Systemic sclerosis: an update for clinicians

Recent advances in the management of systemic sclerosis highlight the importance of early diagnosis and assessment, before irreversible tissue injury has occurred. This review will discuss diagnosis, subtyping, and the major clinical features and their management.

Systemic sclerosis is a multisystem connective tissue disease. The last 10 years have seen a number of key advances in assessment and management. Although there is still no 'cure' for systemic sclerosis, much can be done for the associated digital vascular disease and internal organ involvement. Although a rare disease, with a prevalence in the order of 2.6 cases/10 000 (0.026%) (Arnett et al, 2001), systemic sclerosis is associated with significant morbidity and mortality. Women are more commonly affected than men (3:1).

Unlike most other connective tissue diseases, systemic sclerosis is not primarily an inflammatory disease and therefore steroids are seldom indicated. However, when systemic sclerosis occurs in overlap with other connective tissue diseases, for example with systemic lupus erythematosus or with myositis, then there can be a significant inflammatory component necessitating cautious use of steroids.

The pathogenesis of systemic sclerosis is not fully understood, but most likely involves a complex interplay of excessive fibrosis, vascular abnormalities and abnormalities of the immune system. Much research is ongoing into the underlying molecular and cellular mechanisms, the overall aim being to identify and understand the roles of key mediators (for example endothelin-1 and transforming growth factor-β; Jimenez and Derk, 2004) which might be targets for therapeutic intervention. The key point for clinicians is that the clinical features of systemic sclerosis result primarily from a combination of fibrosis and ischaemic atrophy. The most characteristic fibrotic manifestation is scleroderma (thickening and hardening of the skin), and the most characteristic vascular manifestation is severe Raynaud's phenomenon. While both of these can be extremely painful and disabling, it is the fibrosis and ischaemia of internal organs which can be life-threatening.

This review will discuss diagnosis (including subtyping), and the major clinical features and their management, highlighting recent advances, in particular in the identification and treatment of pulmonary arterial hypertension and pulmonary fibrosis. Two scenarios are described to illustrate the differences between the two major subtypes: limited cutaneous and diffuse cutaneous. Because of the multisystem nature of systemic sclerosis, those affected can present to almost any specialist.

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Diagnosis and subtyping

Diagnosis

Although systemic sclerosis is often termed 'scleroderma', strictly speaking scleroderma is only one manifestation of systemic sclerosis. Scleroderma can occur in a number of other diseases, for example in the different types of localized scleroderma. 'Localized' scleroderma, meaning localized to the skin and underlying tissues and not associated with internal organ involvement, can be extensive, as in the generalized morphoea variant, and can be mistaken for systemic sclerosis. A key point in diagnosing systemic sclerosis is that the skin involvement almost invariably commences distally (fingers, feet and face) and is almost always associated with Raynaud's phenomenon. The American Rheumatism Association preliminary criteria for the diagnosis of systemic sclerosis (Masi et al, 1980) state that a patient must have either:

1. The major criterion – skin thickening proximal to the metacarpophalangeal joints or
2. Two minor criteria:
   Sclerodactyly (skin thickening of the fingers) (*Figure 1*)
   Digital pitting scars of the fingertips (*Figure 2*)
   Bibasilar pulmonary fibrosis (*Figure 3*).

However, these criteria are not sensitive and many patients with systemic sclerosis do not fulfill them. For example, a patient with Raynaud's phenomenon, sclerodactyly, oesophageal dysmotility, abnormal nailfold capillaries and a positive anticentromere antibody does not fulfull the American Rheumatism Association criteria but clearly has systemic sclerosis. Thus criteria to recognize early disease have been proposed, incorporating autoantibody status and nailfold microscopy (LeRoy and Medsger, 2001).

Subtyping

There are two major subtypes: limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis

Figure 1. Sclerodactyly of the fingers in a patient with systemic sclerosis: the skin looks tight and was thickened on palpation. The patient has fixed flexion deformities, and is unable to fully extend the fingers. She has areas of healed ulceration over the proximal interphalangeal joints.

(LeRoy et al, 1988) (*Case studies 1* and *2*). These are separated on the basis of the extent of the skin involvement. In limited cutaneous systemic sclerosis, skin involvement is confined to distal to the elbows, knees and neck (the face is often involved) whereas in diffuse cutaneous systemic sclerosis there is proximal limb and/or truncal involvement. This is a key point because the two subtypes have different natural histories, autoantibody associations and prognoses. The importance of subtyping has only been recognized relatively recently, but this has major implications for both clinical practice and research studies. For example, new treatments aimed at suppressing early, aggressive diffuse cutaneous systemic sclerosis would be inappropriate for those with limited cutaneous systemic sclerosis.

Figure 2. Severe digital ischaemia, leading to gangrene of a fingertip, in a patient with systemic sclerosis. The digit to the right of the image demonstrates digital pitting.

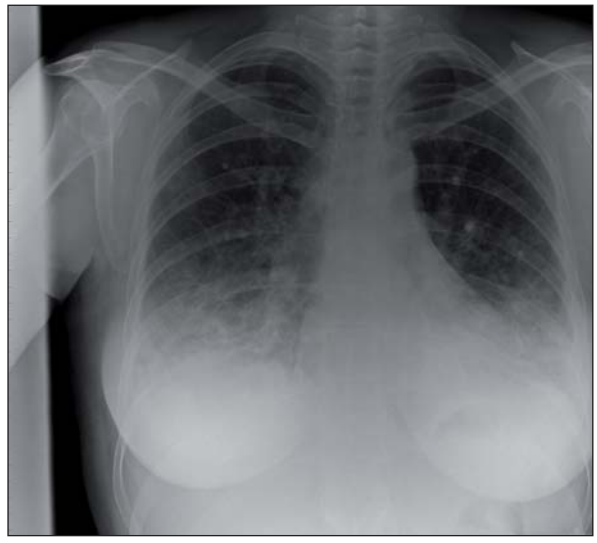


Figure 3. Chest radiograph showing bilateral basal fibrotic changes in a patient with systemic sclerosis.

There is a misconception that limited cutaneous systemic sclerosis is a 'mild' form of the disease. This is untrue. Although in diffuse cutaneous systemic sclerosis there is a higher incidence of early internal organ involvement (heart, lung, kidney), patients with limited cutaneous systemic sclerosis, in whom Raynaud's phenomenon often precedes other clinical manifestations by many years, may have severe gastrointestinal disease and

Case Study 1

A 40-year-old woman with a 20-year history of Raynaud's phenomenon attended the accident and emergency department with an infected ulcer of her left middle finger. Over the last 2 years she had had heartburn, with some recent swallowing difficulty.

On examination, she had slight tightening of the skin of her fingers, but no flexion deformities. There was an ulcer of the tip of her left middle finger, which was extremely tender, and some telangiectases of her face and lips. She was referred to the rheumatologist who confirmed the suspected diagnosis of limited cutaneous systemic sclerosis and prescribed antibiotics, a calcium-channel blocker, a proton pump inhibitor and analgesia. One week later there was no improvement in the ulcer and she was admitted for intravenous iloprost and surgical debridement of the fingertip. The results of investigations included a normal full blood count and erythrocyte sedimentation rate, a positive anticentromere antibody, abnormal nailfold microscopy with dilated loops and areas of avascularity, oesophageal hypomotility on barium swallow and reflux oesophagitis on gastroscopy. Five years later she continued to have recurrent ulcers of her fingers but was otherwise well with no new symptoms. Her rheumatologist reviewed her regularly, including monitoring of her echocardiogram and pulmonary function tests.

there is a late mortality from pulmonary arterial hypertension. As a generalization, limited cutaneous systemic sclerosis tends to be associated with more pronouced vascular manifestations (e.g. severe Raynaud's phenomenon, telangiectases, pulmonary arterial hypertension) whereas in diffuse cutaneous systemic sclerosis the fibrotic manifestations may be more evident (e.g. widespread skin thickening, pulmonary fibrosis). Both limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis may occur in overlap with other connective tissue diseases. The acronym 'CREST' (calcinosis, Raynaud's, oesophageal dysmotility, sclerodactyly, telangiectases), although useful in that it reminds the clinican of five of the key features of systemic sclerosis, is now seldom used in sybtyping: most patients with what was termed CREST have limited cutaneous systemic sclerosis.

Clinical features and their investigation

A detailed discussion of all the clinical features of systemic sclerosis, their investigation and management is outwith the scope of this review. This section gives a brief overview of the main clinical manifestations (*Table 1*) and highlights key points with an emphasis on recent advances in diagnosis.

Systemic sclerosis affects the skin, the digital vasculature and the internal organs. Confronted by a patient with either a definite or suspected diagnosis of systemic sclerosis, the key issues are:

1. Is this systemic sclerosis and if so, is it limited cutaneous systemic sclerosis or diffuse cutaneous systemic sclerosis?
2. Is this early or late disease?
3. Which organs are likely to be involved from the history and examination?
4. What investigations are necessary at this stage?

Case Study 2

A 41-year-old woman presented with a 6-month history of puffy, swollen fingers, causing difficulty making a fist. Initially the rheumatologist queried inflammatory arthritis, but when reviewed 2 months later she had developed skin tightening of her fingers and hands, with flexion contractures of her fingers. She also reported recent development of Raynaud's phenomenon.

When reviewed a further 4 months later, she reported worsening of her skin tightness and increasing breathlessness and on examination had skin thickening most pronounced distally but extending proximally to involve upper arms, feet, lower legs, face and anterior chest wall. Pulmonary function testing showed a restrictive defect and high resolution computed tomography showed basal fibrosis with 'ground-glass' shadowing. Other investigation results included a normal full blood count, normal erythrocyte sedimentation rate, and a positive anti-Scl-70 (anti-topoisomerase-1) antibody.

She commenced treatment with monthly intravenous cyclophosphamide infusions (for 6 months) and prednisolone 10 mg daily, in addition to a calcium-channel blocker for her Raynaud's phenomenon and a proton pump inhibitor for heartburn. She had her blood pressure checked regularly, and was told to have her blood pressure checked immediately in the event of any new or deteriorating symptoms.

Is this systemic sclerosis and if so, it is limited or diffuse cutaneous?

The diagnosis of systemic sclerosis, and subtype, is made on clinical grounds as already discussed above. In the patient who presents with suspected systemic sclerosis, for example with Raynaud's phenomenon which has recently become more severe, then useful screening tests are the antinuclear antibody (which should be negative or only weakly positive in primary (idiopathic) Raynaud's phenomenon) and nailfold microscopy. Abnormal nailfold capillaroscopy (*Figure 5*) in the patient with Raynaud's phenomenon confers a relative risk of underlying connective tissue disease in the order of 13 (Carpentier and Maricq, 1990). If no light microscope is available then the nailfold capillaries may be visualized using an ophthalmoscope or dermatoscope.

Systemic sclerosis-specific autoantibodies associate with particular phenotypes (Reveille et al, 2003). The two systemic sclerosis-specific antibodies of most value in current practice are anticentromere, present in around 50–70% of patients with limited cutaneous systemic sclerosis, and anti-Scl-70 (also termed anti-topoisomerase-I), present in 30–40% of patients with diffuse cutaneous systemic sclerosis. There is an association between anti-Scl-70 and pulmonary fibrosis. Other autoantibodies sometimes found in patients with systemic sclerosis and their associations include anti-U1-RNP (overlap syndromes), anti-PM-Scl (myositis), anti-Ro (sicca symptoms), and the anti-RNA polymerases I, II and III (I and III are highly specific for systemic sclerosis but of low prevalence).

Is this early or late disease?

This is especially relevant in patients with diffuse cutaneous systemic sclerosis, who are at high risk of early, potentially life-threatening internal organ involvement in the first 3–5 years of their disease. Therefore patients with early diffuse cutaneous systemic sclerosis should be referred to a specialist centre and carefully monitored. The greater the extent of the skin involvement, as assessed using a clinical skin scoring system, the higher the mortality (Clements et al, 1990; Shand et al, 2007). In limited cutaneous systemic sclerosis the internal organ involvement most likely to be life-threatening is pulmonary arterial hypertension and (in contrast to internal organ involvement in diffuse cutaneous systemic sclerosis) this usually develops once the disease is well established, in other words many years after diagnosis.

Which organs are likely to be involved from the history and examination?

A detailed history and examination is required to identify which organs are likely to be involved (*Table 1*). Always check the blood pressure – patients with early diffuse cutaneous systemic sclerosis are at risk of renal crisis, especially in the first 5 years of their disease. Therefore

at-risk patients, as in *Case study 2*, should be advised to have regular blood pressure checks, and to attend immediately for a blood pressure check if they develop any new symptoms (e.g. headache, new breathlessness).

What investigations are necessary at this stage?

At the first assessment, the key investigations to perform on all patients are: urinalysis, full blood count and biochemical profile, erythrocyte sedimentation rate and/or C-reactive protein, autoantibody screen, nailfold microscopy (if possible), chest X-ray, pulmonary function tests (with transfer factor) (Wells et al, 1997) and an echocardiogram. Other investigations may be indicated on the basis of the history and examination. For example, most patients will require upper gastrointestinal investigations. All patients with systemic sclerosis should be under regular review, in order to identify internal organ involvement

Table 1. Key clinical manifestations of systemic sclerosis (this is not a comprehensive list)

'Organ'system	Clinical problem	Key symptoms and signs	Key investigations (if applicable)
Skin and subcutaneous tissues	Scleroderma	Skin thickening	Clinical skin score (although this is a clinical assessment rather than an investigation)
	Telangiectases	Telangiectases (blanch on pressure)	
	Calcinosis	Firm 'lumps' usually at pressure points (*Figure 4a*)	Easily visualized on plain radiography (*Figure 4b*)
Peripheral vasculature	Digital ischaemia	Raynaud's phenomenon, digital ulcers, gangrene	Nailfold microscopy. Ankle–brachial pressure indices to exclude concomitant lower limb large vessel disease
Gastrointestinal tract	Oesophageal dysmotility, gastro-oesophageal reflux, stricture	Difficulty swallowing and reflux symptoms	Barium swallow, gastroscopy, manometric studies
	Gastric antral vascular ectasia ('water-melon stomach')	Features of acute or chronic gastrointestinal bleeding	Gastroscopy
	Small bowel involvement with bacterial overgrowth	Symptoms of malabsorption, intestinal pseudo-obstruction, intestinal failure	Breath test for malabsorption, barium studies, plain radiography
	Lower bowel dysmotility and anorectal dysfunction	Constipation, faecal incontinence	Anorectal manometry
Lung	Pulmonary fibrosis	Breathlessness, basal crackles	Chest radiograph, pulmonary function tests (with diffusion), high resolution computed tomography
	Pulmonary arterial hypertension	Breathlessness, loud pulmonary component to second heart sound	Echocardiogram as a screening test (with estimation of the pulmonary artery pressure) (Denton et al, 1997), pulmonary function tests (looking for relatively normal lung volumes but reduced gas transfer), chest radiography, right heart catheterization (in specialist centres)
Heart	Conduction defects and arrhythmias	Palpitations, syncopy	Electrocardiogram, 24-hour electrocardiogram, chest radiography, echocardiogram, creatine kinase, troponin-1
	Pericardial effusion or pericarditis	Breathlessness, chest pain, signs of effusion or pericarditis	
	Myocardial fibrosis or myocarditis	Breathlessness, tachycardia, signs of heart failure	
Kidney/ genitourinary	Accelerated hypertension or renal crisis	Raised blood pressure, hypertensive retinopathy	Urinalysis, serum creatinine, estimated glomerular filtration rate
	Erectile dysfunction	Impotence	
Joint/tendon	Contractures	Contractures (for example of the fingers) (*Figure 1*), tendon friction rubs	
	Peripheral arthritis	Synovitis	Plain radiographs, rheumatoid factor (some patients develop a systemic sclerosis/rheumatoid arthritis overlap)
Muscle	Myopathy	Proximal muscle weakness	Creatine kinase, electromyography, muscle biopsy, magnetic resonance imaging
	Myositis	Proximal muscle weakness and tenderness	
Nervous system	Trigeminal neuropathy, carpal tunnel syndrome, peripheral neuropathy, autonomic neuropathy	Vary according to nature of problems	Nerve conduction studies for entrapment or peripheral neuropathy
Other	Sicca syndrome	Dry eyes, dry mouth	Schirmer's test

at an early stage by careful clinical assessment backed up by relevant investigations. For example, it is now widely accepted that all patients with systemic sclerosis should have regular pulmonary function tests and echocardiogram (with estimation of the pulmonary artery pressure) to help identify interstitial lung disease and pulmonary arterial hypertension. The pulmonary artery pressure can be elevated in patients with systemic sclerosis for two main reasons: pulmonary arterial hypertension (mainly in patients with limited cutaneous systemic sclerosis) and secondary to pulmonary fibrosis (seen in both limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis).

Management

The management of systemic sclerosis may be considered under the following headings:

1. General measures for all patients
2. Disease-modifying drugs (Charles et al, 2006)
3. Treatment of organ-specific manifestations, including digital ischaemia.

General measures

Systemic sclerosis is a frightening diagnosis for a patient. Therefore patient education is all important, including emphasis (when appropriate) that many patients with systemic sclerosis have relatively few symptoms, and that many aspects of the disease can be treated. Ideally all patients should be cared for by a skilled multidisciplinary team including a physiotherapist, occupational therapist and podiatrist. Toe ulceration and other foot problems are common in systemic sclerosis and can be a major problem (Sari-Kouzel et al, 2001) (*Figure 6*).

Disease-modifying drugs

The great challenge in systemic sclerosis is to identify disease-modifying drugs which will:

1. Prevent progression of disease in patients with early diffuse cutaneous systemic sclerosis. Despite several recent clinical trials there is currently no drug proven to favourably influence disease course, although there is some evidence in favour of immunosuppression (Nihtyanova et al, 2007). Ideally all patients with early diffuse cutaneous systemic sclerosis should be entered into clinical trials.
2. Prevent progression of vascular disease, especially in patients with limited cutaneous systemic sclerosis. Disappointingly a multicentre, placebo-controlled trial (Gliddon et al, 2007) reported that quinapril did not confer benefit on the vascular manifestations of limited cutaneous systemic sclerosis (primary endpoint number of new ischaemic ulcers). Further studies of drugs with the potential to remodel the vasculature are required.

Treatment of organ-specific manifestations

Although at present there is no 'cure' for systemic sclerosis, there are a number of effective treatments for organ-specific manifestations. The key points are:

Digital ischaemia

While conservative measures (keeping warm, stopping smoking) are important for all patients, most will also require drug treatment (Wigley, 2002). Calcium-channel blockers are first line (Thompson et al, 2001). Other vasodilators may also be tried. In patients with systemic sclerosis (in contrast with those with primary Raynaud's phenomenon), Raynaud's phenomenon is associated with structural vascular abnormality and can progress to ulceration and gangrene (*Figures 2* and *6*). Therefore acute digital ischaemia and/or digital ulceration in a patient with systemic sclerosis is a medical emergency as

Figure 4. a. Infected calcific bursitis in a patient with systemic sclerosis. b. The plain radiograph showing extensive calcinosis in the prepatellar bursa. This is a particularly severe case.

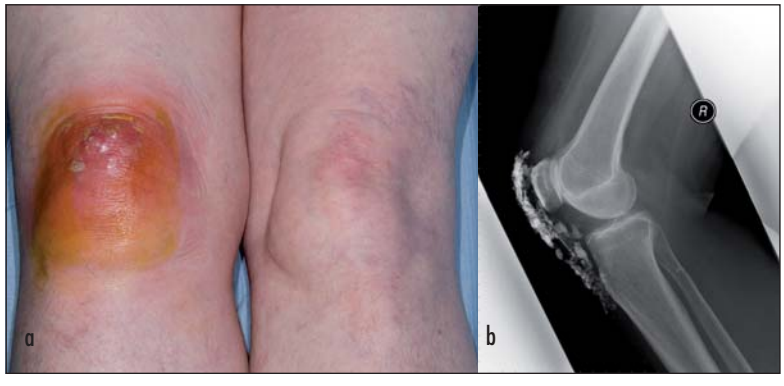


Figure 5. Nailfold capillaroscopy showing (a) normal capillaries and (b) enlarged, abnormal capillaries with areas of loop drop-out in a patient with systemic sclerosis.

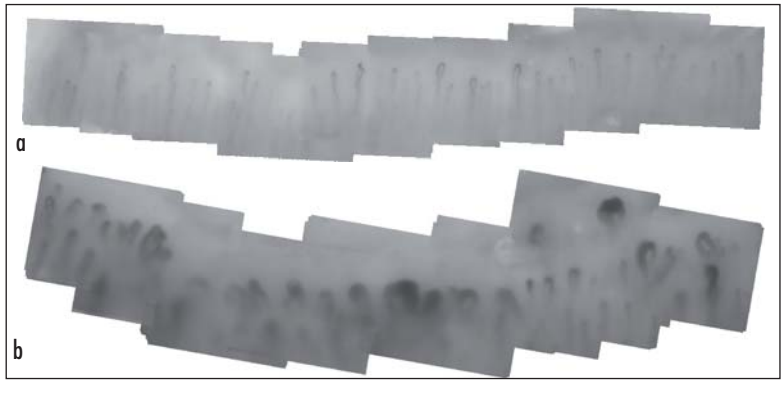
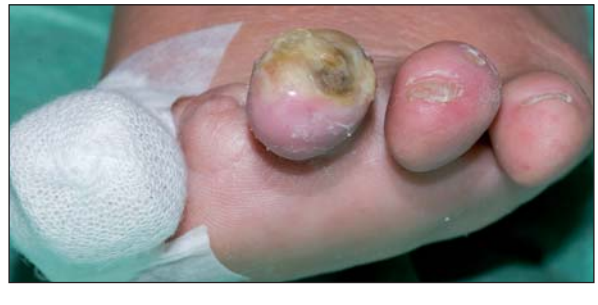


Figure 6. Ulceration and ischaemia of the third toe in a patient with systemic sclerosis. The second toe has been amputated.



the patient is at high risk of losing the digit (*Case study 1*). In the UK, intravenous prostanoids (Wigley et al, 1994) are first-line management for severe ischaemia or ulceration, along with antibiotics, analgesics, and sometimes surgery (usually debridement of infected or necrotic tissue, less commonly amputation or digital sympathectomy).

Gastrointestinal

Proton-pump inhibition, often required in high dosage, has revolutionized the lives of many patients with systemic sclerosis, as this can be extremely effective in controlling symptoms of reflux. Some patients benefit from prokinetic drugs, such as metoclopramide. Antibiotics (often given cyclically) should be prescribed for bacterial overgrowth. A small proportion of patients develop intestinal failure and these patients should be identified early because nutritional support, including with total parenteral nutrition (Brown et al, 2008), may be life-saving.

Pulmonary fibrosis

Two studies (Hoyles et al, 2006; Tashkin et al, 2006) have shown that cyclophosphamide (in the UK-based study given with low dose prednisolone; Hoyles et al, 2006) confers benefit in systemic sclerosis-associated pulmonary fibrosis, although this benefit was modest. Another point to highlight is that experience of lung transplantation in patients with systemic sclerosis is increasing (Schachna et al, 2006), therefore transplantation should be considered in carefully selected patients.

Pulmonary arterial hypertension

This has been an exciting area in systemic sclerosis-related therapeutics in recent years because a range of therapies is now available: prostanoids (intravenous, subcutaneous or inhaled) (Badesch et al, 2000; Olschewski et al, 2002; Oudiz et al 2004), endothelin-receptor antagonists (Rubin et al, 2002), and phosphodiesterase inhibitors (Galie et al, 2005). These advances in management, including early diagnosis and initiation of treatment, are leading to improved survival (Williams et al, 2006). Therefore if pulmonary hypertension is suspected, on the basis of clinical features and/or a raised estimated pulmonary artery pressure on echocardiography, then the patient should be referred to a pulmonary hypertension unit for further assessment including right heart catheterization.

Accelerated hypertension or renal crisis

This is a medical emergency. The patient must be hospitalized. The improved treatment of renal crisis, including use of angiotensin-converting enzyme (ACE) inhibition, means that renal crisis is no longer the major contributor to disease-related mortality (now overtaken by pulmonary fibrosis and pulmonary hypertension; Steen and Medsger, 2007). A proportion of patients requiring dialysis become dialysis independent. As with the lung, there is increasing experience with transplantation.

Cardiac

Broadly speaking cardiac problems are treated as in patients without underlying systemic sclerosis.

Overlap syndromes

Patients with systemic sclerosis and overlapping features with systemic lupus erythematosus, myositis, sicca syndrome or rheumatoid arthritis should be treated similarly to other patients with these diseases but with the proviso that steroids must be used cautiously, especially in patients with early diffuse cutaneous systemic sclerosis, as there is an association between high dose steroid use and the development of renal crisis (Steen and Medsger, 1998).

Other

There are many other aspects to treatment, including surgical debulking (in specialist units) of areas of calcinosis, and camouflage and laser treatment of telangiectases. A key point is always to consider whether other treatment options are available.

Conclusions

Systemic sclerosis is a multisystem disease characterized by fibrosis and ischaemia, and associated with major morbidity and mortality. There are two major subtypes – limited and diffuse cutaneous – and a key advance has been the recognition of the importance of subtyping, both for the clinician and for the researcher, as the two subtypes have different natural histories and prognoses.

Systemic sclerosis affects the skin, the peripheral vasculature and most internal organs and therefore its clinical features are diverse. All patients with systemic sclerosis should be under regular review, assessing for development or progression of any aspect of their disease. This regular review will include checks of cardiorespiratory function, the aim being to identify subclinical disease: many patients with systemic sclerosis do not complain of breathlessness as exercise tolerance is often impaired for other reasons, such as immobility.

There is no longer any place for therapeutic nihilism in patients with systemic sclerosis; although we still need to find a drug which will cure the disease, many of the internal organ manifestations can be effectively treated or at least ameliorated. Clinical trials in systemic sclerosis have in the past been difficult to mount or unsatisfactory because of the rarity of the disease and the failure to adequately subtype disease. International clinical trial networks are now in place, facilitating clinical trials of new treatment approaches. **BJHM**

Conflict of interest: Dr Herrick has undertaken consultancy work for Actelion and spoken at meetings sponsored by Actelion.

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KEY POINTS

- Systemic sclerosis is characterized by fibrosis and ischaemic atrophy and therefore differs from other connective tissue diseases, most of which have a major inflammatory component.
- There are two major subtypes – limited cutaneous and diffuse cutaneous – with different natural histories, autoantibody associations and prognoses.
- 'Scleroderma' (skin thickening) is the most typical clinical manifestation of systemic sclerosis, but may occur in other conditions.
- Although there is no cure for systemic sclerosis, many effective treatments are available for the different organ-based manifestations.
- Cardiorespiratory disease (mainly pulmonary fibrosis and pulmonary hypertension) is now the major contributor to mortality and should be identified early.
- Increased understanding of pathophysiology is directing development of new avenues of therapy.
- International networking of clinicians with an interest in systemic sclerosis is facilitating clinical trials.