no longer a leading cause of death in scleroderma, accounting for less than 5% of all-cause mortality in affected patients.[22] Renal crisis occurs predominately in patients with early diffuse scleroderma of less than four years' duration. Other risk factors for the development of renal crisis include the presence of anti-RNP polymerase III antibody and doses of corticosteroids greater than 15 mg/day.[23] Management of renal crisis is with ACE inhibitors and aggressive control of hypertension. Features of poor prognosis include older age, creatinine levels above 270 μmol/L at diagnosis, male gender, congestive cardiac failure and uncontrolled hypertension by day three of treatment.[24]

Cardiac disease

It is estimated that 15 to 35% of patients with scleroderma will develop cardiac disease and this remains subclinical in many cases.[25] A small but significant number of deaths can be attributed to cardiac involvement. Cardiac disease arises due to a combination of impaired cardiac microcirculation and myocardial fibrosis, leading to arrhythmias and ventricular wall dysfunction. Both pericarditis and pericardial effusion are occasionally seen.

Management of cardiac disease focuses on optimising systolic and diastolic function with rhythm and rate control, control of hypertension, appropriate diuresis and ventricular remodelling therapies (e.g. ACE inhibitors).

Gastrointestinal involvement

Gastrointestinal involvement is frequent in patients with scleroderma, with the oesophagus and stomach most commonly affected, followed by the anorectum and small bowel.[6] In many patients, gastrointestinal involvement is a major contributor to diminished health-related quality of life.

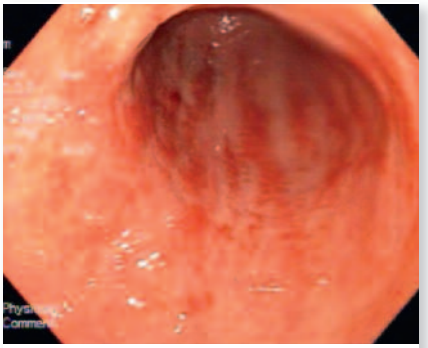


Figure 4. Endoscopic images of gastric antral vascular ectasia ('GAVE'; also known as watermelon stomach).

IMAGE COURTESY OF DR P. DE CRUZ, GASTROENTEROLOGY DEPARTMENT, ST VINCENT'S HOSPITAL, MELBOURNE, VIC.

Gastro-oesophageal disease results from a combination of oesophageal dysmotility, abnormal lower oesophageal sphincter tone and delayed gastric emptying. These factors can result in gastro-oesophageal reflux disease (GORD) of varying severity requiring proton pump inhibition, often in combination with prokinetic agents. Uncontrolled GORD may also exacerbate ILD.

Gastric antral vascular ectasia refers to mucosal capillary dilatations in the stomach, which also can occur in the small bowel (Figure 4). In a primary care setting, affected patients may present with iron-deficiency anaemia. Supportive management consists of replenishing iron stores with oral or intravenous iron infusions; packed red blood cell infusions are reserved for patients with severe symptomatic anaemia. More definitive therapy consists of upper gastrointestinal endoscopy with laser or argon photocoagulation, which may need to be repeated at regular intervals.

Small bowel involvement can include small bowel intestinal bacterial overgrowth, dysmotility and pseudo-obstruction with resultant gastrointestinal symptoms (e.g. nausea, vomiting, bloating, abdominal discomfort, diarrhoea and constipation) and malnutrition. Although these

problems may require specialist multidisciplinary input from a gastroenterologist, rheumatologist and dietitian, cyclical antibiotics for small bowel intestinal bacterial overgrowth (e.g. selective antibiotics such as tetracyclines, quinolones and imidazoles for the first 10 days of the month, repeated if necessary), and antiemetics and prokinetics for dysmotility can be used to alleviate the symptoms.

Faecal incontinence is an under-recognised and under-reported manifestation in scleroderma, affecting up to 20% of patients, and is due to atrophy of the internal anal sphincter.[26] The management of this consists of rectal tampons, pelvic floor strengthening, surgical procedures to repair rectal prolapses and strengthen the pelvic floor, as well as a sacral neuromodulation.

Erectile dysfunction

Erectile dysfunction is common in men with scleroderma and is associated with increasing age and disease severity. As in the general population, treatment of erectile dysfunction includes addressing psychological factors; cessation of offending medications; improving physical fitness; use of phosphodiesterase inhibitors; and consideration of vacuum or implantable devices.[27]

HEALTH-RELATED QUALITY OF LIFE

As a multisystem disease, scleroderma has a marked impact on quality of life. A survey found fatigue, Raynaud's phenomenon, hand stiffness, joint pain and difficulty sleeping to be the most commonly reported symptoms impacting on quality of life (between 79 and 89% of respondents).[28]

CONCLUSION

Scleroderma is a complex and challenging multisystem connective tissue disease. A high clinical suspicion for the disease, along with adequate surveillance for end-organ complications may greatly improve the quality of life and survival of patients. Rapidly progressive scleroderma requires early referral of the patient and an aggressive approach to treatment. However, most patients will have a slowly progressive course and can be managed with vigilant screening, monitoring and timely intervention. MT

REFERENCES

References are included in the pdf version of this article available at www.medicinetoday.com.au.

ACKNOWLEDGEMENT

Dr Thakkar is funded by an NHMRC postgraduate scholarship and the Australian Scleroderma Interest Group (ASIG) Clinical Research Fellowship. Systemic sclerosis research at St Vincent's Hospital Melbourne is supported by a University of Melbourne Early Career Researcher Grant.

COMPETING INTERESTS: Drs Thakkar, Moore, Stevens and Nikpour are part of Australian Scleroderma Interest Group (ASIG). Funding for research undertaken by ASIG is provided by Scleroderma Australia, Arthritis Australia, Actelion Australia, Bayer, CSL Biotherapies, GlaxoSmithKline Australia and Pfizer.

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REFERENCES

1. Jimenez SA, Derk CT. Following the molecular pathways toward an understanding of the pathogenesis of systemic sclerosis. Ann Intern Med 2004; 140: 37-50.
2. Roberts-Thomson PJ, Jones M, Hakendorf P, et al. Scleroderma in South Australia: epidemiological observations of possible pathogenic significance. Intern Med J 2001; 31: 220-229.
3. Nikpour M, Stevens WM, Herrick AL, Proudman SM. Epidemiology of systemic sclerosis. Best Pract Res Clin Rheumatol 2010; 24: 857-869.
4. Le Guern V, Mahr A, Mouthon L, Jeanneret D, Carzon M, Guillevin L. Prevalence of systemic sclerosis in a French multi-ethnic county. Rheumatology (Oxford) 2004; 43: 1129-1137.
5. Broen J, Coenen M, Radstake TR. Genetics of systemic sclerosis: an update. Curr Rheumatol Rep 2012; 14: 11-21.
6. Geyer M, Müller-Ladner U. The pathogenesis of systemic sclerosis revisited. Clin Rev Allergy Immunol 2010; 40: 92-103.
7. Masi AT. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee, Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980; 23: 581.
8. LeRoy EC, Medsger TA, Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol 2001; 28: 1573-1576.
9. Avouac J, Fransen J, Walker UA, et al. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis 2011; 70: 476-481.
10. Koenig M, Joyal F, Fritzler MJ, et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum 2008; 58: 3902-3912.
11. 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.
12. Nikpour M, Hissaria P, Byron J, et al. Prevalence, correlates and clinical usefulness of antibodies to RNA polymerase III in systemic sclerosis: a cross-sectional analysis of data from an Australian cohort. Arthritis Res Ther 2011; 13: R211.
13. Nashel J, Steen V. Scleroderma mimics. Curr Rheumatol Rep 2011; 14: 39-46.
14. Kowal-Bielecka O, Landewe R, Avouac J, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis 2009; 68: 620-628.
15. Nihtyanova SI, Brough GM, Black CM, Denton CP. Clinical burden of digital vasculopathy in limited and diffuse cutaneous systemic sclerosis. Ann Rheum Dis 2008; 67: 120-123.
16. Proudman SM, Stevens WM, Sahhar J, Celermajer D. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. Intern Med J 2007; 37: 485-494.
17. Proudman SM. Why screen patients with scleroderma for lung complications? Med Today 2010; 11(2): 63-68.
18. Condliffe R, Kiely DG, Peacock AJ, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med 2008; 179: 151-157.
19. Humbert M, Yaici A, de Groote P, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: Clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011; 63: 3522-3530.
20. Moore O, Goh N, Corte T, et al. Extent of lung disease on high-resolution CT lung is a predictor of mortality in scleroderma-related lung disease. Rheumatology 2012; 51 (Suppl 2): ii3-ii5.
21. Taskin DP, Elashoff R, Clements PJ, et al. Cyclophosphamide verses Placebo in Scleroderma Lung Disease. N Engl J Med 2006; 354: 2655-2666 .
22. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007; 66: 940-944.
23. Khanna D, Denton CP. Evidence-based management of rapidly progressing systemic sclerosis. Best Pract Res Clin Rheumatol 2010; 24: 387-400.
24. Rhew EY, Barr WG. Scleroderma renal crisis: new insights and developments. Curr Rheumatol Rep 2004; 6: 129-136.
25. Kahan A, Coghlan G, McLaughlin V. Cardiac complications of systemic sclerosis. Rheumatology (Oxford) 2009; 48 (Suppl 3): iii45-iii48.
26. Thoua NM, Schizas A, Forbes A, Denton CP, Emmanuel AV. Internal anal sphincter atrophy in patients with systemic sclerosis. Rheumatology (Oxford) 2011; 50: 1596-1602.
27. Walker UA, Tyndall A, Ruszat R. Erectile dysfunction in systemic sclerosis. Ann Rheum Dis 2009; 68: 1083-1085.
28. Bassel M, Hudson M, Taillefer SS, Schieir O, Baron M, Thombs BD. Frequency and impact of symptoms experienced by patients with systemic sclerosis: results from a Canadian National Survey. Rheumatology (Oxford) 2011; 50: 762-767.