Introduction

Systemic sclerosis (SSc) is an autoimmune rheumatic disease characterised by fibrosis of skin and internal organs; vasculopathy presenting as Raynaud's phenomenon may lead to digital ulceration and gangrene requiring urgent intravenous vasodilator therapy. SSc may also manifest features of other connective tissue diseases, known as SSc overlap syndromes.

We present a 55 year-old male with anti-U1RNP positive limited cutaneous systemic sclerosis (lcSSc)/rheumatoid arthritis (RA) overlap syndrome who developed acute-onset acral ischaemia leading to extensive gangrene. There were constitutional symptoms at the outset and a marked inflammatory response with no evidence of infection, suggesting a diagnosis of vasculitis on a background of vasculopathy. The case was notable for the rapid progression of gangrene which then responded well to immunosuppression; conventional management with vasodilators had proven unhelpful. Dry gangrene in this setting can be managed conservatively to avoid extensive amputation and a poor functional outcome.

Case presentation

A 55-year-old male non-smoker presented acutely with fever, joint pain, and cold, painful extremities. He had a background of non-erosive rheumatoid arthritis diagnosed 6 years previously (rheumatoid factor positive, anti-cyclic citrullinated peptide (anti-CCP) negative). This was well-controlled on methotrexate until 2 years prior to this admission when he developed features of a lcSSc overlap syndrome with Raynaud's phenomenon (RP), sclerodactylly, telangiectasia and sicca symptoms. Anti-nuclear antibody (ANA) was positive (titre of 1:640) with anti-RNP (U1RNP) specificity.

On examination he had cold digits with small joint synovitis of the hands and feet. The rest of the examination was unremarkable. Blood tests on admission showed a raised white cell count of 21.1 x 10^9/L (neutrophil count 17.8 x 10^9/L), C-reactive protein (CRP) 301 mg/L, and were otherwise normal. Chest x-ray and urine dip showed no evidence of infection.

Initial management was with empirical intravenous antibiotics, oral corticosteroids (prednisolone 20 mg od) and continuous prostaglandin analogue (iloprost) infusion. He spiked temperatures and inflammatory markers rose further; antibiotic therapy was broadened. A transoesophageal echocardiogram showed no vegetations and multiple set of blood cultures returned negative. CT chest, abdomen and pelvis did not reveal an occult source of sepsis.

One week into admission, necrosis of the hands and feet developed. Therapeutic dose low-molecular weight heparin was added along with clopidogrel and iloprost infusion was uptitrated. Despite this there was further deterioration of the extremities. Magnetic resonance angiography revealed no macrovascular occlusions responsible for the upper or lower limb gangrene. He received treatment with three daily doses of intravenous methylprednisolone (500 mg) and CRP fell to 153 mg/L. Unfortunately, by day 10 wet
gangrene of the lower limbs had developed and he underwent bilateral below knee amputations (BKAs).

Postoperatively he was managed on intensive care with prednisolone 60 mg daily and infusions of intravenous immunoglobulin (IVIG) over 5 days. This led to demarcation of tissue gangrene with no further progression of necrosis (Figure 2a). Ulnar and radial pulses were strong. CRP fell rapidly and antibiotics were stopped (Figure 1). Mycophenolate mofetil (MMF) was initiated as treatment for presumed vasculitis.

Further investigation had been unremarkable, including negative tests for anticientromere/anti-ScI70 antibodies, anti-neutrophil cytoplasmic antibody (ANCA), antiphospholipid antibodies, cryoglobulins and serology for viruses hepatitis B, C and HIV. Lipid profile was within normal limits.

He was reviewed by plastic surgery who advised amputation at both elbows. Following discussion, it was decided to continue conservative management as long as his gangrene remained dry, and to await autoamputation. Over time there was a slow but definite improvement in the more proximal areas of his hands that had initially appeared non-viable. He continued with monthly IVIG, a weaning dose of prednisolone, and vasodilator therapy including sildenafil. MMF was uptitrated to 1g BD. Rivaroxaban was added.

He was eventually discharged to rehabilitation following a 4 month admission and learnt to mobilise independently on prostheses. Over the subsequent year, both of his fifth digits autoamputated but the remaining digits did not. He eventually proceeded to limited surgical resection of his remaining necrotic digits 18 months after the acute presentation (Figure 2b). He remains in remission on medical therapy. He has significant functional impairment as a consequence of the hand gangrene and subsequent surgery to his fingers, but he manages well.

Discussion

We describe a case of severe gangrene in a patient with anti-U1RNP-positive lcSSc/RA overlap. The acute presentation was marked by fever, elevated inflammatory markers and rapidly progressive acral ischaemia leading to gangrene. We felt that the case was best described as a combination of vasculitis (fever, high CRP) in the setting of SSc-vasculopathy (pre-existing RP). Whilst conventional vasodilator strategies appeared to be of limited benefit, the combination of immunosuppression and IVIG was associated with improvement and eventual recovery. We discuss here a number of interesting points raised.

It is unknown how many SSc patients develop critical ischaemia; of 1168 patients attending the Royal Free hospital, London, 1.6 % of patients developed critical digital ischaemia and 1.4 % progressed to gangrene (1). Raynaud’s phenomenon is a typical feature of SSc patients with anti-U1-RNP antibodies and critical digital ischaemia in these patients is well-recognised; the Digital Ulcers Outcome registry reported an incidence of gangrene of 24.6 % (n = 114) (2). The standard approach to the management of such cases should include an assessment for proximal vessel disease, consideration of co-existent disorders such as SLE, vasculitis and cryoglobulinaemia, and exclusion of
prothrombotic states and thromboembolic disease. Management of such patients should comprise vasodilators including intravenous prostanoid, treatment of concurrent sepsis, consideration of anti-platelet/anticoagulation, and, where appropriate, surgical resection (3). In our patient, digital ischaemia was refractory to all such therapies. Intravenous corticosteroids, followed by IVIG, were therefore commenced for a likely vasculitic component. The patient responded well to this with resolution of fever, normalisation of inflammatory markers, and no further progression of the gangrene.

Of some interest here is the possible role of IVIG in promoting stabilisation of the inflammatory process. We decided to use it here due to its emerging role in the treatment of ANCA-associated vasculitis (4) and for its potential utility in the management of various aspects of SSc, including skin disease, although this benefit is rather slow and modest (5). There is as yet no trial of IVIG in SSc digital ischaemia.

A vital part of the evaluation of patients with SSc is characterisation of the autoantibody profile, both for diagnostic and prognostic purposes. Our patient was positive for U1RNP, associated with overlap SSc syndromes; these affect around one fifth of SSc cases (6). Of note, ANCA-associated vasculitis has been described in association with SSc and U1RNP patients (7). Originally, U1RNP antibody positivity was thought to imply a milder disease course as in the subset of patients first described in 1972 (8) when the term ‘mixed connective tissue disease’ was proposed. These patients exhibited overlap features of SSc, SLE, RA and myositis but were thought to have minimal pulmonary, renal and cerebral involvement and a good prognosis. Since that description, however, further evidence has suggested that these patients often do not follow a mild course, but tend to evolve to a more defined disorder; in fact, pulmonary involvement is now recognised to be present in around 75% of cases, in particular pulmonary hypertension and interstitial lung disease (9). The original group of patients had a mortality of 36.4% at 12 years (10).

A notable aspect of this case was the success of conservative medical strategies over major surgical intervention in the treatment of this patient’s hand necrosis. The role of surgery in the management of SSc digital ischaemia is controversial; while amputation for areas of wet gangrene is unavoidable, it is recognized that dry gangrenous areas tend to autoamputate with less resultant tissue loss (11), as in the case presented. With medical treatment, the proximal portion of his hands and digits that had initially appeared non-viable slowly improved and debridement only to the level of the metacarpophalangeal joint was eventually required. He retains a degree of manual function as a result.

**Conclusion**

This was an unusual case of severe gangrene in an overlap connective tissue disease patient. U1RNP antibodies may not imply a mild disease course in this group. IVIG may warrant further investigation as a therapeutic tool in critical digital ischaemia refractory to conventional treatment. Medical strategies can be pursued over major surgery in this setting so long as necrosis remains dry.

**Figure legend**
Figure 1 Graph showing C-reactive protein serum levels during first fifty days of admission with significant interventions noted.

Figure 2a Necrotic hands two weeks after presentation—plastics recommendation at this juncture was amputation at the elbows.

Figure 2b Hands after limited surgical resection conducted following full recovery and long remission

References