# Systemic sclerosis

## A step-by-step guide to a difficult diagnosis

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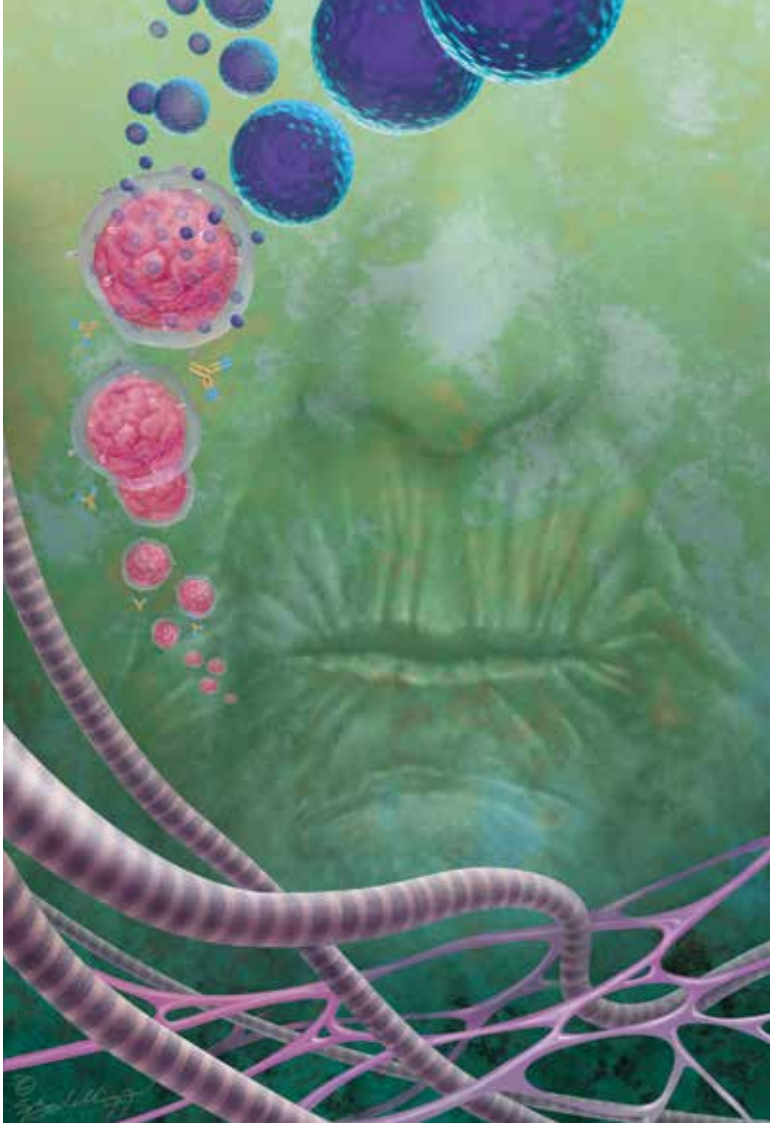
**Systemic sclerosis is an uncommon condition but the associated complications can have severe adverse effects on a patient's quality of life and survival. A multimodal, multidisciplinary approach to management of disease manifestations is essential.**





### KEY POINTS

- **Systemic sclerosis (SSc), or scleroderma, is a multisystem autoimmune disease characterised by vasculopathy and fibrosis.**
- **Adult-onset Raynaud's phenomenon or Raynaud's phenomenon complicated by digital ulceration or infarction should prompt consideration of connective tissue disorders including SSc.**
- **Early identification of severe, life-threatening organ manifestations can result in improved quality of life and survival.**
- **Management of patients with SSc is multifaceted and dependent on individual disease manifestations.**

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Systemic sclerosis (SSc), commonly referred to as scleroderma, is a multisystem autoimmune condition characterised by inflammation, vasculopathy and fibrosis of both the skin, which becomes thickened, and internal organs. Although the condition is uncommon, with reported incidences ranging between 0.27 and 22.8 per million,[1] the complications of the disease can have devastating effects on a patient's quality of life and survival. Symptoms of SSc and its complications can, however, be nonspecific, leading to delays in diagnosis. Earlier recognition of the disease and common or important disease manifestations can improve patient outcomes.[1]

The aetiology of SSc remains unclear, with a combination of genetic susceptibility and environmental triggers proposed to contribute to the pathogenesis. Possible environmental triggers include exposure to silica, vinyl chloride and organic solvents.[1]

In this article, the diagnosis of SSc is discussed and key considerations in identifying and managing common and important disease manifestations are outlined.

### Identifying systemic sclerosis

Patients with SSc are typically women who present with Raynaud's phenomenon, the characteristic cold-induced

**Figure 1.** Cold-induced blue colour change in the hand of a patient with scleroderma. Additional changes of pallor plus or minus erythema are characteristic of Raynaud's phenomenon.

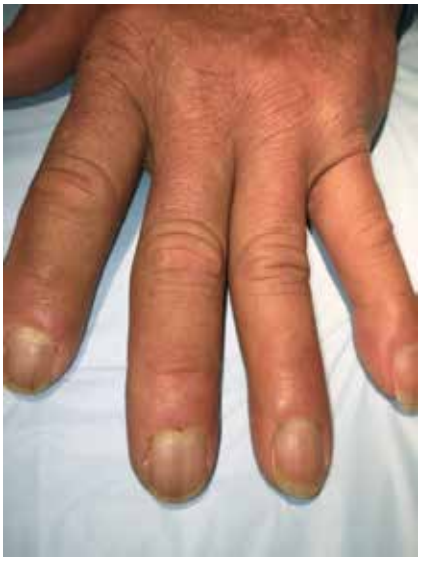

**Figure 2.** Skin thickening of the digits is a feature of Raynaud's phenomenon. Note the small haemorrhage in the nailfold of the third digit.

triphasic colour change of the peripheries of blue, white then red (Figure 1). Evidence of skin thickening of the digits (sclerodactyly) and signs of digital ischaemia, such as digital tip ulceration, ragged cuticles and dilated nailfold capillaries with haemorrhages (Figure 2), help distinguish Raynaud's phenomenon of SSc from benign primary Raynaud's phenomenon. Various methods of magnification such as dermoscopy can be used to view the nailfold capillaries. The presence of abnormal nailfold capillaries including capillary dropout, dilatation and haemorrhage (Figure 3) are suggestive of an underlying autoimmune connective tissue disease such as SSc.

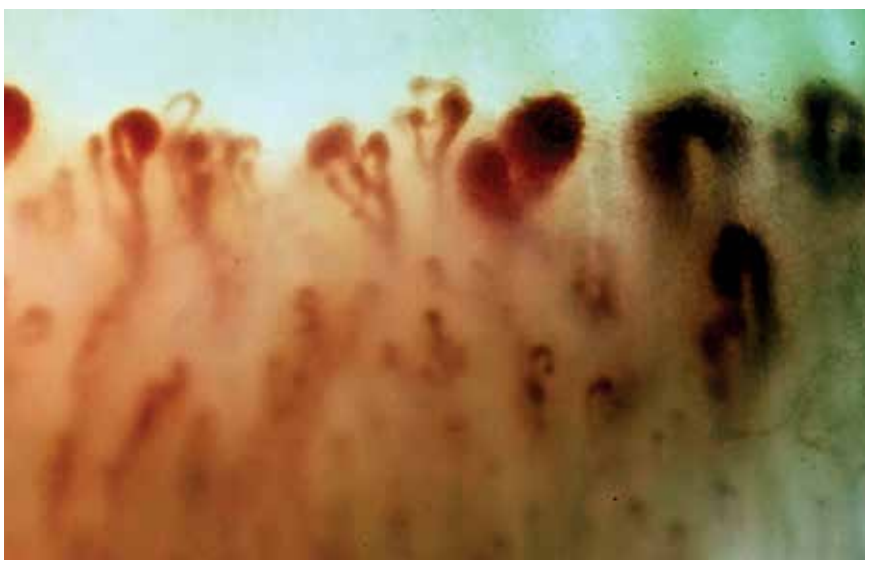

**Figure 3.** Abnormal nailfold capillaries seen under magnification in a patient with Raynaud's phenomenon.

The diagnosis of SSc is supported by the development of additional clinical manifestations and a positive antinuclear antibody (ANA) test, usually in high titre. This is often, but not always, accompanied by the presence of SSc-specific autoantibodies such as anticentromere or antitopoisomerase 1 (Scl-70) antibodies. The onset of SSc occurs most commonly in the fourth and fifth decades of life, although symptoms such as Raynaud's phenomenon can be present for decades in some patients and, rarely, SSc can present in childhood.

## Classification criteria for systemic sclerosis

Classification criteria for SSc have been developed for research, but also provide useful insights into the clinical features that contribute to making a diagnosis of SSc in clinical practice.

Traditional classification criteria, including the 1980 American College of Rheumatology (ACR) and 2001 Leroy and Medsger classification criteria, focused on patients with well-established disease. The new 2013 ACR and European League against Rheumatism (EULAR) criteria were developed to identify patients earlier in the disease process (Box).[2] They include immunological, vascular and fibrotic facets of disease pathogenesis while remaining feasible for use in clinical practice. Compared with previous classification criteria, the 2013 ACR/EULAR criteria are more sensitive and specific for the diagnosis of SSc, with 91% and 92% sensitivity and specificity, respectively.[2] 2013 ACR/EULAR classification criteria incorporate a scoring system taking into account the key pathophysiological features of SSc: fibrosis (sclerodactyly and interstitial lung disease); vasculopathy (Raynaud's phenomenon, digital ulcers, digital pitting, telangiectasia, abnormal nailfold capillaries and pulmonary arterial hypertension [PAH]); and autoimmunity

(SSc-related autoantibodies: anticentromere, antitopoisomerase I and anti-RNA polymerase III).

The diagnosis of SSc can be difficult in the absence of characteristic features. Key disease mimics to differentiate from SSc include nephrogenic systemic fibrosis, scleromyxoedema, eosinophilic fasciitis, generalised morphea and diabetic cheiroarthropathy. A diagnosis can be supported by using a combination of:

- the patient history (e.g. diabetes and diabetic cheiroarthropathy, and temporal association with gadolinium contrast in the case of nephrogenic systemic fibrosis);
- characteristic examination (e.g. waxy papules of scleromyxoedema and woody appearance of eosinophilic fasciitis [cutaneous mucin deposition characterised by generalised waxy papules and skin thickening that usually occurs in association with monoclonal gammopathy]); and
- investigations including biopsy of affected skin for histological confirmation.

## Clinical manifestations

Although all of the skin of patients with SSc is abnormal histopathologically, SSc is divided into two clinical subsets based on the extent of skin involvement: limited and diffuse (Table 1). Patients with limited SSc have skin thickening from the hands to below the elbows and below the knees. Limited SSc may also involve the face, but does not extend below the neck. In patients with diffuse SSc the skin becomes thickened beyond these areas, particularly on the upper arms and legs and it may involve the trunk. In patients with early diffuse disease, tendon friction rubs on passive movement of joints develop due to fibrinous involvement of tendon sheaths. The presence of tendon friction rubs suggests more extensive skin involvement is likely and is associated with worse prognosis. The most commonly involved sites include the wrists, elbows, knees and ankles.

In early diffuse SSc, skin thickening may not have reached its full extent at the time of diagnosis. Conversely, the skin of patients with diffuse SSc may soften and apparently improve, typically after five years or so. Rapid progression of disease or the identification of antibodies associated with diffuse disease, such as antibodies to Scl-70 or RNA polymerase III, may assist in identifying this disease subset early in the disease course.

Some patients have features of another connective tissue disorder in addition to either limited or diffuse SSc. These patients are said to have an 'overlap' syndrome. Patients with SSc sine scleroderma, a rare entity, have typical manifestations of SSc with no skin involvement.

The extent of visceral disease can vary, regardless of subtype. In general, diffuse disease progresses rapidly and is associated with more visceral involvement and higher mortality than limited SSc.

## Common problems in systemic sclerosis

There is no cure for SSc. Although historically many therapies have been unsuccessful, several are currently available to manage common and more serious sequelae.

### Raynaud's phenomenon and digital ulcers

The most common symptom of SSc is Raynaud's phenomenon due to vasculopathy and vasospasm of small vessels in the digits. This can be extremely painful and result in digital pitting and ulceration, pulp atrophy and critical digital ischaemia with secondary tissue necrosis. Alternative causes of ischaemia should also be considered in patients with SSc including thrombophilia, proximal vessel occlusion or thromboembolism.

Control of environmental and behavioural factors is key to maintaining core body temperature and avoiding Raynaud's phenomenon. These include smoking cessation, cold and stress avoidance and wearing warm clothing. Calcium channel blockers are frequently used for their vasodilatory effect, to reduce the severity and frequency of episodes of Raynaud's phenomenon. When necrotic tissue develops or a digital ulcer fails to heal, aggressive wound care and vasodilatory therapy can aid healing and may prevent secondary soft tissue infection and osteomyelitis. Antiplatelet therapy, typically aspirin, is instituted. Additional vasodilatory measures include the use of topical glyceryl trinitrate, phosphodiesterase-5 inhibitors, prostacyclin infusions and sympathectomy. Wounds should be debrided with caution and amputation avoided due to ongoing poor wound healing. A collaborative, multidisciplinary approach includes wound care nurses, rheumatologists and plastic surgeons.

**FEATURES OF THE 2013 ACR/EULAR CLASSIFICATION CRITERIA FOR SYSTEMIC SCLEROSIS*[2]**

**Fibrotic**

- Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints [9]
- Skin thickening of fingers: puffy fingers [2] or sclerodactyly of the fingers (distal to metacarpophalangeal joints but proximal to the proximal interphalangeal joints) [4]†

**Vascular**

- Finger tip lesions: digital tip ulcers [2] or fingertip pitting scars [3]†
- Telangiectasia [2]
- Abnormal nailfold capillaries [2]
- Pulmonary arterial hypertension or interstitial lung disease [2]
- Raynaud's phenomenon [3]

**Immunological**

- SSc-related autoantibodies: anticentromere and/or antitopoisomerase I or anti-RNA polymerase III [3]

* Points are assigned to each feature (denoted in squared brackets) and added together to achieve a total score. Patients with a total score of nine or higher can be classified as having SSc.
† Only the higher score should be counted.

Abbreviations: ACR/EULAR = American College of Rheumatology/European League against Rheumatism; SSc = systemic sclerosis.

**TABLE 1. CHARACTERISTICS OF LIMITED AND DIFFUSE SYSTEMIC SCLEROSIS**

| Characteristic | Limited | Diffuse |
|---|---|---|
| ***Skin involvement*** | Below elbows and knees<br>On the face, not extending below neck | Extends proximal to forearm and knees<br>Face and trunk often involved |
| ***Disease course*** | Gradual onset | Rapid |
| ***Complications of disease*** | | |
| Raynaud's phenomenon | ++++ | ++++ |
| Renal crisis | + | +++ |
| Pulmonary arterial hypertension | ++ | ++ |
| Interstitial lung disease | ++ | ++ |
| Arthritis | ++ | ++ |
| Gastrointestinal disease | ++++ | ++++ |
| Antibodies | Anticentromere Ab | Antitopoisomerase I Ab<br>Anti-RNA polymerase III Ab |

+ = rare; ++ = uncommon; +++ = common; ++++ = most patients experience symptoms.
Abbreviation: Ab = antibodies.

## Musculoskeletal manifestations

Musculoskeletal manifestations that result in pain or functional limitations have a significant impact on a patient's quality of life and independence. Polyarthralgia is a common symptom experienced early in the course of SSc. Clinical arthritis is often evident and disease-modifying antirheumatic drugs can be used to manage the inflammatory arthritis associated with SSc. Glucocorticoids should be avoided where possible due to the risk of precipitating renal crisis.

Joint contractures develop due to the tethering of skin and periarticular soft tissues in up to 55% of patients with SSc, particularly in those with diffuse SSc. Occupational therapists can provide resources to help maintain a patient's functional capacity. Unfortunately, despite relaxation of the skin over time, joint contractures due to skin tightening may not improve.

Muscle weakness can occur for multiple reasons. These include arthralgia or arthritis, joint contractures and skin thickening limiting mobility, and secondary muscle wasting. Additionally, vasculopathy and fibrosis of muscle fibres, resulting in sclerodermatous myopathy contributes to muscle weakness. In a small group of patients with SSc, overlap occurs with polymyositis.[3,4]

## Gastrointestinal tract dysfunction

Gastrointestinal tract dysfunction is the most common internal complication of SSc. Progressive gastrointestinal vasculopathy and fibrosis can affect the gastrointestinal tract at any level, from restricted mouth opening to loss of anal tone, rectal prolapse and faecal incontinence. In addition to pathology occurring in the general population, SSc is often associated with gastro-oesophageal reflux, gastroparesis, constipation and diarrhoea.

Patients with gastrointestinal manifestations of SSc are challenging to manage. Diagnosis of the underlying pathology can be difficult. A good example of this is nausea and abdominal bloating. This can result from poor motility resulting in gastroparesis, constipation, pseudo-obstruction or, rarely, volvulus. Alternatively, small intestinal bacterial overgrowth may also manifest as abdominal discomfort and bloating. Clues such as the vomiting of undigested food several hours after a patient has eaten helps distinguish gastroparesis from adverse effects from therapies used for other disease manifestations – e.g. methotrexate. Similarly, key considerations in the assessment of dysphagia include oesophageal dysmotility, polymyositis and stricture. New-onset dysphagia should be investigated with barium studies and/or endoscopy with dilatation if necessary. The incidence of Barrett's oesophagus is not significantly increased in patients with SSc. Causes of diarrhoea in patients with SSc include infective aetiologies, constipation with overflow diarrhoea, pancreatic insufficiency and small intestinal bacterial overgrowth.

Malnutrition is an important complication of SSc. It may be related to any combination of restricted mouth opening, gastro-oesophageal reflux, gastroparesis limiting oral intake, malabsorption from small intestinal bowel overgrowth, gastrointestinal fibrosis, pancreatic

insufficiency and comorbid depression. Dietitian input for education and caloric and nutritional supplementation provide substantial support. Treatment of individual components and supplementation, can be insufficient, however, and the institution of enteral or parental nutrition may be required.

Gastrointestinal bleeding in patients with SSc can result in significant and symptomatic iron deficiency anaemia, requiring iron supplementation and blood transfusion. Telangiectasia, commonly seen in the skin of patients with SSc, can be present throughout the gastrointestinal tract, resulting in intestinal bleeding. Commonly, gastric antral vascular ectasia, resulting in a 'watermelon stomach' appearance, can be a source of recurrent gastrointestinal blood loss that may be controlled with regular endoscopic argon laser therapy.

## Key problems not to miss

### Scleroderma renal crisis

Scleroderma renal crisis (SRC) is a serious, life-threatening complication of SSc that until recently was associated with high mortality. Greater recognition and early introduction of ACE inhibitors have significantly improved survival of these patients, although renal replacement therapy with dialysis or renal transplantation is still often required. Risk factors for SRC include diffuse SSc disease, particularly in the first five years of the disease, the presence of antibodies to RNA polymerase III and the use of glucocorticoid therapy.

In patients with SRC, hypertension typically occurs abruptly with the rapid development of malignant hypertension. An acute kidney injury without cellular casts or glomerular haematuria, secondary microangiopathic haemolytic anaemia and acute pulmonary oedema develop if the hypertension is left untreated. Urgent hospitalisation and treatment of patients is imperative, with invasive blood pressure monitoring and treatment with a short-acting ACE inhibitor. Patients with early diffuse SSc, particularly those with antibodies to RNA polymerase III, should be advised to monitor their blood pressure several times per week and elevations that are 40 mmHg above their usual systolic blood pressure should prompt urgent medical review. There are no proven preventive strategies for SRC.

### Cardiac manifestations

PAH is another life-threatening manifestation of SSc occurring as a result of pulmonary vasculopathy and dysfunctional vascular remodelling. Interstitial lung disease (ILD), chronic thromboembolic disease and left ventricular dysfunction

**TABLE 2. MORE SERIOUS AND LIFE-THREATENING MANIFESTATIONS OF SYSTEMIC SCLEROSIS (SSc)**

| Complication | Key features | Management | Key practice points |
|---|---|---|---|
| Critical digital ischaemia and ulcers | • Irreversible discolouration of digits<br>• Skin or soft-tissue necrosis | • Wound care<br>• Antiplatelet therapy, e.g. aspirin<br>• Combination vasodilatory therapy, e.g. topical glyceryl trinitrate, calcium channel antagonists (dihydropyridines, e.g. nifedipine or amlodipine), 5-phosphodiesterase inhibitors (e.g. sildenafil, tadalafil) and prostacyclin infusions | • Exclude proximal vascular occlusion<br>• Amputation should be avoided where possible<br>• Osteomyelitis should be considered where soft tissue infection is evident |
| Pulmonary arterial hypertension (PAH) | • Unexplained dyspnoea should prompt consideration of PAH<br>• Patients with SSc are screened for PAH with annual pulmonary function tests and echocardiography<br>• Right heart catheterisation is required for diagnosis | • Therapeutic options include prostacyclin pathway agonists (inhaled iloprost, IV epoprostenol), endothelin receptor antagonists (e.g. bosentan, ambrisentan and macitentan) and 5-phosphodiesterase inhibitors (e.g. sildenafil, tadalafil) and may be used in combination<br>• The role of anticoagulation is controversial | • Alternative causes of pulmonary hypertension including chronic thromboembolic disease, ILD and left ventricular dysfunction and contributing factors such as obstructive sleep apnoea and thyroid disease should be considered<br>• Multidisciplinary care should be co-ordinated in a centre with PAH expertise |
| Interstitial lung disease (ILD) | • Patients with early diffuse SSc should have pulmonary function tests every 3-6 months in the first 2 years<br>• Dyspnoea, bibasal crackles, a restrictive defect on pulmonary function tests and/or reduced diffusing capacity should prompt imaging with high-resolution computed tomography (HRCT) of the chest | • Cyclophosphamide or mycophenolate are used for extensive or progressive ILD based on extent of disease on HRCT and changes in pulmonary function tests | • After diagnosis of ILD, repeat HRCT is usually not required unless symptoms progress or change over one year |
| Scleroderma renal crisis | • Abrupt onset hypertension (increase >40 mmHg in systolic blood pressure [BP])<br>• New acute kidney injury<br>• Microangiopathic haemolytic anaemia<br>• Acute pulmonary oedema | • ACE inhibitors (short-acting preferred, e.g. captopril)<br>• Urgent hospitalisation to normalise BP<br>• Invasive or close BP monitoring | • Can occur in any patient with SSc<br>• Risk factors include diffuse SSc, antibodies to RNA polymerase III and use of glucocorticoid therapy |
| Arrhythmia | • Palpitations<br>• Dizziness or syncope | • According to risk, inpatient cardiac monitoring or 24-hour Holter monitoring<br>• When arrhythmia is detected, insertion of a pacemaker or defibrillator should be considered | • Ventricular bigeminy is a risk factor for fatal arrhythmia |

can also contribute to PAH in patients with SSc (Table 2 and Figure 4).

PAH can be asymptomatic in the early stages but should be considered in a patient with unexplained dyspnoea or progressive reduction in exercise capacity. If left untreated, the one-year survival of patients with SSc and PAH can be as low as 50%. Screening with annual transthoracic echocardiography and pulmonary function tests has led to earlier identification of patients with PAH,

**TABLE 2. MORE SERIOUS AND LIFE-THREATENING MANIFESTATIONS OF SYSTEMIC SCLEROSIS continued**

| Complication | Key features | Management | Key practice points |
|---|---|---|---|
| Gastro-oesophageal reflux | • Nausea<br>• Reflux/heartburn<br>• Dysphagia | • Avoid foods precipitating symptoms of reflux and meals late in the evening. Elevate the head of the bed<br>• Regular proton pump inhibitor therapy<br>• Barium swallow and/or endoscopy to exclude obstructive lesion | • Gastrointestinal manifestations are vascular with gastrointestinal bleeding or as a result of fibrosis leading to dysmotility<br>• Vascular lesions can occur at any point along the gastrointestinal tract |
| Gastroparesis | • Nausea and vomiting<br>• Abdominal discomfort and bloating | • Consider medications that may contribute to nausea and abdominal discomfort<br>• Adjust oral intake with dietitian support and trial of prokinetic agents (e.g. domperidone) before meals | |
| Small intestinal bacterial overgrowth | • Abdominal discomfort/bloating<br>• Diarrhoea<br>• Malnutrition/weight loss | • The diagnosis can be confirmed by hydrogen breath test<br>• Use cyclical antibiotics | |
| Pseudo-obstruction or volvulus | • Nausea/vomiting<br>• Constipation<br>• Abdominal distension/discomfort | • Inpatient supportive and symptomatic measures are required<br>• Manage constipation<br>• Prokinetics are used in the absence of a mechanical obstruction | |
| Gastrointestinal bleeding | • Iron deficiency anaemia<br>• Haematemesis/malaena | • Transfusions of red blood cells and iron<br>• Consider endoscopic evaluation and local treatment of bleeding sites | |

earlier treatment initiation and improved survival and is now standard of care for all patients with SSc. The value of echocardiography can be limited by an inability to estimate the systolic pulmonary artery pressure due to the absence of a tricuspid regurgitant jet, as occurs in up to 40% of patients. New screening algorithms based on elevated serum N-terminal pro-BNP (NT pro-BNP) levels and increased forced vital capacity to diffusing capacity ratio (e.g. greater than 1.8) show promise and may be cost-effective.[5] Right heart catheterisation is essential to confirm the diagnosis of PAH. Medications for PAH are managed by specialists and are listed in Table 2.

Myocardial ischaemia and patchy fibrosis result in cardiomyopathy in some patients with SSc. More commonly, pericardial disease and pulmonary hypertension are associated with pericardial effusions. Conduction system dysfunction can lead to sudden death with ventricular arrhythmia or heart block.

## Interstitial lung disease

ILD is a common manifestation seen in patients with more severe SSc, including those with diffuse disease. In conjunction with regular clinical assessment, regular screening with pulmonary function tests assists in identifying patients with ILD before the development of symptomatic disease. Dyspnoea, bibasal crepitations, a restrictive defect on pulmonary function tests and/or reduced diffusing capacity should prompt high-resolution computed tomography (HRCT). HRCT is used to confirm ILD and assess the extent of disease. In established stable ILD, this is not routinely repeated unless symptoms progress or change.

Untreated, the course of ILD in patients with SSc can be highly variable. Reduction in diffusing capacity is the best predictor of prognosis. Male sex, more extensive disease on HRCT and comorbid PAH are associated with a worse prognosis.[6] The Scleroderma Lung Studies have provided evidence for the use of cyclophosphamide and mycophenolate in patients with SSc-related ILD.[7,8]

## Malignancies

Several observational studies have reported a higher rate of malignancy both in patients with limited and in those with diffuse disease.[9,10] More recently, antibodies to RNA polymerase III have been shown to be associated with a greater risk of malignancy, typically within two years

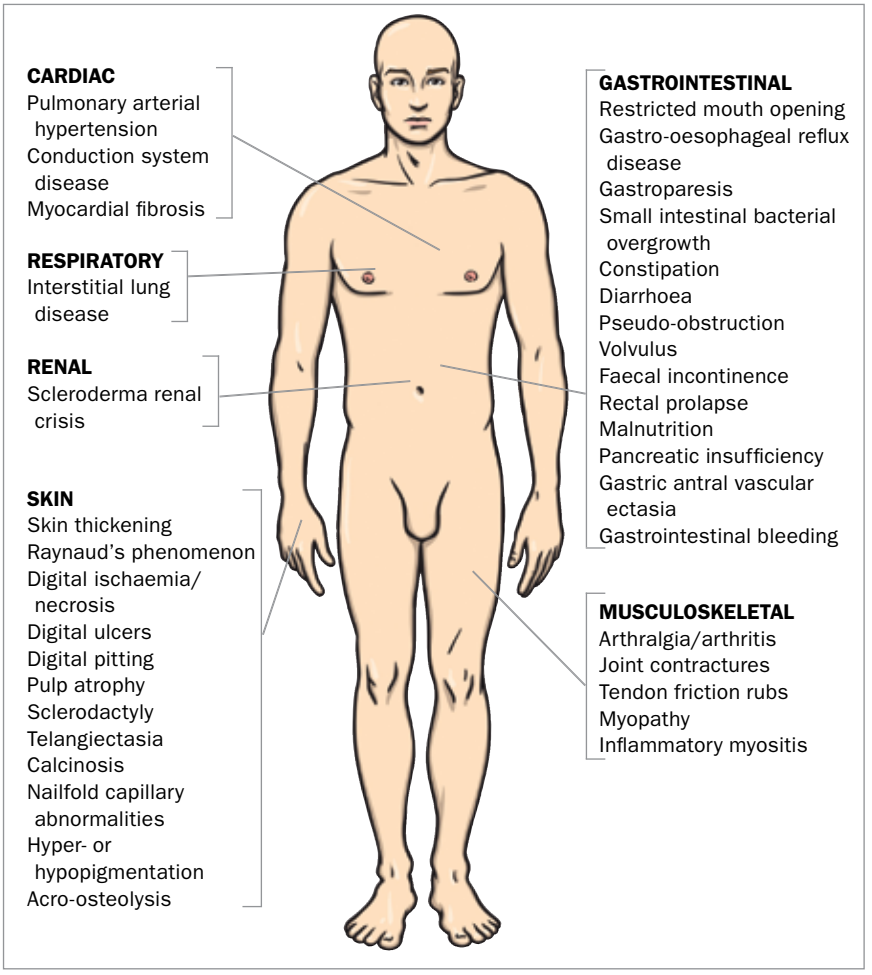


**Figure 4.** Disease manifestations of systemic sclerosis.

of diagnosis of SSc, irrespective of disease subtype.[11] A recent diagnosis of SSc with this autoantibody should prompt increased vigilance for solid organ malignancy and nonmelanoma skin cancers in particular.

## Summary

SSc is a multisystem autoimmune disorder with characteristic features of vasculopathy and fibrosis. A multimodal, multidisciplinary approach to management of disease manifestations is essential. In recent years, better outcomes in patients with SSc have been seen. Central to this has been early diagnosis of SSc and early identification of common and life-threatening complications. MT

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