Severe gangrene in a patient with anti-RNP positive limited cutaneous systemic sclerosis/rheumatoid arthritis overlap syndrome caused by vasculopathy and vasculitis

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Abstract

In this paper, we describe a case of a male patient with anti-U1RNP positive limited cutaneous systemic sclerosis/rheumatoid arthritis overlap syndrome, who presented acutely with rapidly progressive digital ischemia, which lead to extensive gangrene. Management with conventional vasodilator therapy was unsuccessful. There were constitutional symptoms and a marked inflammatory response in the absence of evidence of infection, implying a component of vasculitis underlying the presentation. Treatment with immunosuppression and intravenous immunoglobulin led to resolution of the inflammatory process with no further progression of tissue necrosis. Here we discuss pertinent issues raised by the case, including the management of digital ischemia and gangrene in this context and the relevance of the anti-U1RNP in systemic sclerosis overlap syndromes.

Keywords: Systemic sclerosis, overlap syndrome, anti-U1RNP, gangrene, IVIG

Introduction

Systemic sclerosis (SSc) is an autoimmune rheumatic disease characterized by fibrosis of skin and internal organs. Vasculopathy presenting as Raynaud's phenomenon (RP) 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 ischemia 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 to be 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 RA diagnosed 6 years previously (rheumatoid factor positive, anti-cyclic citrullinated peptide negative). His condition had been well controlled with methotrexate until 2 years before this admission, when he developed features of an lcSSc overlap syndrome, who developed acute-onset acral ischemia 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 to be unhelpful. Dry gangrene in this setting can be managed conservatively to avoid extensive amputation and a poor functional outcome.

On examination, the patient 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 21.1×10⁹/L (neutrophil count 17.8×10⁹/L) and C-reactive protein (CRP) 301 mg/L, but were otherwise normal. A chest x-ray and urine dip showed no evidence of infection.

The initial management was with empirical intravenous antibiotics, oral corticosteroids (prednisolone 20 mg od), and continuous prostaglandin analog (iloprost) infusion. The patient’s body temperature spiked,
and inflammatory markers rose further; the antibiotic therapy was broadened. A transesophageal echocardiogram showed no vegetations, and multiple sets of blood cultures returned negative. Computed tomography of the chest, abdomen, and pelvis did not reveal an occult source of sepsis.

One week into admission, necrosis of the hands and feet developed. A therapeutic dose of low-molecular weight heparin was added along with clopidogrel, and iloprost infusion was uptitrated. Despite this, there was further deterioration in the extremities. A magnetic resonance angiography revealed no macrovascular occlusion responsible for the upper or lower limb gangrene. The patient 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 the patient underwent bilateral below-knee amputations.

Postoperatively, the patient was managed in the intensive care unit 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. The CRP fell rapidly, and antibiotics were stopped (Figure 1). Mycophenolate mofetil (MMF) was initiated for the treatment of presumed vasculitis (unfortunately despite the request of the medical team no operative specimens were sent for histological analysis).

Further investigation had been unremarkable, including negative tests for anti-centromere/anti-Scl70 antibodies, anti-neutrophil cytoplasmic antibody (ANCA), antiphospholipid antibodies, cryoglobulins, and serology for viruses hepatitis B, C, and HIV. Lipid profile was within normal limits.

The patient was examined by a plastic surgeon, who advised amputation at both elbows. Following discussion, it was decided to continue conservative management as long as the patient’s gangrene remained dry, and to await auto-amputation. Over time, there was a slow but definite improvement in the more proximal areas of patient’s 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.

The patient was eventually discharged to rehabilitation following a 4-month admission and learned to use prostheses independently. Over the subsequent year, both of his fifth digits auto-amputated, but the remaining digits did not. He eventually proceeded with limited surgical resection of his remaining necrotic digits 18 months after the acute presentation (Figure 2b). He remains in remission on medical therapy. The patient 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 ischemia 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). While 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 points raised.

It is unknown how many SSC patients develop critical ischemia; of 1168 patients attending the Royal Free Hospital in London, 1.6% developed critical digital ischemia, and 1.4% progressed to gangrene (1). Critical digital ischemia in patients with anti-U1RNP antibody is well recognized; 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 coexistent disorders such as systemic lupus erythematosus (SLE), vasculitis, and cryoglobulinemia, and exclusion of prothrombotic states and thromboembolic disease. The management of such patients should comprise vasodilators including intravenous prostanoïd, treatment of concurrent sepsis, consideration of anti-platelet/anticoagulation, and where appropriate, surgical resection (3). In our patient, digital ischemia 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, normalization of inflammatory markers, and no further progression of the gangrene.

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

A vital part of the evaluation of patients with SSC is characterization 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, the U1RNP antibody positivity was thought to imply a milder disease course as in the subset of patients first described in 1972 when the term “mixed connective tissue disease” was proposed (8). These patients exhibited overlap features of SSC, SLE, RA, and myositis, but they 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 recognized 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 ischemia 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 the patient’s hands and digits that had initially appeared non-viable slowly improved, and debridement only to the level of the metacarpophalangeal joints was eventually required. He retains a degree of manual function as a result.

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

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References