Systemic sclerosis

This review updates the clinician on the pathogenesis, differential diagnosis and spectrum of disease in systemic sclerosis. The wide range of current therapeutic options and future targeted molecular therapies are also explored.

Systemic sclerosis, often referred to as 'scleroderma', is a highly heterogeneous connective tissue disease. Although uncommon, it affects many organ systems and so is a major cause of morbidity and mortality in those affected. A range of clinicians may be involved in the care of patients with systemic sclerosis. The clinical spectrum of disease, including the significance of Raynaud's phenomenon and overlap with other autoimmune disorders, will be discussed. Relevant investigations (including immunological tests), advances in treatment and future targeted molecular therapies will be explored. This article gives an overview for the general physician: more detailed discussions can be found in recent review articles cited below.

Epidemiology

The incidence of systemic sclerosis is approximately 10–20 cases/million per year. This is increasing, possibly as a result of improved awareness and diagnosis (Nikpour et al, 2010). Females are more commonly affected, often during child-bearing years, with a female to male ratio ranging from 3:1 to 8:1 (Valentini and Black, 2002). Familial cases of systemic sclerosis reflect how genetic factors contribute to pathogenesis, and indeed a family history is the most significant risk factor known for the development of systemic sclerosis. The high prevalence in Choctow Indians has been linked to a single nucleotide polymorphism in the fibrillin-1 gene. A number of environmental and occupational agents (e.g. silica and organic solvents) may induce a scleroderma-like phenotype: these are listed in *Table 1* (Gabrielli et al, 2009).

Pathogenesis

A full review of the current understanding of the pathogenesis of systemic sclerosis is beyond the scope of this article. There is a complex interplay between vascular and immune abnormalities, and fibrosis. These will be discussed in turn, correlating pathophysiology with the clinical phenotype.

Vascular abnormalities

Endothelial injury with vascular dysfunction is believed to be an early event in the development of systemic sclerosis (Gabrielli et al, 2009; Katsumoto et al, 2011). Progressive obliteration of the microvessels, with episodes of ischaemia-reperfusion injury to the skin and internal organs, is thought to contribute to the development of fibrosis and organ dysfunction (Hummers et al, 2009).

A vasculopathy of the small blood vessels contributes to the digital ischaemia which is often an early manifestation of systemic sclerosis and which can progress to irreversible tissue injury with gangrene. Telangiectases are another very visible manifestation of this microangiopathy. Pulmonary artery hypertension is a further vascular manifestation, this time affecting large vessels. Scleroderma renal crisis is another potentially life-threatening vascular manifestation of systemic sclerosis (Hummers et al, 2009).

Immunological abnormalities

An early perivascular infiltrate of mononuclear cells is seen in systemic sclerosis, including B and T lym-

Table 1. Scleroderma 'mimics' (i.e. conditions other than systemic sclerosis and localized scleroderma)

Congenital	Stiff skin syndrome
	Genetic disorders (premature ageing syndromes), e.g. Werner's syndrome
Inflammatory/ autoimmune	Eosinophilic fasciitis
	Graft *vs* host disease
	Nephrogenic systemic fibrosis
	Scleroedema
	Scleromyxoedema
	Diabetic cheiroarthropathy
	Thyroid disease
	Amyloidosis, carcinoid syndrome, phaeochromocytoma, phenylketonuria, porphyria cutanea tarda
Drug/chemical induced	Aniline-contaminated rapeseed oil (toxic oil syndrome)
	L-tryptophan (eosinophilia-myalgia syndrome)
	Bleomycin, carbidopa, pentazocine
Occupational exposure	Epoxy resins, polyvinyl chloride, radiation fibrosis, silica
Miscellaneous	Paraneoplastic

From Haustein (2005); Nashel and Steen (2012)

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phocytes, macrophages and mast cells (Gabrielli et al, 2009). The presence of specific autoantibodies in patients with systemic sclerosis further denotes an immune component; the significance of these will be discussed later.

Tissue fibrosis

Systemic sclerosis is characterized by intense fibrosis, for example of the skin and of the lung bases. The fibrotic response seen in systemic sclerosis is an unregulated variant of normal wound healing and of embryonic tissue development (Bhattacharyya et al, 2011). The normal architecture of tissues is replaced by excess extracellular matrix proteins, including collagen and fibrillin (Bhattacharyya et al, 2011). Transforming growth factor beta (TGF-β) is a key profibrotic mediator in systemic sclerosis.

The spectrum of systemic sclerosis disorders

'Scleroderma' refers to a thickening of the skin. It may be localized to the skin and subcutaneous tissues (when it is often termed 'morphoea'). In systemic sclerosis, scleroderma occurs together with involvement of the internal organs. Systemic sclerosis may occur with features of other connective tissue diseases, i.e. overlap syndromes, which will be discussed later.

It is important for the clinician to be aware of a group of 'scleroderma mimics', i.e. conditions causing scleroderma other than systemic sclerosis or localized scleroderma (*Table 1*). These can be distinguished by careful clinical assessment. Sparing of the extremities or the absence of Raynaud's phenomenon make systemic sclerosis unlikely (although in diffuse cutaneous systemic sclerosis the onset of Raynaud's phenomenon can occur after the onset of skin thickening).

Diagnosis and classification of systemic sclerosis

There is no single diagnostic test for systemic sclerosis. The diagnosis is clinical, but may be informed by the results of investigations, e.g. by autoantibody status. New diagnostic criteria are in joint development by the American College of Rheumatology and the European League Against Rheumatism (Fransen et al, 2012). The currently used American College of Rheumatology preliminary criteria (Masi et al, 1980) are thought to be insufficiently sensitive, especially for limited cutaneous systemic sclerosis. These criteria are either skin thickening proximal to the metacarpophalangeal joints or two of: sclerodactyly (skin thickening of the fingers), digital pitting scars of the fingertips, bibasilar pulmonary fibrosis.

Systemic sclerosis is usually divided into two subtypes, limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis, based on the extent of the skin involvement: in diffuse cutaneous systemic sclerosis, skin thickening is not confined to the extremities but extends to involve proximal limb and/or trunk. Key features of the subtypes are presented in *Table 2*. The acronym CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangiectases) was previously used to describe limited cutaneous systemic sclerosis but has fallen out of favour, largely because patients with diffuse cutaneous systemic sclerosis may also have all the features of CREST.

Table 2. Subtypes of systemic sclerosis

Limited cutaneous systemic sclerosis	Diffuse cutaneous systemic sclerosis
Raynaud's phenomenon for many years	Onset of Raynaud's phenomenon within a year of skin change
Skin change limited to hands, feet, face and forearms	Truncal and acral skin involvement
Late onset of pulmonary artery hypertension, trigeminal neuralgia, calcinosis and telangiectases	Early onset of pulmonary fibrosis, renal failure, myocardial involvement, and gastrointestinal disease

From LeRoy et al (1988)

Clinical manifestations

Systemic sclerosis may involve most of the internal organs, so a full history and physical examination are necessary. Clinical features and the approach to their investigation are summarized in *Table 3*. The clinician must be ever vigilant as to the varied manifestations of systemic sclerosis. Rarely, organ involvement may occur in the absence of skin thickening (systemic sclerosis sine scleroderma). The different cutaneous manifestations of systemic sclerosis, digital vasculopathy (including Raynaud's phenomenon), and overlap syndromes with other autoimmune disorders are further discussed below.

Cutaneous manifestations

A variety of skin changes may be seen in systemic sclerosis in addition to the characteristic feature of scleroderma. Often the scleroderma begins with non-pitting oedema of the extremities that gradually hardens to produce the classical scleroderma appearance (Krieg and Takehara, 2009). In patients with the diffuse cutaneous subtype of systemic sclerosis, the skin thickening then extends proximally. When the skin later atrophies, it may soften and skin involvement may therefore be more difficult to detect. The degree of skin involvement has a prognostic role, as the higher the initial skin score, the worse the prognosis. Other skin changes that may be seen include hypo- and hyperpigmentation, telangiectases (*Figure 2*) and calcinosis (Krieg and Takehara, 2009). Trophic changes including the loss of the sebaceous glands result in dry skin, and there may be intense pruritis (Krieg and Takehara, 2009). Skin disease can cause significant morbidity with pain, ulceration and joint contractures, including of the fingers (*Figure 3*).

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Table 3. Clinical manifestations of systemic sclerosis (this is not an exhaustive list)

Organ system (prevalence)	Clinical manifestations	Brief descriptions and summary points	Suggested investigations and assessments
Skin and subcutaneous tissue	Scleroderma	Skin thickening (including sclerodactyly), tethering, trophic changes, microstomia	Skin scoring systems, e.g. modified Rodnan, skin biopsy (rarely needed)
	Telangiectases	Dilated superficial blood vessels, blanch with pressure	
	Calcinosis	Calcium-containing deposits which may ulcerate through skin	Plain radiographs
Musculoskeletal	Contractures	Contractures of fingers and at other sites (e.g. elbows, ankles), may be associated with tendon friction rubs	Functional assessment of disability related to contractures
	Arthritis	Peripheral synovitis (especially in patients with rheumatoid arthritis overlap)	Radiographs of hands and feet to detect erosive change, immunology: rheumatoid factor+/- anti-CCP antibodies
Muscle (15–20%)	Myopathy or myositis	Pain, proximal muscle weakness, tenderness on palpation	Creatinine kinase, electromyelogram, magnetic resonance imaging, muscle biopsy
Gastrointestinal (50–90%)	Oesophageal dysmotility	Gastrointestinal reflux, dysphagia	Upper gastrointestinal endoscopy, barium swallow, manometric studies
	Oesophageal stricture or Barrett's oesophagus	Secondary to chronic oesophageal reflux	Upper gastrointestinal endoscopy, biopsy of suspicious lesion(s)
	Gastroparesis	Early satiety, nausea and vomiting, regurgitation, abdominal pain	Gastric emptying studies
	Gastric antral vascular ectasia ('watermelon stomach')	Acute and chronic gastrointestinal bleeding, iron deficiency anaemia	Upper gastrointestinal endoscopy
	Small bowel dysmotility +/- bacterial overgrowth	Malabsorption, pseudo-obstruction and risk of perforation, intestinal failure	Barium studies, breath test for malabsorption, plain abdominal radiograph
	Large bowel dysmotility and anorectal involvement	Altered bowel habit, abdominal pain, faecal incontinence	Anorectal manometry, other investigations as appropriate for altered bowel habit
Respiratory (40–80%)	Interstitial lung disease	May be asymptomatic, shortness of breath, dry cough, reduced exercise tolerance. Fine bibasal crackles on auscultation	Chest radiograph, high resolution computed tomography scan of thorax (*Figure 1*), pulmonary function tests (with transfer factor)
	Pulmonary arterial hypertension	May be asymptomatic, shortness of breath, reduced exercise tolerance. On examination, accentuation of second heart sound at the pulmonary area, features of right-sided heart failure	Transthoracic echocardiogram, including estimation of pulmonary artery pressure. Pulmonary function tests (with transfer factor). Right heart catheter in specialist centres
	Restrictive ventilatory defect	Secondary to restrictive chest wall skin involvement	Pulmonary function tests
	Aspiration pneumonitis	Secondary to oesophageal dysmotility	Blood tests including inflammatory markers, chest X-ray
Cardiac (20–25%)	Conduction system disturbance or arrhythmia	May be asymptomatic, palpitations, syncope	Electrocardiogram, 24-hour (or longer) rhythm monitoring, e.g. Holter
	Myocarditis or myocardial fibrosis	Chest pain, palpitations, heart failure	Cardiac troponins for risk stratification in suspected acute coronary syndrome
	Pericarditis or pericardial effusion	Chest pain, shortness of breath, heart failure	Chest radiograph, transthoracic echocardiogram
Renal (5–10%)	Scleroderma renal crisis	Acute kidney injury, hypertensive emergency, microangiopathic haemolytic anaemia	Urine dip and renal function, haemolytic screen, blood film (looking for red cell fragments)
Peripheral vascular (90–95%)	Raynaud's phenomenon	Colour change (triphasic) of the extremities	Capillaroscopy (to look for 'scleroderma pattern' in patients presenting with Raynaud's phenomenon)
	Digital or peripheral ischaemia		Clinical assessment: finger pulp loss, necrosis, gangrene, arterial Dopplers with ankle–brachial pressure index to exclude proximal large vessel disease
Nervous system (5%)	Peripheral neuropathy, autonomic neuropathy, carpal tunnel syndrome, trigeminal neuralgia	Varying symptoms and signs according to nature of lesion; carpal tunnel syndrome, common in early diffuse cutaneous systemic sclerosis, may improve once initial inflammatory phase resolves	Nerve conduction studies for peripheral lesions
Other	Secondary Sjögren's syndrome	Sicca symptoms: dry eyes, dry mouth	Schirmer's test

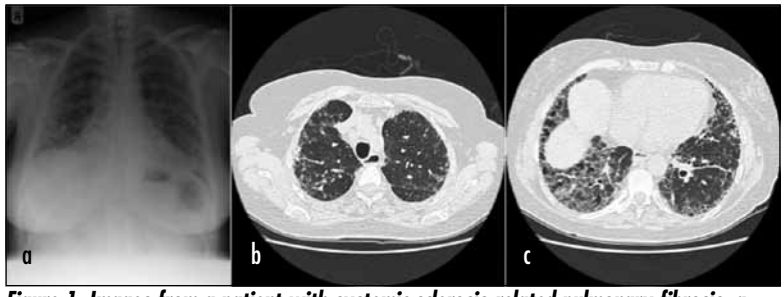
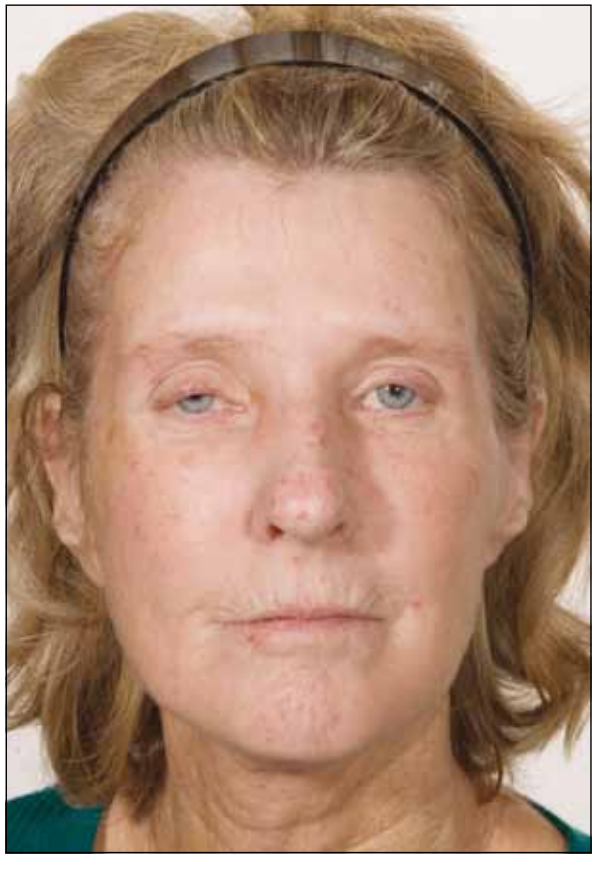


Figure 1. Images from a patient with systemic sclerosis-related pulmonary fibrosis. a. Chest radiograph demonstrating bibasal opacification consistent with pulmonary fibrosis. b. High resolution computed tomography image through the upper zones demonstrating peripheral predominantly interstitial shadowing. c. High resolution computed tomography chest image through the lung bases showing both interstitial and airspace shadowing, the appearances are in keeping with non-specific interstitial pneumonia. There is also significant traction bronchiectasis.

Raynaud's phenomenon or digital vasculopathy

Raynaud's phenomenon classically presents as a triphasic colour change of the fingers (and often the toes) in response to cold or emotional stimuli (Wigley, 2002; Goundry et al, 2012). Typical attacks consist of a colour change from white (ischaemia), to blue (deoxygenation), and then painfully red (reperfusion) (Goundry et al, 2012). While up to 12.5% of men and 20% of women report symptoms consistent with Raynaud's phenomenon (Goundry et al, 2012), in most patients this is primary (idiopathic).

Figure 2. Cutaneous features of systemic sclerosis, with telangiectases (particularly over the nose) and puckering of the skin around the mouth.



Raynaud's phenomenon associated with systemic sclerosis differs from primary Raynaud's phenomenon in that it is generally more severe and can progress to irreversible tissue injury with ulceration and critical ischaemia (*Figure 4*). Raynaud's phenomenon is present in over 95% of patients with systemic sclerosis. Features that may alert the clinician to the presence of a systemic sclerosis-spectrum disorder in the patient presenting with Raynaud's phenomenon, and the need for further investigation are listed below (Kallenberg, 1990):

Figure 3. Sclerodactyly (the skin is tight and shiny) with fixed flexion deformities of the fingers (the patient is unable to place the palmar aspects of the hands together).

Figure 4. Digital ulceration in a patient with systemic sclerosis. There is a healing digital ulcer of the fingertip.

- Age of onset ≥30 years
- Severe ischaemic pain and/or ischaemic lesions, e.g. necrosis, gangrene
- Features of a connective tissue disease (including autoantibodies)
- Abnormal nailfold capillaroscopy.

The presence of a systemic sclerosis-specific antibody and abnormal nailfold capillaroscopy (both described below) are independent predictors for the development of systemic sclerosis in the patient presenting with Raynaud's phenomenon (Koenig et al, 2008).

Overlap with other autoimmune diseases

In up to 20% of patients, systemic sclerosis may overlap with other connective tissue diseases including polymyositis, systemic lupus erythematosus and Sjögren's syndrome. Systemic sclerosis-rheumatoid arthritis overlap is increasingly recognized. Other autoimmune disorders associated with systemic sclerosis include autoimmune thyroid disease, coeliac disease and primary biliary cirrhosis.

Investigations

Table 3 suggests investigations of relevance to discrete organ involvement. The significance of autoantibodies, and some specialist investigations are described below.

Autoantibodies

Antinuclear antibody (ANA) is positive in approximately 95% of patients. Extractable nuclear antigens (ENA) are seen in over 50% of patients with systemic sclerosis (Nihtyanova and Denton, 2010). The three most frequently observed are listed below; these are usually mutually exclusive (Nihtyanova and Denton, 2010). These may aid the clinician not only in the diagnostic process, but also provide prognostic information including likely subtype and the risk of specific organ involvements.

- Anti-centromere antibody: associated with limited cutaneous systemic sclerosis (50–70% of patients) and pulmonary artery hypertension. Protective against pulmonary fibrosis and scleroderma renal crisis
- Anti-topoisomerase antibody (anti-Scl-70): associated with diffuse cutaneous systemic sclerosis (30–40% of patients), pulmonary fibrosis and digital vasculopathy
- Anti-RNA polymerase III antibody: associated with diffuse cutaneous systemic sclerosis and scleroderma renal crisis.

Other autoantibodies that may be found in systemic sclerosis patients include anti-Ro/La (sicca symptoms), anti-PM-Scl (myositis) and anti-U1-RNP (overlap syndromes).

Specialist investigations

Nailfold capillaroscopy is a non-invasive tool that allows direct visualization of the digital microvasculature: abnormalities in systemic sclerosis include capillary dilation, haemorrhages, areas of avascularity and distortion of the normal nailfold architecture (Cutolo et al, 2010) (*Figure 5*). Thermography, which measures surface temperature, is available in some specialist centres (*Figure 6*): responses to a temperature challenge can help differentiate between primary and systemic sclerosis-related Raynaud's phenomenon.

Prognosis

Despite there being no 'cure' for systemic sclerosis, the prognosis has improved in the past few decades. The cause of systemic sclerosis-related death has changed – whereas previously this was mostly the result of the scleroderma renal crisis, this is now mainly a result of pulmonary artery hypertension and pulmonary fibrosis (Steen and Medsger, 2007; Tyndall et al, 2010).

Management of systemic sclerosis

General management for all patients with systemic sclerosis

Although in the past there has often been a nihilistic attitude towards treatment of systemic sclerosis, this has changed. A great deal can be done to reduce pain and morbidity, and to improve quality of life and survival.

The management of systemic sclerosis is truly multidisciplinary in nature, including physiotherapy, occupa-

Figure 5. Nailfold capillaroscopy. a. Normal capillaroscopy pattern in a healthy subject. b. Abnormal capillaroscopy in a patient with systemic sclerosis demonstrating gross capillary enlargement and distortion of the normal nailfold architecture.

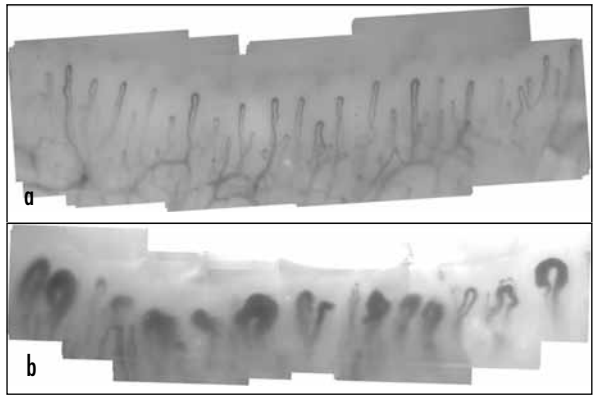
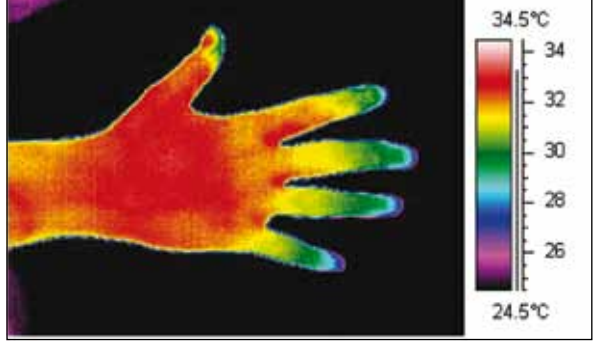


Figure 6. Thermographic image from a patient with Raynaud's phenomenon at 23°C, showing a marked temperature gradient between the distal fingers and the dorsum of the hand.



tional therapy, podiatry and dietetics. The psychological distress associated with the diagnosis of systemic sclerosis may be considerable and patients may benefit from input from a specialist nurse and/or psychologist.

General and organ-specific treatment modalities, possible disease-modifying therapy and current areas of research including targeted molecular therapeutics are briefly reviewed here. It is outwith the scope of this review to discuss in detail treatment of digital ischaemia and of all the internal organ involvements: these are described in the European League Against Rheumatology recommendations (Kowal-Bielecka et al, 2009).

Organ-specific management

Raynaud's phenomenon

General measures for all patients with Raynaud's phenomenon include avoiding cold exposure, wearing warm clothes and smoking cessation. If general measures are ineffective, then drug treatment is indicated (Herrick, 2011). Calcium-channel blockers, e.g. nifedipine, are first-line therapy: although side effects are common, these may be less troublesome with sustained-release preparations. Angiotensin II receptor antagonists, e.g. losartan, are also widely used. Other options include angiotensin-converting enzyme (ACE) inhibitors, alpha blockade and selective serotonin-reuptake inhibitors (Goundry et al, 2012). Digital ulcers, which may be infected, should be promptly assessed and treated appropriately. Intravenous prostanoids, e.g. iloprost, confer benefit in patients with systemic sclerosis and active digital ulcers. The endothelin-1 receptor antagonist bosentan is licenced for prevention of recurrent ulcers (Kowal-Bielecka et al, 2009). Digital (palmar artery) sympathectomy is a highly specialist intervention that may be considered in Raynaud's phenomenon unresponsive to the above drug therapies (this is usually in the context of non-healing digital ulcers and/or critical ischaemia).

Gastrointestinal

Gastrointestinal involvement is very common in systemic sclerosis, occurring in 50–90% of patients (Forbes and Marie, 2008). Malnutrition may be multi-factorial in aetiology, e.g. reduced oral intake, oesophageal dysmotility, small bowel overgrowth and pancreatic exocrine deficiency. Delayed gastric emptying from gastroparesis may contribute to gastro-oesophageal reflux (Forbes and Marie, 2008). Symptomatic gastro-oesophageal reflux disease may be treated with proton pump inhibition and prokinetic agents (Gyger and Baron, 2012). Bleeding from gastric antral vascular ectasia ('watermelon stomach') may be amenable to endoscopic treatment with laser or argon plasma coagulation (Gyger and Baron, 2012). Small bowel overgrowth should be appropriately treated with antibiotic therapy.

Co-existent coeliac disease should be considered in view of the autoimmune basis of systemic sclerosis, and treated with a gluten-free diet. Anorectal involvement is seen in approximately 40% of patients (Forbes and Marie, 2008) and faecal incontinence may be a major cause of morbidity. There is increasing experience in the use of sacral nerve stimulation (Forbes and Marie, 2008). The timely and judicious use of different enteral and parenteral feeding routes may be life saving.

Renal

Scleroderma renal crisis occurs in 5–10% of systemic sclerosis patients. This may present with acute onset hypertension, acute kidney injury, fever, hypertensive retinopathy, encephalopathy and pulmonary oedema (Denton et al, 2009). Steroid therapy is associated with an increased risk of scleroderma renal crisis (Kowal-Bielecka et al, 2009). Earlier diagnosis and ACE inhibitors have radically improved the prognosis of scleroderma renal crisis. ACE inhibition may prevent or even reverse renal failure (Steen and Medsger, 2007). Renal recovery may occur even if renal replacement therapy is established (Tyndall et al, 2010).

Respiratory

Pulmonary artery hypertension and pulmonary fibrosis now have the most dramatic impact on overall survival in systemic sclerosis (Le Pavec et al, 2010). For pulmonary artery hypertension there is a range of effective therapeutic options available, which are leading to improved survival (Williams et al, 2006). These include endothelin receptor antagonists (e.g bosentan), phosphodiesterase inhibitors (e.g. sildenafil) and prostanoids (inhaled, intravenous or subcutaneous) (Nihtyanova and Denton, 2007). Early diagnosis of pulmonary artery hypertension is essential: active screening of patients includes regular (ideally annual) transthoracic echocardiography. The gold standard for the diagnosis of systemic sclerosis-related pulmonary artery hypertension is right-heart catheterization, which also enables an assessment of the response of the pulmonary vasculature to vasodilators, thus directing therapy (Wells et al, 2009). Patients with pulmonary artery hypertension, or suspected pulmonary artery hypertension, should be referred to a specialist pulmonary artery hypertension centre.

Cyclophosphamide, a cytotoxic agent, should be considered in the treatment of pulmonary fibrosis (Kowal-Bielecka et al, 2009; Wells et al, 2009), based upon evidence from two high-quality randomized controlled trials, the scleroderma lung study and fibrosing alveolitis in scleroderma trial (Kowal-Bielecka et al, 2009). The scleroderma lung study showed a modest benefit in forced vital capacity from cyclophosphamide compared to placebo (2.53% at 12 months) (Tashkin et al, 2006), findings supported by the fibrosing alveolitis in scleroderma trial (Hoyles et al, 2006). Cyclophosphamide can cause significant toxicity, e.g. bone marrow suppression and haemorrhagic cystitis, and so should be used with caution.

Skin disease

There is some suggestion from two randomized controlled trials that methotrexate improves the skin score in early diffuse systemic sclerosis (Kowal-Bielecka et al, 2009). Although methotrexate and other immunosuppressive agents including cyclophosphamide, mycophenolate mofetil and azathioprine are used by many clinicians for skin thickening (Kowal-Bielecka et al, 2009), there is no good evidence base that these confer benefit. A European observational trial addressing this issue is currently underway.

Cardiac

The majority of patients with systemic sclerosis have cardiac involvement (conducting system, myocardial and/or pericardial) although this may be subclinical (Kahan et al, 2009). Heart failure may occur as a primary myocardial process, or secondary to pulmonary artery hypertension. Left ventricular dysfunction should be treated with standard therapy, e.g. ACE inhibition or diuretics (Kahan et al, 2009). A high index of suspicion should be maintained for conduction system disease. The insertion of an implantable cardiac defibrillator is indicated in the presence of potentially life-threatening ventricular arrhythmias.

Steroids and disease-modifying drugs

Steroid therapy is relatively contraindicated in patients with systemic sclerosis because of concerns of an increased risk of scleroderma renal crisis. However, they may be indicated in patients with myositis, other overlap syndromes, and often in combination with cyclophosphamide in patients with interstitial lung disease. Doses used should be kept as low as possible. With the success of disease-modifying antirheumatic drugs in other autoimmune rheumatic diseases, there has been great interest in trying to identify drugs with the potential to favourably influence the underlying disease process (including skin thickening) in systemic sclerosis. However, to date no disease-modifying antirheumatic drug has been shown to be unequivocally effective (Quillinan and Denton, 2009). Although mycophenolate mofetil, methotrexate and azathioprine are used by many clinicians, their effectiveness remains unknown (Quillinan and Denton, 2009).

Future therapeutic targets

A rapidly developing understanding of the pathological mechanisms underpinning systemic sclerosis has led to an expanding number of novel therapies entering clinical trial. Targeted therapies towards the vascular, immune and aberrant fibrotic responses in systemic sclerosis are being or have recently been investigated. These include targeting of the profibrotic pathway with the tyrosine kinase inhibitor imatinib, B-cell depletion (CD20), e.g. rituximab, and interleukin-6 receptor inhibition, e.g. tocilizumab. The results of multicentre studies of haematopoietic autologous stem cell transplantation are eagerly awaited.

Conclusions

Systemic sclerosis remains a challenging disease. There have been significant advances in the understanding of its aetiopathogenesis. For the clinician, the key point is that a careful history and physical examination are required at the time of diagnosis and regularly during follow up, with a high index of clinical suspicion for the varied manifestations of systemic sclerosis (the aim being to identify internal organ involvement at an early stage). The management of systemic sclerosis requires a multidisciplinary approach. Advances in the therapeutics of systemic sclerosis have been translated into an improvement in survival. The development of novel therapeutics based upon the increased understanding of the molecular basis of systemic sclerosis is an exciting emerging area. The development of international systemic sclerosis clinical trial networks is helping to facilitate high quality research. BJHM

Computed tomography images in Figure 1 *are reproduced courtesy of Dr Roger Chisholm.*

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KEY POINTS

- Systemic sclerosis is a highly heterogeneous, multi-system autoimmune connective tissue disease.
- There is a differential diagnosis to scleroderma (skin thickening) including localized scleroderma (morphoea), eosinophilic fasciitis and drug/chemical induced.
- Aetiopathogenesis is complex, including abnormalities of the vascular and immune systems with an aberrant fibrotic response.
- Respiratory disease (pulmonary fibrosis and pulmonary artery hypertension) is now the leading cause of systemic sclerosis-related death.
- There is a range of effective treatments for Raynaud's phenomenon or digital ischaemia and for organ involvement.
- New treatments are in development based on advances in understanding of the aberrant molecular and cellular biology in systemic sclerosis.

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