A GP's guide to scleroderma

This article discusses the systemic forms of scleroderma, including manifestations that should alert the GP to the need for investigation and early specialist referral. Advances in drug treatment have resulted in improved symptomatic control and prognosis.

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Scleroderma comprises a group of conditions ranging from localised patches of thickened skin to a widespread multisystem disorder capable of causing significant morbidity and mortality if left untreated.

Overall, scleroderma has an estimated prevalence of 8 to 9 per 100,000 in Sydney,[1] comparable with prevalence rates overseas. It is estimated that new cases occur at a rate of 0.6 to 19 per 1,000,000 per annum.[2]

The usual age of onset is between 45 and 65 years. The incidence is higher in females than in males (3:1).

While scleroderma occurs in many different racial groups, the limited variant occurs more commonly in Caucasians, and young African American females have an increased risk of systemic scleroderma and more severe disease.

Classification and diagnostic features

Scleroderma can be divided into localised and systemic forms. The localised forms can be further broken down into various categories depending on their morphological appearance: localised morphoea, generalised morphoea, linear scleroderma and *en coup de sabre* (linear lesion often involving the face or scalp).

Although some localised forms involve extensive areas of skin, they are not associated with visceral disease.

The extent of skin and internal organ involvement is used to classify systemic scleroderma (known as systemic sclerosis) into limited cutaneous and diffuse cutaneous disease. Rarely, patients can present with internal organ involvement in the absence of any skin thickening, known as *scleroderma sine scleroderma*.

IN SUMMARY

- **Features suggesting that Raynaud's phenomenon is secondary to an underlying illness such as scleroderma include: digital pitting, ulceration or gangrene, oedema of hands and fingers, abnormality of nailfold capillaries and a positive antinuclear antibody. They require rheumatological referral.**
- **Patients with diffuse systemic sclerosis must be regularly monitored for hypertension, symptoms of breathlessness and progression of skin thickening because early intervention can help prevent significant end-organ damage.**
- **Oesophageal or symptomatic cardiac involvement should prompt early referral to a gastroenterologist or cardiologist.**
- **There is increasing evidence for the beneficial effects of immunosuppressive medication, particularly in rapidly progressive diffuse disease.**
- **It is important to advise maintenance of ambient warmth in those with secondary Raynaud's, as well as general skin care of digits. This can help with preventing ulceration, gangrene and breakdown of digits. Calcium channel blockers should also be used.**

This article will focus on only systemic sclerosis. Possible causes and pathogenesis are discussed in the box on page 52,[3-5] and diagnostic features are listed in Table 1.

Limited cutaneous systemic sclerosis

By definition, patients with limited disease have skin thickening restricted to the hands, feet, face and neck (Figure 1). They tend to present with prominent vascular manifestations, and almost all of these patients will have Raynaud's phenomenon as their initial presenting feature.

Raynaud's phenomenon manifests clinically as sequential colour changes of the fingers and toes, initially white, then blue and finally a blushed reddish colour (Figure 2). This well demarcated colour change is an exaggerated vascular response to cold temperature or emotional stress and is believed to result from vasoconstriction of digital arteries.

Patients with limited disease often manifest signs of CREST syndrome: Calcinosis, Raynaud's phenomenon, oEsophageal dysmotility, Sclerodactyly, Telangiectasia.

Internal organ involvement is not as common in limited systemic sclerosis as it is in the diffuse form, although a minority of patients with limited disease develop pulmonary hypertension and, less frequently, interstitial lung fibrosis (Table 2).[6] Patients with limited disease are at risk of developing large vessel occlusive disease, independent of other vascular risk factors.[7]

Figure 1. Scleroderma affecting the face and neck. Note the skin tightening around the face with decreased oral aperture and thinning of the lips.

Figure 2. Raynaud's phenomenon.

Diffuse cutaneous systemic sclerosis

Patients with diffuse disease typically develop more extensive skin sclerosis involving the trunk and proximal (as well as distal) extremities. These patients are also at greater risk of developing significant lung, renal and cardiac disease. They need to be monitored closely because they can develop end-organ involvement before they manifest symptoms. Early intervention can prevent irreversible damage.

Differential diagnoses

Primary Raynaud's phenomenon

Up to 15% of the general population suffer symptoms of Raynaud's phenomenon. Most of these patients have primary Raynaud's and therefore have no identifiable cause. These

Table 1. Diagnostic features of systemic sclerosis

Limited disease

- Raynaud's phenomenon
- Skin thickening restricted to distal extremities and face
- Calcinosis, oesophageal dysmotility and telangiectasia (often seen)
- Antinuclear antibody with a centromere staining pattern (often present, but laboratory markers are generally unhelpful)

Diffuse disease

- Proximal limb and/or truncal skin thickening
- Raynaud's phenomenon
- Multiorgan involvement
- Autoantibody against an extractable nuclear antigen such as topoisomerase (may be present)

What is the aetiology and pathogenesis of systemic sclerosis?

Aetiology

Although a lot is known about abnormalities of immune, endothelial and fibroblast cell function in systemic sclerosis, the trigger for these abnormalities is poorly understood. The aetiology is thought to be multifactorial, involving a combination of environmental factors, either a virus or a toxin and genetic predisposition.

While familial occurrence is unusual, clusters have been noted in several families. Results from a murine model of scleroderma (the 'tight skin mouse')[3] and twin studies in humans[4] support a role for genetic factors.

Certain drugs and chemicals have been implicated in the aetiology of systemic sclerosis. Silicone exposure in breast implants has received a lot of publicity; however, a recently published meta-analysis has confirmed that no association exists between silicone in breast implants and systemic sclerosis.[5]

Other agents have been implicated in causing a 'scleroderma-like' disease that has skin thickening but no visceral involvement. These include vinyl chloride and petroleum-based solvents, such as paint thinners and benzene. Some drugs (including bleomycin, pentazocine and cocaine) have also been implicated.

Pathogenesis

The pathogenesis of scleroderma originates with vascular and endothelial cell changes, which are precursors to the skin thickening. There is an imbalance in the regulation of vascular tone: endothelins, potent vasoconstrictors that are also fibrogenic, are found to be in excess, while nitric oxide, a natural vasodilator, is depleted.

A number of cytokines have been investigated as potential instigators of fibrosis. It is likely that an interplay between different cytokines causes activation of fibrogenic fibroblasts, which results in fibrotic changes.

Activated T-cells are also believed to be integral in the pathogenesis of scleroderma, and are found in increased numbers in the skin in early disease. Some of the currently used therapies for scleroderma use agents that suppress B and T lymphocyte activity.

Table 2. Clinical features of limited and diffuse systemic sclerosis[6]

Clinical feature	Limited cutaneous sclerosis	Diffuse cutaneous sclerosis
Raynaud's phenomenon	99% *	90%
Arthralgia	90%	98%
Tendon friction rubs	5%	70%
Calcinosis	40%	20%
Telangiectasia	90%	60%
Oesophageal dysmotility	90%	80%
Small bowel involvement	60%	40%
Interstitial lung disease	10–30%	70%
Pulmonary hypertension	25%	5%
Renal crisis	1%	20%
Cardiomyopathy	10%	15%

* Proportion of patients with the feature.

patients are typically young females (female:male ratio, 4:1) and their symptoms usually begin during their teenage years. These females often have a family history of Raynaud's phenomenon. The course of primary Raynaud's is benign, and ischaemic injury to the fingers is typically absent.

It is important to try to exclude an underlying cause in patients before labelling them as having primary Raynaud's phenomenon because those with underlying connective tissue diseases such as scleroderma often do go on to develop ischaemic injury to the digits (Figure 3).

Raynaud's secondary to other diseases

Secondary Raynaud's phenomenon has many causes, including connective tissue disease. Over 90% of all patients with scleroderma suffer Raynaud's phenomenon, but Raynaud's can also occur in patients who have rheumatoid arthritis, systemic lupus erythematosus and dermatomyositis.

Other causes of Raynaud's phenom enon include drugs (beta blockers, ergots), thoracic outlet syndrome, cervical rib and arteriosclerosis.

Other disorders

Exposure to polyvinyl chloride, Spanish rape seed oil toxicity, carcinoid syndrome and methysergide toxicity can all cause skin changes that can look like systemic sclerosis. These disorders are all rare.

Prognosis and approach to management

The natural history of systemic sclerosis ranges from an indolent disease that persists for many years to a rapidly progressive and fatal condition that affects lung and kidney function. The prognosis is generally worse with the diffuse form of the disease: the 10-year survival is approximately 55%, compared with 70% for the limited form. However, with more aggressive immunotherapy

Figure 3. Ischaemic digits. Note the resorption and ulceration of terminal aspects of the digits. There is fixed flexion deformity due to fibrous contractures.

Figure 4. A chest x-ray showing bilateral basal pulmonary fibrosis.

being instituted earlier in the disease, survival is improving.

Treatment of systemic sclerosis can be grouped under two broad categories:

- treatment of specific organ-based manifestations (such as oesophageal dysmotility, hypertension and digital ulceration)
- disease-modifying therapy to control the underlying disease process.

Specific manifestations and their treatment

Raynaud's phenomenon

Patients with limited sclerosis often have Raynaud's phenomenon for many years before the onset of other signs of scleroderma, whereas in those with diffuse disease the interval tends to be much shorter.

Features that suggest an underlying illness such as scleroderma include:

- digital pitting
- ulceration or gangrene
- oedema of fingers and hands
- abnormalities of nailfold capillaries on capillaroscopy
- a positive antinuclear antibody (ANA).

A centromere staining pattern on the ANA is suggestive of limited disease, whereas a speckled pattern in the presence of antibodies to certain extractable nuclear antigens (e.g. topoisomerase) suggests diffuse disease.

A suspicion of underlying connective tissue disease should prompt rheumatological referral because early intervention, particularly in diffuse disease, can help prevent significant end-organ damage leading to respiratory and renal compromise.

The management of Raynaud's phenomenon should begin in a graduated fashion, with emphasis on maintaining both peripheral and central body warmth, particularly in winter. Measures such as gloves, woollen socks, body warmers and thermal underwear are advisable during colder weather. Maintenance of ambient warmth is important in trying to prevent severe Raynaud's and ischaemic digits (Figure 3).

Patients should be strongly advised against smoking, and aggravating drugs (e.g. beta blockers and ergot-containing compounds) should be discontinued.

Along with these measures, pharmacological therapy is usually necessary. This includes calcium channel blockers. Long acting nifedipine (Adalat Oros) is usually the drug of choice. Dosages ranging from 30 to 120 mg daily can be employed and should be titrated to effect and tolerability. The main limiting adverse effects are postural hypotension, (about which the patient should be warned), facial flushes and headaches.

Prazosin can also be used to treat Raynaud's phenomenon, as can topical nitrates applied directly to the hands and fingers, but headaches are often the limiting factor. Parenteral agents, such as intravenous prostacyclin and intra-arterial guanethidine, are useful agents for pain refractory to the above measures and for pregangrenous threatened digits. Failure to respond to conservative measures and basic pharmacological intervention should trigger prompt rheumatological referral.

Renal disease

Clinically, the most important manifestation of scleroderma kidney is rapidly progressive renal failure and/or accelerated hypertension. Only 10 to 15% of patients develop a renal crisis, the great majority of these occurring within the first five years of disease. Those with diffuse disease are at greatest risk, particularly if the skin thickening is rapidly progressive. Patients are also at highest risk during winter months. A case–control study has found that the use of oral corticosteroids in scleroderma patients at doses greater than 15 mg/day increases their risk of renal crisis.[8]

While autopsy evidence indicates that most patients with scleroderma have changes in the kidney, only a small minority present with clinical involvement. Presentations include symptoms and signs typical of malignant hypertension: headache, altered vision, encephalopathy, myoclonus, heart failure and seizures.

Laboratory data may show normal or elevated serum creatinine, proteinuria and microscopic haematuria, although often the urinary sediment is benign. Patients may also present with a micro-angiopathic haemolytic anaemia.

Malignant hypertension is a medical emergency, and urgent admission to hospital is required. Since the advent of ACE inhibitors, renal crisis is becoming increasingly uncommon, but nonetheless patients must have their blood pressure monitored closely. Hypertension in the absence of other signs and symptoms may herald impending crisis and should always be treated. The drugs of choice are the ACE inhibitors, which improve both renal function and survival.

Patient support and information

Various associations around Australia provide information and support to patients affected by scleroderma. Contacts for regional groups and email and fax numbers can be found at the Scleroderma Australia website. Patients can also phone the Arthritis Foundation's freecall number and be transferred to the relevant State branch.

Scleroderma Australia website
www.scloz.org
Arthritis Foundation
1800 011 041
Scleroderma Foundation of Victoria
(03) 9288 3651
Scleroderma Association of NSW
(02) 9411 3459 or 1800 068 061
Scleroderma Group of the ACT
(02) 6258 1074
Scleroderma Association of Queensland
(07) 5527 0490
Tasmanian Scleroderma Friendship Group
(03) 6229 4478
South Australian Scleroderma/SLE Group
(08) 8379 5711
Arthritis Foundation of Western Australia
(08) 9388 2199
Arthritis Foundation of Northern Territory
(08) 8948 5232

Pulmonary involvement

Pulmonary disease is common in diffuse sclerosis, usually manifesting as interstitial lung disease (Table 2 and Figure 4). Much less commonly, in the limited form, patients can develop primary pulmonary hypertension. These days, it is pulmonary involvement, particularly in diffuse disease, that results in increased mortality and morbidity. The development of primary pulmonary hypertension is an ominous sign because survival, even with treatment, is often only three years.

Interstitial disease

The most common symptoms of interstitial disease are dry cough and dyspnoea, but as many as one-third of the patients remain asymptomatic. Chest examination reveals fine inspiratory crackles, but chest x-ray may show no abnormalities in early disease. Pulmonary function tests and high resolution CT of the lungs are more sensitive and are usually abnormal.

Specialist referral at this stage is important because early intervention with intravenous cyclophosphamide (Cycloblastin, Endoxan-Asta) appears to improve the outcome. All patients with diffuse disease should be regularly monitored for the presence of pulmonary involvement.

Pulmonary hypertension

Primary pulmonary hypertension occurs in a small percentage of patients with limited disease, whereas patients with interstitial lung involvement develop secondary pulmonary hypertension. Symptoms include cough and exertional dyspnoea, although up to one-third of patients remain asymptomatic until the disease is advanced.

Chest examination findings suggestive of pulmonary hypertension include a prominent A wave on jugular venous pressure examination, a right ventricular S_4 (fourth heart sound) and a loud P_2 (pulmonary component of second heart sound). Chest x-ray may reveal prominent pulmonary arteries. On lung function testing, a disproportionately decreased diffusing capacity for carbon monoxide (DLCO) in the absence of a restrictive lung volume pattern is also suggestive. Echocardiography is a useful tool for assessing the presence and progression of pulmonary hypertension.

Treatment is difficult and includes a combination of nifedipine, warfarin and prostacyclin analogues, either intravenously or inhaled.

Gastrointestinal involvement

Almost all patients with scleroderma, both diffuse and limited, develop gastrointestinal involvement. All sections of the gastrointestinal tract can be involved, from the mouth to the distal colon. Most of the problems are related to disordered motility resulting from abnormal collagen deposition and fibrosis of the smooth muscle layers.

Symptoms include dysphagia, heartburn, cough after swallowing, bloating, diarrhoea and intestinal pseudo-obstruction resulting from an atonic bowel.

Oesophageal involvement is almost universal in patients with scleroderma. Prompt gastrointestinal referral is appropriate because early investigation with endoscopy, oesophageal motility or gastric emptying studies will expedite commencement of proton pump inhibitors and prokinetic agents. These agents may prevent later complications such as oesophageal ulceration and stricture formation. Other simpler measures include frequent small meals, elevation of the head of the bed, cessation of smoking and reduction in alcohol intake.

Small bowel involvement is common and manifests as pain, bloating, constipation, diarrhoea and weight loss. Investiga-

tion reveals the presence of small bowel bacterial overgrowth, and treatment with antibiotics is helpful.

Cardiac involvement

Symptomatic cardiac involvement is uncommon in scleroderma. However, when it occurs there is an unfavourable prognosis, with five-year mortality rates of 75%. Manifestations include pericarditis, pericardial effusions, myocardial fibrosis (which can result in arrthymias), and congestive cardiac failure.

Appropriate investigations include ECG and 24-hour Holter monitoring, chest x-ray and echocardiography. Symptomatic cardiac involvement should prompt early cardiology referral.

Musculoskeletal involvement

Patients with diffuse disease may present with arthralgias, myalgias, skin puffiness and flexor tenosynovitis. The arthritis is not destructive and is generally mild. The presence of severe arthritis should make one think of an overlap syndrome.

Disease-modifying therapy

Penicillamine

Penicillamine (D-Penamine) is a drug that affects collagen biosynthesis and has an immune modulating effect. Its exact role in systemic sclerosis is not well understood. However, it is one of the few agents for which there is evidence to show a decrease in skin thickening with its use. It is generally used in all patients with diffuse disease. Its use in those with limited disease is less well defined. Recent studies suggest that high dose penicillamine confers little advantage over low doses. Most clinicians now use between 375 and 500 mg daily. Adverse effects are related to drug dosage and include renal toxicity and leucopenia.

Cyclophosphamide

A role for immunosuppressive medication, in particular intravenous cyclophosphamide in combination with corticosteroids, has been demonstrated in rapidly progressive diffuse disease. It results in decreased skin thickening and improvement of fibrosing alveolitis of the lungs. Once fibrosis is established, the role of immune suppression is limited. Long term high dose corticosteroids have been implicated in precipitating renal crisis, and the use of low dose steroids in isolation should be restricted to patients with symptomatic serositis, arthritis and tenosynovitis.

Experimental approaches

Newer investigational approaches to the treatment of systemic sclerosis include recombinant human relaxin, a polypeptide hormone that inhibits collagen synthesis. Autologous stem cell transplantation remains an experimental approach.

Follow up protocol

Patients with diffuse disease require close monitoring (e.g. monthly checks), particularly during early stages of the

disease. They should have regular blood pressure monitoring, and history and examination should focus on new respiratory symptoms, progression of skin thickening and gastrointestinal complaints. New symptoms and signs should prompt rheumatological referral.

Those with limited disease can occasionally develop multisystem features, in particular respiratory and gastrointestinal involvement and primary pulmonary hypertension. Follow up of these patients should focus on skin care of fingers to avoid ulceration, gangrene and tissue breakdown. Patients with threatened digits that fail to respond to early therapeutic measures should be referred promptly for treatment with intravenous prostacyclin.

Pregnancy in patients with scleroderma

Studies have shown that fertility rates are generally not affected by systemic sclerosis. Rates of premature births and small full-term infants are increased in women with scleroderma.

Women with early diffuse scleroderma should wait until their disease stabilises before becoming pregnant, to decrease the risk of renal crisis. High-risk pregnancy management should be standard for all scleroderma pregnancies because of the high frequency of premature births.

Conclusion

Advances in drug treatment have resulted in improved symptomatic control and prognosis in scleroderma. Patients with diffuse systemic sclerosis must be regularly monitored for hypertension, symptoms of breathlessness and progression of skin thickening because early intervention can help prevent significant end-organ damage. MT

References

1. Englert H, Small-McMahon J, Davis K, O'Connor H, Chambers P, Brooks P. Systemic sclerosis prevalence and mortality in Sydney 1974-88. Aust N Z J Med. 1999; 29: 42-50.
2. Medsger TA Jr. Epidemiology of systemic sclerosis. Clin Dermatol 1994; 12: 207-216.
3. Siracusa LD, McGrath R, Ma Q, et al. A tandem duplication within the fibrillin 1 gene is associated with the mouse tight skin mutation. Genome Res 1996; 6: 300-313.
4. Feghali CA, Wright TM. Epidemiologic and clinical study of twins with scleroderma. Arthritis Rheum 1995; 38: S308.
5. Janowsky EC, Kupper LL, Hulka BS. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med 2000; 342: 781-790.
6. Klippel JH, Dieppe PA, editors. Rheumatology. 2nd ed. St Louis: Mosby, 1998.
7. Ho M, Veale D, Eastmond C, Nuki G, Belch J. Macrovascular disease and systemic sclerosis. Ann Rheum Dis 2000; 59: 39-43.
8. Steen VD, Medsger TA Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum 1998; 41: 1613-1619.