Systemic sclerosis

ABSTRACT

Systemic sclerosis is a complex autoimmune connective tissue disease which carries a significant burden of disease-related morbidity including potentially life-threatening complications. Systemic sclerosis can affect all the major organs and therefore, although the disease is uncommon, many hospital-based specialists are involved in patient care. Vascular disease (e.g. Raynaud's phenomenon) is an almost universal symptom in patients with systemic sclerosis and is often the earliest manifestation of the disease. Systemic sclerosis not uncommonly can overlap with other rheumatological conditions (e.g. rheumatoid arthritis and myositis). During the past few decades there have been major advances in understanding the pathogenesis of systemic sclerosis and these are driving advances in treatment. There are now a number of effective treatments to manage many of the different organ-based complications. Autologous haemopoietic stem cell transplantation is a potential treatment option in highly selected patients. This review updates the clinician about epidemiology, pathogenesis, differential diagnosis, the wide clinical spectrum of disease, and current and emerging treatments for systemic sclerosis.

Systemic sclerosis is a complex autoimmune connective tissue disease which carries a significant burden of disease-related morbidity. Systemic sclerosis can affect all the major organs, so many hospital-based specialists are involved in patient care. Vascular disease is an almost universal symptom in patients with systemic sclerosis and is often the earliest manifestation of the disease. Systemic sclerosis not uncommonly can overlap with other rheumatological conditions. Advances in understanding the pathogenesis of systemic sclerosis are driving advances in treatment. There are now a number of effective treatments to manage many of the different organ-based complications. Autologous haemopoietic stem cell transplantation is a potential treatment option in highly selected patients. This review updates the clinician about epidemiology, pathogenesis, differential diagnosis, the wide clinical spectrum of disease, and current and emerging treatments for systemic sclerosis.

Dr Michael Hughes, Consultant Rheumatologist, Department of Rheumatology, Royal Hallamshire Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield S10 2JF

Professor Ariane L Herrick, Professor of Rheumatology, Centre for Musculoskeletal Research, The University of Manchester, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester and NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester

Correspondence to: Dr M Hughes
(Michael.hughes-6@postgrad.manchester.ac.uk)

Epidemiology

Systemic sclerosis is a relatively rare rheumatological condition (compared to rheumatoid arthritis which affects around 1 in 100). In the UK, the prevalence of systemic sclerosis has been reported to be 8.2 per 100 000 (Allcock et al, 2004). Like many other rheumatological conditions, women are more commonly affected than men, with a reported ratio of between 3:1 to 8:1 (Valentini and Black, 2002). Systemic sclerosis can present at any age including during childhood. The peak age of onset was reported to be between 20 and 50 years (Mayes et al, 2003), but a study examining data from the UK Clinical Practice Research Datalink found it was later at between 55 and 69 years (Royle et al, 2018). Later-onset disease, male gender and African-Caribbean origin have been reported to be associated with a more severe disease course.

Pathogenesis

The pathogenesis of systemic sclerosis is a complex interplay of vasculopathy, immune system activation and widespread tissue fibrosis (Katsumoto et al, 2011). Genetic factors likely contribute towards disease susceptibility and could explain some of the clinical heterogeneity of the disease (Denton and Khanna, 2017). Exposure to certain chemicals or occupational causes (e.g. vinyl chloride and organic solvents) have been reported to trigger the development of systemic sclerosis-like disorders which share some genetic similarities with systemic sclerosis (Denton and Khanna, 2017). Environmental factors likely play a significant role in disease pathogenesis in some individuals with systemic sclerosis. Epigenetic modifications may play a key role in linking genetic and environmental factors (Altorok et al, 2015).

Vascular disease is believed to play a central (and potentially even the initiating) role in the pathogenesis of systemic sclerosis. Systemic sclerosis vasculopathy is characterized by a progressive angiopathy with remodelling, for example, of the digital and pulmonary arteries and microcirculatory abnormality. Most likely vascular injury (of unknown cause) and dysfunction causes local tissue ischaemia which promotes tissue fibrosis. Fibroblast to myofibroblast transition is believed to be a key event, and is driven by a number of profibrotic factors, in particular transforming growth factor-beta (Denton and Khanna, 2017). There is widespread activation of the immune system evidenced by the detection of systemic sclerosis-associated autoantibodies (discussed later) and the rich infiltration of immune cells (e.g. B- and T-lymphocytes) in skin biopsies of patients with early diffuse cutaneous systemic sclerosis (Katsumoto et al, 2011). The association between anti-RNA polymerase III antibodies and malignancy in a proportion

of patients with systemic sclerosis further highlights the importance of 'autoimmunity' in the pathogenesis of systemic sclerosis (Denton and Khanna, 2017).

Systemic sclerosis-spectrum disorders

The term 'scleroderma' refers to thickening of the skin (*Figure 1*). This can be localized (e.g. morphoea or linear scleroderma) or can occur in association with involvement of the internal organs (i.e. in systemic sclerosis). Systemic sclerosis can occur in overlap with other autoimmune connective tissue diseases (e.g. Sjögren's syndrome and myositis) or with rheumatoid arthritis. A wide range of conditions can mimic systemic sclerosis (*Table 1*). Therefore, the clinician must maintain a high index of clinical suspicion and perform a comprehensive clinical assessment (history and physical examination) and request key investigations (e.g. systemic sclerosis-associated antibodies and nailfold capillaroscopy) (both discussed later).

In general, a diagnosis of systemic sclerosis is highly unlikely in the absence of Raynaud's phenomenon or if skin thickening spares the extremities. However, Raynaud's phenomenon can occur after the onset of scleroderma in patients with diffuse (rather than limited) cutaneous disease. Rarely, systemic sclerosis can occur in the absence of skin thickening and with involvement of the internal organs (systemic sclerosis sine scleroderma). Patients with mixed connective tissue disease may show features of a systemic sclerosis-like phenotype along with features of systemic lupus erythematosus, myositis and rheumatoid arthritis.

Diagnosis and classification of systemic sclerosis

There is no single diagnostic test for systemic sclerosis. The diagnosis is usually based on clinical features but is strongly supported through findings from targeted investigations (e.g. systemic sclerosis-associated antibodies and nailfold capillaroscopy). The 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for systemic sclerosis are a useful aid for clinicians when diagnosing systemic sclerosis (van den Hoogen et al, 2013) (*Table 2*). However, it must be remembered that these are not diagnostic criteria but are intended to facilitate clinical research.

Systemic sclerosis is divided into subsets: limited and diffuse cutaneous systemic sclerosis, based upon the distribution of the skin thickening (*Table 3*) (LeRoy et al, 1988). The term 'CREST' (calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly and telangiectases) was previously used to describe patients with the limited subset of the disease, but the term is falling out of favour, because patients with diffuse disease can also develop all of these manifestations. However, CREST is a useful aide memoire for some of the cardinal features of systemic sclerosis.

Classification of the disease is very important because this provides the clinician with an invaluable insight into the likely disease course and prognosis (*Table 3*). It is important to closely observe and regularly reassess patients with early disease. For example, the skin distribution in very early disease may appear to be consistent with limited disease but can progress proximally as the disease progresses. Akin to many other rheumatological diseases, there is increasing emphasis on very early diagnosis (Avouac et al, 2011). A very early diagnosis of systemic sclerosis should be suspected in the presence of certain red flags: Raynaud's phenomenon, puffy fingers and positive antinuclear antibody, confirmed by the presence of systemic sclerosis autoantibodies and/or capillaroscopic findings consistent with systemic sclerosis.

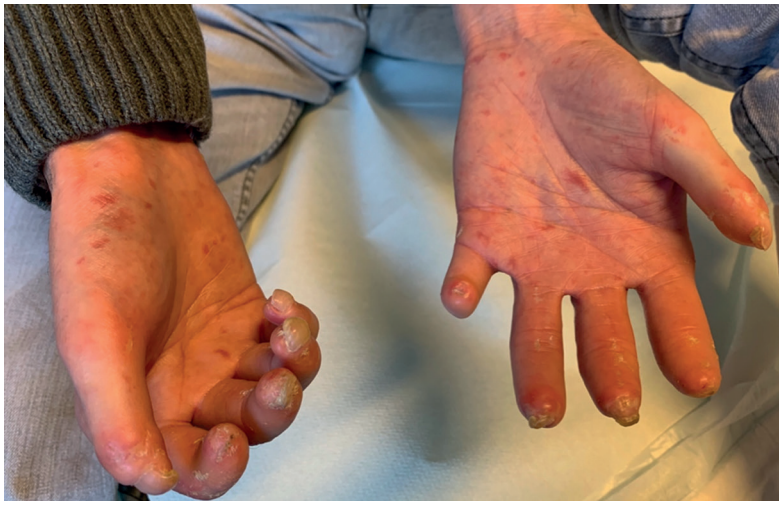

Figure 1. The hands of a patient with late diffuse cutaneous systemic sclerosis. There are significant contractures of the fingers and shortening of the digits including from acro-osteolysis. There are multiple telangiectases and areas of ischaemic tissue loss present.

Table 1. Scleroderma 'mimics'

Congenital	■ Stiff skin syndrome ■ Genetic disorders (premature ageing syndromes, e.g. Werner's syndrome)
Inflammatory or autoimmune	■ Eosinophilic fasciitis ■ Graft *vs* host disease ■ Nephrogenic systemic fibrosis ■ Scleroedema ■ Scleromyxodema ■ Diabetic cheiroarthropathy ■ Thyroid disease ■ Amyloidosis, carcinoid syndrome, phaeochromocytoma, phenylketonuria, porphyria cutanea tarda
Drug or 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

Reproduced from Hughes and Herrick (2012)

Table 2. The American College of Rheumatology/European League Against Rheumatism Criteria for systemic sclerosis

Item	Sub-item(s)	Weight/score
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)		9
Skin thickening of the fingers (only count the higher score)	Puffy fingers	2
	Sclerodactyly of the fingers	4
Fingertip lesions (only count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectases		2
Abnormal nailfold capillaries		2
Pulmonary artery hypertension and/or interstitial lung disease (maximum score is 2)	Pulmonary artery hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon		3
Systemic sclerosis-related autoantibodies (maximum score is 3*)	Anticentromere	3
	Anti-topisomerase I	
	Anti-RNA polymerase III	

*From van den Hoogen et al (2013). Systemic sclerosis-like disorders (*Table 1*) should be excluded. A total score of ≥9 points is required for patients to be classified as having systemic sclerosis. * Any antibody = 3 points but can not have more than 3 points (very rare to have two antibodies)*

Table 3. Disease subsets in systemic sclerosis

Limited cutaneous systemic sclerosis	Diffuse cutaneous systemic sclerosis
Raynaud's phenomenon for many years before the onset of skin thickening	Recent onset of Raynaud's phenomenon in close proximity (before or after) the onset of skin thickening
Distal skin involvement (hands, forearms, feet and below the level of the knees), face and neck	As per limited cutaneous systemic sclerosis but can affect the proximal upper and lower limbs and trunk
Late onset of pulmonary arterial hypertension	Early cardiac, lung, gastrointestinal and kidney involvement
Telangiectases	Tendon friction rubs (associated with the scleroderma renal crisis)
Many are anticentromere positive: associated with pulmonary arterial hypertension	Many are anti-Scl-70 (anti-topoisomerase) positive: associated with lung fibrosis, or anti-RNA polymerase III positive: associated with scleroderma renal crisis and cancer

From LeRoy et al (1988)

Clinical manifestations of systemic sclerosis

By virtue of being a multi-organ disease, systemic sclerosis is associated with a myriad of symptoms and signs. Therefore, the clinician must obtain a medical full history including (but not limited to) features of digital or peripheral ischaemia (e.g. attacks of Raynaud's phenomenon and a history of digital ulcers), or features of an overlap rheumatological condition (e.g. joint swelling or photosensitivity) and a drug and occupational history (e.g. relevant chemical exposures). A full physical examination should be performed including assessing for the presence and extent of skin thickening, digital ischaemic lesions (e.g. pitting scars and ulcers), other cutaneous manifestations (e.g. calcinosis and telangiectases) and cardiovascular and respiratory symptoms (e.g. for signs suggestive of interstitial lung disease and/or pulmonary hypertension).

Skin

Sclerodermatous skin involvement may change during the course of the disease. Initially the fingers can have a very puffy appearance and early diffuse cutaneous systemic sclerosis is sometimes mistaken for (and treated as) an inflammatory arthritis. Subsequently the skin undergoes progressive fibrosis. Later in the disease, the skin may atrophy and can look relatively normal if the patient presents late. However, many patients will still have a significant burden of hand disability (e.g. from hand or finger contractures) (*Figure 1*) despite improvement in the skin.

Other cutaneous manifestations include telangiectases (cutaneous dilated blood vessels) (*Figures 1* and *2*) which are a very visible manifestation of systemic sclerosis vasculopathy and can be associated with significant body image issues. Calcinosis (subcutaneous and/or intracutaneous calcium deposition) (*Figure 2*) occurs in 20–40% of patients and is often subclinical. Calcinosis is easily apparent on plain radiography but can also be assessed using other imaging techniques (e.g. computed tomography) (Hughes et al, 2019). Calcinosis can ulcerate through skin or become infected and can cause local pressure effects. Significant pruritus is often seen in patients with early diffuse cutaneous systemic sclerosis. Hypo- and hyperpigmentation can result in significant cosmetic skin changes.

Digital vascular disease

A spectrum of digital vascular disease is seen in patients with systemic sclerosis ranging from episodic attacks of Raynaud's phenomenon to established tissue ischaemia (e.g. digital pitting scars and ulcers). Over 95% of patients with systemic sclerosis report attacks of Raynaud's phenomenon and this may develop many years (even decades) before or in close relationship to the onset of skin thickening (*Table 3*). Attacks of Raynaud's phenomenon present as episodic colour change and/or sensory symptoms and are triggered by exposure to cold and/or emotional stressors.

The fingers are commonly affected but other sites can be involved including the toes and other vascular beds (e.g. lips and ears). Classically the skin colour progresses (physiological processes in parentheses) through white (ischaemia) to blue (deoxygenation) to red (hyperaemia). Raynaud's phenomenon has a significant (negative) impact on quality of life (Hughes et al, 2015b). Digital ulcers (*Figure 3*) are common in systemic sclerosis, with half of patients reporting

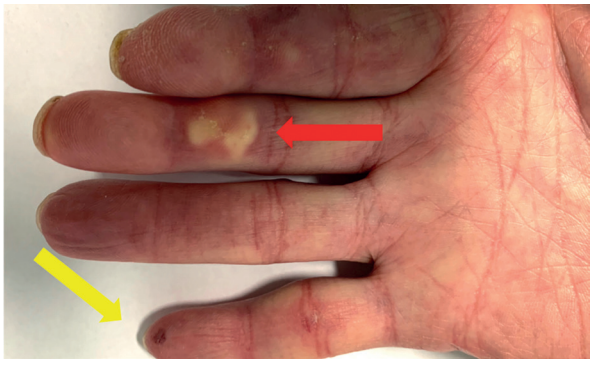

Figure 2. A patient with limited cutaneous systemic sclerosis. Clinically apparent calcinosis was seen (red arrow) and there were also a number of telangiectases present including on the pulp of the little finger (yellow arrow).

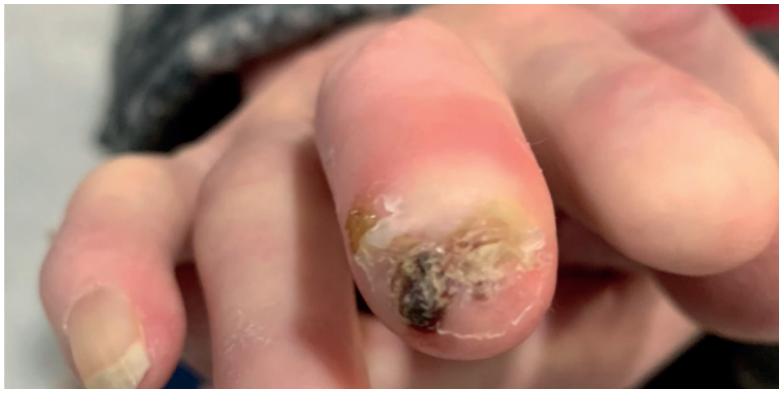

Figure 3. A fingertip digital ulcer in a patient with systemic sclerosis. There is significant overlying hyperkeratosis and the ulcer was associated with significant pain and sleep disturbance. Deep surgical debridement was required.

a history of ulcers. These have a significant impact on hand function including occupation (Hughes and Herrick, 2017). Digital ulcers often occur on the fingertips and over the dorsal (extensor) aspects of the hands overlying the small joints. A minority of patients develop critical digital ischaemia: this is a medical emergency and can result in significant tissue loss including the need for amputation (Sharp et al, 2016).

Cardiovascular and respiratory

Cardiovascular involvement is common in systemic sclerosis and can be life threatening. Primary cardiac involvement (conduction system abnormalities, myocardial and pericardial) (Kahan et al, 2009) is often subclinical. Cardiac disease may occur secondary to other systemic sclerosis-related complications (e.g. pulmonary arterial hypertension). An increased risk of atherosclerotic disease has been reported (Man et al, 2013). Respiratory involvement (i.e. pulmonary fibrosis and pulmonary artery hypertension) is now the leading cause of death. Evidence of interstitial lung disease can be found in around 80% of patients but is only clinically significant in around one third (Denton et al, 2016).

Gastrointestinal and renal

The majority (about 90%) of patients have gastrointestinal involvement and this can affect the entirety of the tract from the mouth to anus. Patients may develop features related to reduced oesophageal motility or gastroparesis: dysphagia and gastrointestinal reflux symptoms are common. Bleeding can occur from gastric antral vascular ectasia (often referred to as the 'watermelon stomach'). Malnutrition is common and often multifactorial including from reduced oral opening and impaired upper limb function or dexterity. Patients can develop malabsorption including that secondary to small bowel bacterial overgrowth. Faecal incontinence is common.

Renal involvement from scleroderma renal crisis used to be the leading cause of death in people with systemic sclerosis. Scleroderma renal crisis typically presents as a hypertensive emergency (e.g. acute pulmonary oedema and a microangiopathic haemolytic anaemia) with new onset renal failure and affects 5–10% of patients with systemic sclerosis (Denton et al, 2009). Risk factors include steroid therapy (>15 mg/day), early disease (<4 years), the diffuse cutaneous subset, rapidly progressing skin disease, tendon friction rubs and anti-RNA polymerase III antibodies (Denton et al, 2009). Patients with a normotensive renal crisis may have a delayed presentation (perhaps because of the absence of warning symptoms) and can be associated with prior exposure to angiotensin-converting enzyme inhibitors (Bruni et al, 2018). Early recognition and prompt treatment with angiotensin-converting enzyme inhibitors are key to the management of scleroderma renal crisis. Renal function may continue to improve even several years after scleroderma renal crisis allowing some patients to discontinue renal replacement therapy (Penn et al, 2007). Other forms of renal involvement are likely underestimated and poorly understood. These include (but are not limited to) proteinuria, albuminuria and antineutrophil cytoplasmic antibody (ANCA)-related glomerulonephritis (Bruni et al, 2018).

Musculoskeletal

The musculoskeletal system is commonly affected in patients with systemic sclerosis – manifestations range from non-specific arthralgia and myalgia to overt inflammatory joint and muscle disease (i.e. arthritis and myositis respectively). Contractures are found especially in diffuse cutaneous disease. Bilateral carpal tunnel syndrome can be seen in patients with early (diffuse) disease and is sometimes the first non-Raynaud's manifestation of systemic sclerosis.

Impact on quality of life

Systemic sclerosis can have a significant (and often neglected) impact on quality of life. The various skin changes can be associated with significant body image dissatisfaction. The disease can have a significant impact on function including all of the activities of daily living and occupation. Patients can develop significant depression, and intimate and personal relationships can be adversely affected.

Investigations

The choice of investigations is directed by clinical assessment, i.e. the presence of symptoms or localizing signs. For example, a hydrogen breath test should be requested if bacterial

Table 4. The major systemic sclerosis autoantibodies and their clinical correlates

Anticentromere antibody	Associated with limited cutaneous systemic sclerosis and pulmonary artery hypertension. Protective against pulmonary fibrosis and scleroderma renal crisis
Anti-topoisomerase (anti-Scl-70) antibody	Associated with diffuse cutaneous systemic sclerosis, pulmonary fibrosis and digital vasculopathy
Anti-RNA polymerase III antibody	Associated with diffuse cutaneous systemic sclerosis and scleroderma renal crisis

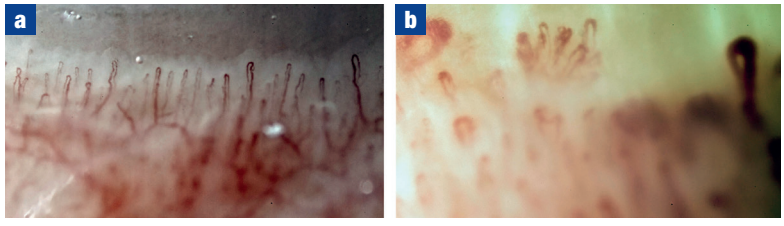

Figure 4. **a.** Normal nailfold capillaroscopy in a healthy subject. The capillaries are homogenous in appearance and regularly distributed. **b.** Abnormal capillaroscopy in a patient with systemic sclerosis. There is evidence of nailfold vasculopathy with 'giant' enlarged capillaries, avascularity and angiogenesis.

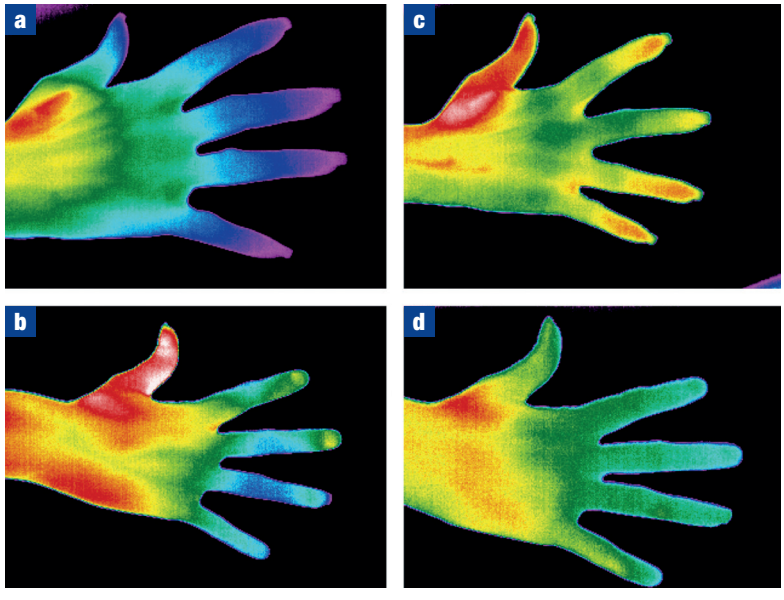

Figure 5. Thermograms of the hands before and after dynamic temperature challenge. **a** and **b.** Thermal images at 23°C and (**c** and **d**) at 30°C. **a** and **c** are from a patient with primary Raynaud's phenomenon and **b** and **d** are from a patient with secondary Raynaud's (systemic sclerosis). At 23°C (**a** and **b**) the fingertips are cooler than the dorsum of the hand in both patients. At 30°C unlike (**c**) in the patient with primary Raynaud's phenomenon, (**d**) there are persisting temperature gradients (fingertips cooler) along all the fingers of the patient with systemic sclerosis.

overgrowth is suspected. Patients with systemic sclerosis should undergo regular (usually annual) cardiorespiratory screening (transthoracic echocardiography and pulmonary function testing) to facilitate the early diagnosis of interstitial lung disease and/or pulmonary hypertension.

Key investigations in the diagnosis of systemic sclerosis include the detection of systemic sclerosis-associated autoantibodies and nailfold capillaroscopy. The importance of these investigations is reflected by their inclusion in the classification criteria for systemic sclerosis (van den Hoogen et al, 2013) (*Table 2*). In a prospective study which included 586 patients who were followed up for 3197 patient years, autoantibodies and microvascular abnormality (as assessed by capillaroscopy) were independent predictors of progression of Raynaud's phenomenon to systemic sclerosis (Koenig et al, 2008). Patients with both predictors were 60 times more likely to develop systemic sclerosis than those with neither.

Autoantibodies

The vast majority (>95%) of patients with systemic sclerosis are antinuclear antibody positive (Steen, 2005). Specific systemic sclerosis-associated autoantibodies are seen in at least half of patients and have clinically relevant or prognostic disease-based associations (*Table 4*). Non-specific extractable nuclear antigen (ENA) reactivities seen in other connective tissue or rheumatological conditions can also be seen (e.g. anti-Ro). Anti-ribonucleoprotein antibody positivity is associated with overlap syndromes.

Nailfold capillaroscopy

Nailfold capillaroscopy is a non-invasive imaging technique which allows the microcirculation to be examined in situ. At the nailfold, the capillaries lie parallel to the surface of the skin rather than perpendicularly as at other sites, allowing the capillaries to be examined in their entirety. Normal capillaries (*Figure 4*) have a regular and homogenous 'hair-pin' like appearance and are reassuring, for example, in a patient presenting with Raynaud's phenomenon. In patients with systemic sclerosis, microvascular alterations include enlarged ('giant') capillaries, microhaemorrhages, avascularity and angiogenesis (*Figure 4*). Capillaroscopy can be performed using low magnification hand-held techniques (ophthalmoscope, dermatoscope, USB microscope) (Baron et al, 2007; Hughes et al, 2015a), a stereomicroscope or high-magnification videocapillaroscopy, which is considered to be the gold standard (Cutolo and Smith, 2013). Increasing use of the USB microscope may help to widen clinicians' access to capillaroscopy.

Other specialist investigations

Infrared thermography (*Figure 5*) measures skin temperature, including after exposure to a cold challenge, and can help distinguish between primary and secondary (e.g. systemic sclerosis) Raynaud's phenomenon (Anderson et al, 2007). At present, thermography is limited to specialist centres, but its use may increase because of the increasing availability of lower cost, portable (e.g. mobile phone) equipment.

Management of systemic sclerosis

General approach to management

There is now a wide range of effective treatments for many organ-based complications in systemic sclerosis. Patient care should be directed by clinicians who are experienced in managing the complexity of disease in systemic sclerosis. Usually rheumatologists direct the care of patients with

systemic sclerosis with input (when appropriate) from organ-based and other hospital-based specialists (e.g. vascular and orthopaedic surgery). Best practice often involves shared care (e.g. alternating appointments) between specialist and local hospital services. Although there is no known cure for systemic sclerosis, *Table 5* outlines possible treatments for many of its clinical manifestation, including those acting on the vascular system (e.g. vasodilators for digital vascular disease) and 'traditional' immunosuppression used in rheumatology (i.e. disease-modifying agents) for certain complications, e.g. interstitial lung disease and myositis. Early diffuse cutaneous systemic sclerosis is a management priority now commonly treated with immunosuppression (Herrick et al, 2017). Detailed guidance can be found in national (e.g. British Society of Rheumatology) (Denton et al, 2016) and international recommendations for treatment of systemic sclerosis (Kowal-Bielecka et al, 2017).

Emerging treatment options

This is a very exciting time for clinical research in systemic sclerosis – a number of studies are recently completed or recruiting examining new drug treatments, including those repurposed from other rheumatological conditions (e.g. biologics used for rheumatoid arthritis). Antifibrotic therapies (e.g. used for idiopathic pulmonary fibrosis) are also being researched, with a study demonstrating benefit from nintedanib in interstitial lung disease (Distler et al, 2019). Autologous stem cell transplantation is a powerful potential treatment for systemic sclerosis (Sullivan et al, 2018), with stabilisation or even improvement including in skin and lung disease. However, because of the potential for treatment-related mortality (of around 5%) patients must be extensively screened before transplantation, in particular to exclude any evidence of heart involvement.

Critical illness in systemic sclerosis

Patients with systemic sclerosis may develop critical illness necessitating intensive care unit admission. Studies have shown either similar or higher mortality of patients with systemic rheumatological conditions compared to 'general' intensive care unit patients (Mustafa et al, 2018). In patients with systemic sclerosis, invasive mechanical ventilation is associated with very high mortality (Pène et al, 2015).

Conclusions

Systemic sclerosis is a serious and complex disease and many hospital-based specialists are involved in the care of patients with this condition. Although there is no known cure, there are a number of effective treatments for many of the organ-based complications. Immunosuppression is usually prescribed in patients with early diffuse cutaneous systemic sclerosis. Autologous stem cell transplantation is a powerful treatment in selected patients. Advances in understanding disease pathogenesis are informing drug development programmes. Patients need to be closely monitored and managed by a dedicated multidisciplinary team. Hospital-based specialists need to be aware of the wide ranging (and potentially treatable) potential clinical manifestations of systemic sclerosis. **BJHM**

This work was supported by the NIHR Manchester Biomedical Research Centre.
Conflict of interest: none.

Allcock RJ, Forrest I, Corris PA, Crook PR, Griffiths ID. A study of the prevalence of systemic sclerosis in northeast England. Rheumatology. 2004 Jan 27;43(5):596–602. https://doi.org/10.1093/rheumatology/keh124

Altorok N, Almeshal N, Wang Y, Kahaleh B. Epigenetics, the holy grail in the pathogenesis of systemic sclerosis. Rheumatology. 2015 Oct;54(10):1759–1770. https://doi.org/10.1093/rheumatology/keu155

Anderson ME, Moore TL, Lunt M, Herrick AL. The 'distal-dorsal

Table 5. Treatment options for systemic sclerosis

Organ system	Clinical manifestation	Examples of treatments*
Skin	Scleroderma	Immunosuppressive therapy (e.g. methotrexate and mycophenolate mofetil) for progressive skin thickening in the context of early diffuse cutaneous disease
Musculoskeletal	Inflammatory arthritis	Disease-modifying therapy (e.g. methotrexate)
Cardiovascular	Heart failure	Usual drug therapies (e.g. angiotensin-converting enzyme inhibitors and diuretics)
	Inflammatory cardiac disease	Immunosuppressive therapy (e.g. corticosteroid and/or cyclophosphamide)
Respiratory	Pulmonary artery hypertension	Endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, prostacyclin analogues
	Interstitial lung disease	Soluble guanylate cyclase agonists, immunosuppressive therapy (e.g. cyclophosphamide and mycophenolate mofetil)
Gastrointestinal	Gastro-oesophageal reflux disease	Lifestyle advice, proton-pump inhibitors
Peripheral vascular	Raynaud's phenomenon, digital ulcers and critical ischaemia	Calcium-channel blockers, phosphodiesterase type 5 inhibitors, angiotensin II receptor blockers, endothelin receptor antagonists, prostacyclin analogues (e.g. intravenous iloprost), wound care for digital ulcers, antibiotic therapy for infected ulcers, surgical debridement or amputation
Renal	Scleroderma renal crisis	Angiotensin-converting enzyme inhibitors

*modified from Hughes (2018). * this not an exhaustive list*

KEY POINTS

- Systemic sclerosis is a complex autoimmune connective tissue disease with vascular, immune and fibrotic components.
- Systemic sclerosis can be divided into limited and diffuse cutaneous subtypes and these differ in their clinical presentation and disease course.
- The majority of patients have Raynaud's phenomenon, and this is often the earliest feature of the disease.
- There are a number of effective treatments for many of the organ-based complications.
- Autologous stem cell transplantation may be a powerful treatment option for some very carefully selected patients.
- Patients with systemic sclerosis need close clinical review including regular cardiorespiratory investigations.
- Patients are best managed by a specialist multidisciplinary team with involvement from many hospital-based specialists.
- There is much ongoing international research including clinical trials of novel drug therapies.

difference': a thermographic parameter by which to differentiate between primary and secondary Raynaud's phenomenon. Rheumatology. 2007 Jan 25;46(3):533–538. https://doi.org/10.1093/rheumatology/kel330

Avouac J, Fransen J, Walker U et al; EUSTAR Group. 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 Mar 01;70(3):476–481. https://doi.org/10.1136/ard.2010.136929

Baron M, Bell M, Bookman A et al. Office capillaroscopy in systemic sclerosis. Clin Rheumatol. 2007 Jun 27;26(8):1268–1274. https://doi.org/10.1007/s10067-006-0489-6

Bruni C, Cuomo G, Rossi FW, Praino E, Bellando-Randone S. Kidney involvement in systemic sclerosis: from pathogenesis to treatment. J Scleroderma Relat Disord. 2018 Feb;3(1):43–52. https://doi.org/10.1177/2397198318758607

Cutolo M, Smith V. State of the art on nailfold capillaroscopy: a reliable diagnostic tool and putative biomarker in rheumatology? Rheumatology. 2013 Nov 01;52(11):1933–1940. https://doi.org/10.1093/rheumatology/ket153

Denton CP, Lapadula G, Mouthon L, Müller-Ladner U. Renal complications and scleroderma renal crisis. Rheumatology. 2009 Jun;48 suppl_3:iii32–iii35. https://doi.org/10.1093/rheumatology/ken483

Denton CP, Hughes M, Gak N et al; BSR and BHPR Standards, Guidelines and Audit Working Group. BSR and BHPR guideline for the treatment of systemic sclerosis. Rheumatology. 2016 Oct;55(10):1906–1910. https://doi.org/10.1093/rheumatology/kew224

Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017 Oct;390(10103):1685–1699. https://doi.org/10.1016/S0140-6736(17)30933-9

Distler O, Highland KB, Gahlemann M et al; SENSCIS Trial Investigators. Nintedanib for systemic sclerosis–associated interstitial lung disease. N Engl J Med. 2019 May 20;NEJMoa1903076. https://doi.org/10.1056/NEJMoa1903076

Herrick AL, Pan X, Peytrignet S et al. Treatment outcome in early diffuse cutaneous systemic sclerosis: the European Scleroderma Observational Study (ESOS). Ann Rheum Dis. 2017 Jul;76(7):1207–1218. https://doi.org/10.1136/annrheumdis-2016-210503

Hughes M. Early diagnosis and management of systemic sclerosis. Prescriber. 2018 Jul;29(7):27–32. https://doi.org/10.1002/psb.1689

Hughes M, Herrick A. Systemic sclerosis. Br J Hosp Med. 2012 Sep;73(9):509–516. https://doi.org/10.12968/hmed.2012.73.9.509

Hughes M, Herrick AL. Digital ulcers in systemic sclerosis. Rheumatology. 2017 Jan;56(1):14–25. https://doi.org/10.1093/rheumatology/kew047

Hughes M, Moore T, O'Leary N et al. A study comparing videocapillaroscopy and dermoscopy in the assessment of nailfold capillaries in patients with systemic sclerosis–spectrum disorders. Rheumatology. 2015a Aug;54(8):1435–1442. https://doi.org/10.1093/rheumatology/keu533

Hughes M, Snapir A, Wilkinson J, Snapir D, Wigley FM, Herrick AL. Prediction and impact of attacks of Raynaud's phenomenon, as judged by patient perception. Rheumatology (Oxford). 2015b Aug;54(8):1443–1447. https://doi.org/10.1093/rheumatology/kev002

Hughes M, Hodgson R, Harris J et al. Imaging calcinosis in patients with systemic sclerosis by radiography, computerised tomography and magnetic resonance imaging. Semin Arthritis Rheum. 2019 Mar;S0049-0172(18)30705-4. https://doi.org/10.1016/j.semarthrit.2019.03.001

Kahan A, Coghlan G, McLaughlin V. Cardiac complications of systemic sclerosis. Rheumatology (Oxford). 2009 Jun;48 Suppl 3:iii45-8. https://doi.org/10.1093/rheumatology/kep110

Katsumoto TR, Whitfield ML, Connolly MK. The pathogenesis of systemic sclerosis. Annu Rev Pathol. 2011 Feb 28;6(1):509–537. https://doi.org/10.1146/annurev-pathol-011110-130312

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 Dec;58(12):3902–3912. https://doi.org/10.1002/art.24038

Kowal-Bielecka O, Fransen J, Avouac J et al; EUSTAR Coauthors. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017 Aug;76(8):1327–1339. https://doi.org/10.1136/annrheumdis-2016-209909

LeRoy EC, Black C, Fleischmajer R et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol. 1988 Feb;15(2):202–205.

Man A, Zhu Y, Zhang Y et al. The risk of cardiovascular disease in systemic sclerosis: a population-based cohort study. Ann Rheum Dis. 2013 Jul;72(7):1188–1193. https://doi.org/10.1136/annrheumdis-2012-202007

Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, Schottenfeld D. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum. 2003 Aug;48(8):2246–2255. https://doi.org/10.1002/art.11073

Mustafa M, Gladston Chelliah E, Hughes M. Patients with systemic rheumatic diseases admitted to the intensive care unit: what the rheumatologist needs to know. Rheumatol Int. 2018 Jul;38(7):1163–1168. https://doi.org/10.1007/s00296-018-4008-2

Pène F, Hissem T, Bérezné A et al. Outcome of patients with systemic sclerosis in the intensive care unit. J Rheumatol. 2015 Aug;42(8):1406–1412. https://doi.org/10.3899/jrheum.141617

Penn H, Howie AJ, Kingdon EJ et al. Scleroderma renal crisis: patient characteristics and long-term outcomes. QJM. 2007 Jun 02;100(8):485–494. https://doi.org/10.1093/qjmed/hcm052

Royle JG, Lanyon PC, Grainge MJ, Abhishek A, Pearce FA. The incidence, prevalence, and survival of systemic sclerosis in the UK Clinical Practice Research Datalink. Clin Rheumatol. 2018 Aug;37(8):2103–2111. https://doi.org/10.1007/s10067-018-4182-3

Sharp CA, Akram Q, Hughes M, Muir L, Herrick AL. Differential diagnosis of critical digital ischemia in systemic sclerosis: report of five cases and review of the literature. Semin Arthritis Rheum. 2016 Oct;46(2):209–216. https://doi.org/10.1016/j.semarthrit.2016.05.001

Steen VD. Autoantibodies in systemic sclerosis. Semin Arthritis Rheum. 2005 Aug;35(1):35–42. https://doi.org/10.1016/j.semarthrit.2005.03.005

Sullivan KM, Goldmuntz EA, Keyes-Elstein L et al; SCOT Study Investigators. Myeloablative autologous stem-cell transplantation for severe scleroderma. N Engl J Med. 2018;378(1):35–47. https://doi.org/10.1056/NEJMoa1703327

Valentini G, Black C. Systemic sclerosis. Best Pract Res Clin Rheumatol. 2002 Dec;16(5):807–816. https://doi.org/10.1053/berh.2002.0258

van den Hoogen F, Khanna D, Fransen J et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013 Nov;65(11):2737–2747. https://doi.org/10.1002/art.38098