Chapter 1
Major Scleroderma Emergencies

Voon H. Ong and Christopher P. Denton

Introduction

Of the immune-mediated rheumatic diseases, SSc has the highest case-specific mortality and substantial non-lethal complications. This is largely related to the significant burden from major organ complications in particular cardiopulmonary involvement. However, some of the complications may present as acute emergencies as listed in Table 1.1. Briefly, acute emergencies in SSc can be broadly classified as acute decompensation of existing organ disease, acute emergencies specific to SSc and other medical and surgical emergencies in SSc including opportunistic infections. Key aspects of these emergencies are covered in other chapters. These include pulmonary hypertension, critical digital ischaemia, hypertensive renal crisis, gastrointestinal disease, issues related to pregnancy and cardiac involvement. Importantly, complications related to overlap disease that may affect a fifth of SSc patients need to be carefully evaluated [1]. The objectives of

V. H. Ong (✉) · C. P. Denton
Centre for Rheumatology and Connective Tissue Diseases, UCL Division of Medicine, London, UK
e-mail: v.ong@ucl.ac.uk; c.denton@ucl.ac.uk

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Table 1.1 Spectrum of key acute emergencies in SSc

SSc-specific emergencies	Digital ischaemia and gangrene
	Hypertensive renal crisis
	GI haemorrhage (gastric antral vascular ectasia)
	Pseudo-obstruction
Decompensation of SSc complications	Worsening of pulmonary hypertension
	Progressive myocardial disease
	Exacerbation of interstitial lung fibrosis
	Malabsorption with nutritional weight loss
Non-SSc acute emergency	Opportunistic infections
	Overlap syndromes[a]
	Pregnancy-related complications[b]
	Peripheral vascular disease

[a]Overlap syndromes include inflammatory muscle disease, inflammatory arthritis, systemic lupus erythematosus, vasculitis
[b]Pregnancy-related issues include pre-eclampsia, premature rupture of the membrane and placenta abruptio GI:Gastrointestinal

this module are to illustrate with case vignettes the major emergencies of SSc of commonly encountered symptoms affecting these patients as a life-threatening event requiring urgent intervention. The complexity of multiorgan involvement in these cases often requires multidisciplinary coordination including rheumatological review and immediate patient's referral to appropriate specialties to ensure adequate joint management.

Case History 1

The first case describes an acute vascular crisis with an uncommon cause and highlights the need to consider a broad differential diagnoses for a common vascular manifestation of SSc complication.

A 62 year old lady with established anti-topoisomerase I antibody associated limited cutaneous systemic sclerosis with mild interstitial lung disease (FVC 79% DLCO 68%) presented with severe pain across all toes with a dry ulcer over her right second toe with dependent oedema up to the knees (Fig. 1.1a, b). Her current vasodilator treatment includes Losartan 100 mg daily and Diltiazem 360 mg in divided doses. She has had cardiac stenting for ischemic heart disease 3 years ago and she is maintained on Aspirin 75 mg daily with isosorbide mononitrate 10 mg daily and Clopidogrel was recently discontinued as part of investigation for haematuria. Although she has had episodic digital ulcers affecting her fingers requiring intravenous prostacyclin infusions, she has never had ulcers affecting her lower limbs. More proximal causes of distal limb gangrene should be evaluated with Doppler imaging and Echocardiogram in particular for valvular abnormalities [2, 3]. Echocardiogram showed only mild aortic stenosis with mean gradient of 9 mmHg with no other major valvular abnormalities. Bilateral lower limb arterial tree assessment showed patent superficial femoral, popliteal, anterior and posterior tibial and peroneal arteries bilaterally with normal triphasic waveforms. Vascular opinion was sought and large vessel cause of gangrene was excluded. She was commenced on intravenous prostacyclin infusion.

Hb 7.4 g/L: platelet 445 x 10^9/L RDW 15.1% [11–16] with positive markers for haemolysis with reticulocytes 171 × 10^9/L(50–150) haptoglobin <0.2 g/L (0.3–1.9) LDH 383 U/L (135–214). Peripheral blood film showed agglutination and polychromasia. DAT was strongly positive with anti-CD3d and negative for IgG. Total Bilirubin 9 umol/L (<21), direct bilirubin 5 umol/L (<5) CRP 2 mg/L (<5) ESR 15 mm/h.

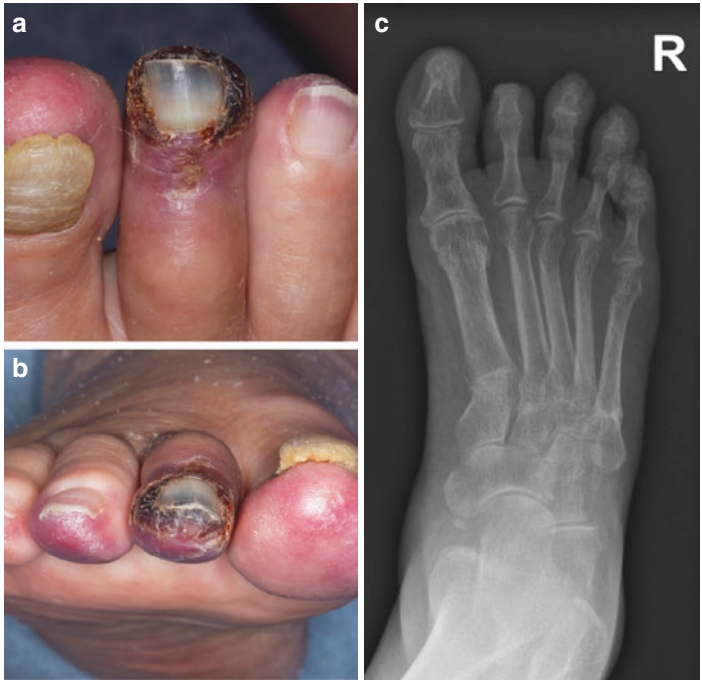

Figure 1.1 Critical digital ischaemia in systemic sclerosis with cryoglobulinaemia. Gangrenous right second toe tip (**a**, **b**). Autoamputation of the affected to at the level of DIP was evident radiologically 6 months post-onset of the gangrenous ulcer (**c**). There was no cortical thinning or osteolysis to suggest osteomyelitis. There was incidental fifth metatarsal base fracture (**c**)

Paraprotein 5 g/L and immunofixation showed immunoglobulin M (IgM) kappa paraprotein.

Cryoglobulin screen showed Type 1 monoclonal IgM kappa cryoglobulin. Iron 6 umol/L (11–36) TIBC 65 umol/L (53–85) transferrin 9.2% (20–40) ferritin 43 ug/L. It is noteworthy that haematuria may reflect the haemoglobinuria related to ongoing haemolysis that occurs during the course of the disease [4]. She was commenced on oral Prednisolone 50 mg daily (1 mg/kg) for autoimmune haemolytic anaemia (AIHA).

Type 1 cryoglobulinaemia is associated exclusively with B cell proliferative diseases mainly monoclonal gammopathy of undetermined significance and less commonly Waldenström macroglobulinaemia and multiple myeloma [5, 6] whereby the sera of these patients contain monoclonal IgM, and more rarely IgG, or IgA cryoglobulins. In almost half of the patients, type I cryoglobulinemia is characterized by severe cutaneous involvement with a lower frequency of glomerulonephritis compared to other types of cryoglobulinemia. Hyperviscosity syndrome contributing to vascular crisis may also occur in due to high concentration of monoclonal cryoglobulins owing to the concomitant lymphoproliferative disorder. Specifically, cutaneous involvement is characterized by presence of symptoms related to cold exposure such as acrocyanosis, livedo, urticaria, cold-induced necrotic purpura, or as in this case with painful ulcers and gangrene of the extremities.

This patient underwent bone marrow aspirate and trephine. Smears were unremarkable. Flow cytometry identified at least 10% population of kappa restricted CD5 negative B cells. MYD88 mutation was negative. The trephine did not show an obvious abnormal lymphoid or plasmacytic infiltrate. Aspirate morphology showed normocellular particles and trails. Trilineage haematopoiesis was seen with normal granulopoiesis and no abnormal infiltrate. Erythropoiesis was normoblastic. Megakaryocytes were seen in adequate numbers with normal morphology. Low levels plasma cells (2%) were seen but these were clustered around the particles.

PET CT did not show any hypermetabolic or pathological lymphadenopathy.

The low frequency and its considerable diverse clinical heterogeneity meant that there is a lack of evidence-based standardised therapies for AIHA. However, only aggressive and prompt treatment can induce a rapid response of dysproteinaemic state and reduce the organ damage caused by cryoglobulin. In light of her progressive gangrene, she also received plasma exchange to transiently remove cryoglobulins from her circulation although a decrease of serum cryo-

globulins was shown to occur in only half the patients and plasma exchange does not prevent formation of new cryoglobulins [7]. Alkylating agents such as cyclophosphamide, bortezomib (a proteasome inhibitor) and rituximab-based regimens are the main therapeutic options to eliminate the B cell clones that produce cryoglobulins. In our patient, prompt start of an integrated therapeutic approach with prostanoid infusion, plasmapheresis, and chemotherapy halted further progression of the occlusive vasculopathy with resultant autoamputation of the affected toe (Fig. 1.1c).

In some cases, these patients may also require ongoing plasmapheresis to control the vascular manifestations of the disease that occur in the presence of even small amounts of monoclonal immunoglobulin that may persists despite effective treatment of the malignancy. Despite these therapeutic measures, these patients may experience ongoing problems, especially skin-related symptoms.

Whilst acute vascular digital crisis and anaemia in SSc are often attributable to associated complications of the disease itself, there are few reported cases of AIHA in SSc and coexisting overlap diseases including lupus, antiphospholipid syndrome and cryoglobulinaemia should be considered as differential diagnoses [8–10].

Case History 2

The second case describes a patient with worsening exertional dyspnoea and reflects the complexity of multiorgan involvement in SSc and important considerations are required to evaluate carefully the individual components of organ-based disease and potential complications.

50 year old lady with established limited SSc diagnosed 20 years ago and she developed pulmonary arterial hypertension 2 years ago that is well controlled on Macitentan 10 mg twice daily and Sildenafil 50 mg thrice daily. Her other medications include Ramipril 10 mg daily, Omeprazole 20 mg daily. She harbours anti centromere (ACA) and anti-Ro-52, -La antibodies. She is a never-smoker.

She presented with increasing exertional breathlessness climbing incline on stairs and hills (Functional Class III) with NT-proBNP 1174 ng/L with troponin 11 ng/L. Cardiac MRI demonstrated right ventricular dilatation with biatrial dilatation (LA 30 cm^2 and RA 31 cm^2) with increased T1 and T2 uptake with patchy septal gadolinium enhancement and preserved left ventricular function. In summary, this tissue characterization is suggestive of progressive myocardial disease. A 24 hour tape showed 2000 ventricular ectopics with first degree heart block with no non-sustained ventricular tachycardia.

A year before the current presentation, she developed an acute episode of pleurisy treated as pneumonia although sputum cultures were negative and shortly after this, she developed acute renal injury with increased protein creatinine ratio 831 mg/mmol (<30) with normal albumin 35 g/L (35–50). Subsequent renal biopsy demonstrated membranous glomerulonephritis. She also developed increasing paraethesiae over left hand and right foot that was confirmed as sensory axonal neuropathy on EMG. She was commenced on mycophenolate but discontinued due to an acute episode of pleuritic chest pain with breathlessness. This was substituted with Azathioprine. It was noted that she had mild lymphopaenia 0.16 × 109/L (1.0–4.0), elevated ESR 63 mm/h and platelets 130×10^9 (140–400) with C3 0.77 g/L (0.9–1.8). dsDNA 7.5 IU/mL (<10) Crithidia lucillae antibody negative.

Serial lung function investigations (Table 1.2) showed a reduction in forced vital capacity (FVC) from 81 to 65 (15–25% reduction of baseline) suggesting interstitial changes with markedly impaired gas transfer. The latter is out of keeping with her recent stable haemodynamics with pulmonary

Table 1.2 Serial lung function for Case 2

	2019	2018	2017
FVC %(value)	67 (2.76)	65 (2.66)	81 (2.95)
DLCO % (value)	25 (2.32)	35 (2.58)	32 (3.0)
KCO % (value)	33 (0.53)	42 (0.67)	46 (0.73)

vascular resistance (PVR) well controlled with high cardiac output (CO) possibly driven by active inflammatory disease (right heart catheter assessment: mean pulmonary arterial (PA) pressure mean 43 mmHg, pulmonary capillary wedge pressure 8 mmHg, CO 9.7 L/min cardiac index 5.4 L/min/M^2 PVR 289 ARU dynes/s/cm PA saturation 64% systemic saturation 86% on finger oximetry but 98% in wedge position), 6 min walk test stable 427 but below 500 several years ago suggesting the possibility of additional pathology such as pulmonary veno-occlusive disease (PVOD) or other lung disease.

Two serial HRCT Chest were compared (Figs. 1.2 and 1.3). There is diffuse ground glass attenuation with centrilobular predominance sparing the periphery. The latter does not favour hypersensitivity pneumonitis. In addition there are cystic appearances and these have enlarged over time (Fig. 1.2). There is dilated pulmonary artery (Fig. 1.3). There is no pleural or pericardial effusion. The CT approach to diag-

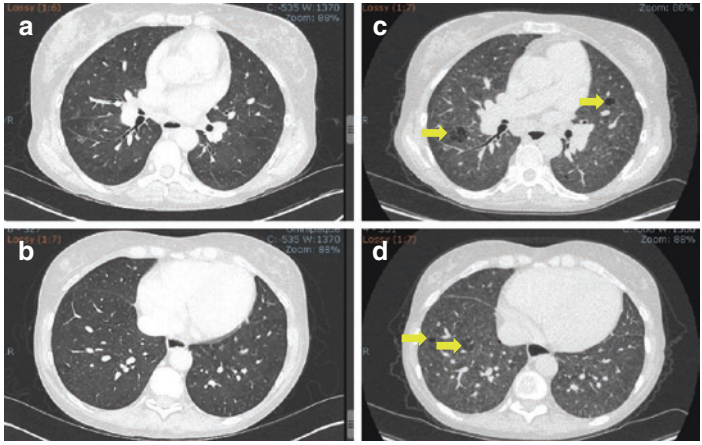

FIGURE 1.2 Progression of parenchymal lung disease in systemic sclerosis. There is centrilobular ground-glass opacification in both lungs with more extensive cystic lung disease (yellow arrows) over 2 year period (Panels **a** and **b** (2017) and **c** and **d** (2019) respectively). There is dilatation of the oesophagus with food debris

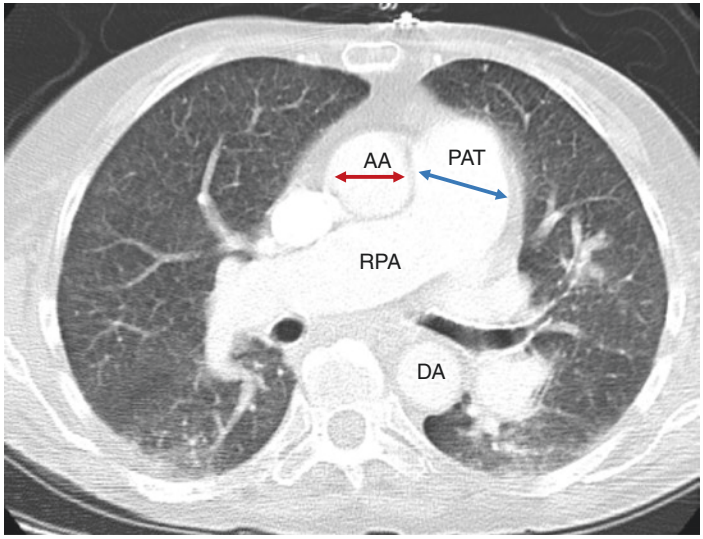

FIGURE 1.3 Features of pulmonary hypertension on contrast CT scan of the chest. Enlarged pulmonary arterial trunk (PAT) is larger than that of the ascending aorta (AA) at the same level. Right pulmonary artery (RPA) is also dilated. Descending aorta (DA) also shown

nosis of PH begins with identifying an enlarged pulmonary artery diameter greater than 29 mm, which is usually larger than that of the ascending aorta at the same level [11]. This diameter must be measured in the axial plane at the bifurcation, orthogonal to the long axis of the pulmonary artery. A variety of parenchymal changes in PH has been described. These include mosaic attenuation in PH due to regional differences in lung perfusion, in addition to diffuse bilateral centrilobular ground-glass opacities (increased lung parenchyma attenuation without obscuration of the underlying vasculature or airways) but without interlobular septal thickening to suggest PVOD. As a subtype of PAH group I, PVOD is an important consideration as there is an unexpectedly high incidence of PVOD in patients with SSc-PH-ILD and it is an unrecognised contributor to the dismal prognosis of

these patients. It is critical to distinguish PVOD from PAH as treating PVOD with vasodilators may lead to fatal pulmonary oedema and death. However, this patient is tolerating Macitentan with well preserved saturations thus the diagnosis of PVOD is less likely.

Interstitial lung fibrosis is a major complication in SSc particularly among those with anti-Scl70 antibody. Those with ACA limited SSc is less likely to develop ILD with cumulative incidence of clinically significant lung fibrosis is 8.5% at later stage of disease [12]. Acute exacerbation of lung fibrosis have been described in SSc-ILD in particular those with overlap diseases [13, 14] although the mechanisms related to acute exacerbation in connective tissue diseases-related ILD are unclear but these few factors like intrinsic factor leading to progression of underlying disease, infection and role of gastro-oesophageal reflux disease with microaspiration may be relevant. Accepting this is a rare entity, management of this disease is largely empirical with recent evidence that early institution of disease modifying agents including biological agents Rituximab may improve survival. In this case, in the context of lupus with presence of Ro antibody, a distinct subtype of interstitial lung disease—lymphocytic interstitial pneumonia (LIP) should be considered [15]. Alternatively, the cysts on HRCT could be due to emphysema in never-smokers in SSc-ILD [16, 17].

Another possible cause of acute deterioration is worsening of PAH. PAH is a progressive disease with the majority of patients succumb as a result of right ventricular (RV) failure. As PAH progresses, the RV must adapt to increases in PVR and afterload [18]. Despite structural remodeling, the RV eventually cannot adapt to the increased afterload resulting in right heart failure. These patients need to be carefully managed to reverse the inciting event and optimise fluid balance, haemodynamics, and RV function and this is best managed by a multidisciplinary team with experience in managing patients with PAH [19]. Any reversible causes of acute decompensation should be appropriately addressed. Patients should be carefully monitored, as RV failure can eventually

lead to multiorgan failure through decreased perfusion to other organs. Fluid balance must be carefully managed in patients with PAH as both hypovolaemia and hypervolaemia can have damaging effects to patients. It is important to note that over-diuresis could lead to a greater worsening of CO further impacting end-organ perfusion.

It is also noteworthy that SSc patients demonstrate peculiar vulnerability to infectious complications in part to intrinsic disease-related immune dysregulation, disease-related factors (such as ILD) and in part to the immunosuppressive treatments including biological therapies. The lung is among the most frequent sites of infection in SSc in particular among those with severe ILD or reflux/aspiration and they are susceptible to developing pneumonia sustained both by common pathogens such as anaerobic bacteria and by opportunistic microorganisms., as well as routine bacterial and viral respiratory pathogens. Oesophageal involvement, like dysmotility disorder or reflux, can also be associated to lung infections. In SSc, the most frequent causes of death not directly related to SSc are infections, pneumonia [20]. Furthermore, many drugs used in SSc treatment, such as cyclophosphamide, mycophenolate and rituximab have been associated to a raised risk of developing infections, mostly bacterial or mycotic pneumonia [21]. Thus, when patients with SSc manifest new respiratory symptoms, especially if treated with immunosuppressive drugs, both routine and opportunistic lung infections should be considered for appropriate diagnostic and therapeutic intervention [22]. It is noteworthy that repeated immune-mediated stimuli from recurrent lung infections has been postulated to be a trigger for pleuropulmonary fibroelastosis (PPFE), a recently described entity characterized by a combination of fibrosis involving the visceral pleura and fibroelastotic changes predominating in the subpleural lung parenchyma have been reported in SSc and may contribute to worsening of respiratory symptoms in SSc-ILD [23, 24]. However, there are no CT appearances to suggest PPFE in this case.

In light of her overlap lupus features with renal disease, neuropathy with likely LIP features on HRCT and possibly myocardial disease, this patient was managed with rituximab and clinical and biochemical parameters related to each of the affected organs will be carefully evaluated for response over time.

Summary

Although SSc is often associated with major organ involvement, serious and potentially life-threatening acute emergencies may occur in the context of acute decompensation or acute exacerbation of chronic complication of SSc. Non-SSc related complications in particular opportunistic infections and overlap immune-mediated overlap disease should be carefully considered as well.

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