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Systemic sclerosis following COVID-19 infection with recurrent corticosteroid-induced scleroderma renal crisis

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SUMMARY

Systemic sclerosis is a complex multisystem connective tissue disease resulting in fibrosis of the skin and internal organs. Exposure to corticosteroids can trigger scleroderma renal crisis, a life-threatening complication of the disease. Autoimmune disease following infection with COVID-19 is being increasingly recognised. The mechanisms of post-COVID-19 autoimmunity are likely multifactorial, involving immune dysregulation, molecular mimicry and the development of cross-reactive antibodies. There are currently only two reported cases of systemic sclerosis occurring post-COVID-19 infection. We present the case of a female patient who developed systemic sclerosis post-COVID-19 infection. Following exposure to corticosteroids, the patient developed scleroderma renal crisis complicated by thrombotic microangiopathy, seizures and acute renal failure. Despite an antibody profile not typically associated with renal crisis (anti-topoisomerase positive, anti-RNA-polymerase III negative), the patient developed recurrent renal crisis with repeated exposure to corticosteroid therapy, highlighting the risk of steroid use in all patients with systemic sclerosis.

BACKGROUND

Systemic sclerosis (SSc) is a chronic multisystem connective tissue disease characterised by widespread vascular dysfunction and progressive fibrosis of the skin and internal organs.[1] SSc is uncommon, being observed most in women with a female-to-male ratio of 3:1.[2] Australia reports one of the highest prevalence of disease worldwide.[2] SSc is associated with premature mortality, with significant impact on patient quality of life and healthcare economy.[3] The clinical features are distinct from other autoimmune conditions, with sclerodactyly seen almost universally.[4] Supportive clinical features include fingertip lesions such as digital ulceration, telangiectasia, nailfold capillary changes, Raynaud's phenomenon and pulmonary manifestations.[4] Interstitial lung disease (ILD) and pulmonary hypertension (pHTN) account for the most common cause of death in patients with SSc.[3] Serology for autoantibodies can aid the diagnosis and enable clinicians to predict the clinical course and severity of disease.

The pathogenesis of SSc involves vascular and endothelial changes leading to defective vasoconstriction and angiogenesis.[5] Endothelial cell damage is caused by increased levels of circulating inflammatory cytokines and growth factors including endothelin-1, interleukin 1 and 6, interferon-gamma, tumour necrosis factor and transforming growth factor-beta.[1] This inflammatory cytokine milieu in combination with intracellular adhesion molecule dysfunction increases vascular permeability, allowing the migration of immune cells into the extracellular matrix.[6] Immune dysfunction and the development of a fibrogenic fibroblast population in the extracellular matrix mediate the fibrotic hallmark of SSc.[7]

Immune dysregulation resulting in autoantibody production is the serological hallmark of SSc with autoantibodies observed in 95% of cases.[8] The most frequent antibodies include anti-topoisomerase-1 (20%–45%), anti-centromere (12%–44%) and anti-RNA-polymerase III (5%–31%).[9] Anti-topoisomerase-1 positivity is seen more frequently with diffuse subtype SSc, with patients typically displaying increased disease activity with more extensive skin involvement, with an increased risk of developing ILD.[7 9] The presence of anti-centromere antibodies is associated with limited cutaneous involvement (CREST phenotype) and type 1 pHTN.[9] RNA-polymerase III antibodies correlate with the strongest risk of developing scleroderma renal crisis (SRC).[10] An overview of scleroderma-associated antibodies and clinical features is included in table 1.

CASE PRESENTATION

A female patient in her 40s presented to a general practitioner with new Raynaud's phenomenon, polyarthralgia of the hands and tightening of the fingers 2 weeks after recovering from a mild COVID-19 illness. The differentials considered at this time included post-viral reactive arthritis and post-COVID-19 autoimmunity. Further investigations revealed a negative rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP), with a strongly positive anti-nuclear antibody (ANA) in a homogeneous pattern. Systemic corticosteroid therapy was commenced with prednisolone 25 mg daily, and a referral sent for outpatient rheumatology review.

Within 3 weeks of corticosteroid therapy, the patient presented to a regional emergency department with progressive fatigue and dyspnoea, headaches and abdominal pain. The patient had a body mass index of 31, with no other comorbidities, and no personal or family history of autoimmune disease. On examination, there was evidence of sclerodactyly with skin thickening extending above the wrist. Skin thickening was also observed on the trunk and face. The patient had additional findings of digital pulp atrophy and telangiectasia. There was no evidence of active synovitis, rash, calcinosis or digital ulceration. Initial serology revealed

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Table 1 Well-described and novel antigens associated with systemic sclerosis autoantibodies and associated clinical features[9]

Antigen	Clinical associations
Centromere	Limited SSc, CREST phenotype, pHTN, protection from ILD
Topoisomerase-1 (Scl-70)	Diffuse SSc, ILD, early organ involvement
RNA-polymerase III	Renal, cutaneous, malignancy, increased mortality
Th/To	pHTN, ILD, gastrointestinal
PM-Scl	Myositis overlap syndromes
U3-RNP (fibrillarin)	pHTN, myositis, younger onset, cardiac involvement
U1-RNP	Myositis, mixed connective tissue disease
Ku	Myositis and joint involvement, SLE overlap
U11/U12-RNP	ILD
Eukaryotic initiation factor 2B	Diffuse SSc, ILD
RNA-binding region-containing protein 3	Malignancy, ILD, gastrointestinal, myopathy
RuvBL1 and RuvsBL2	Diffuse SSc, myositis overlap
Bicaudal D homolog 2	Myositis, ILD
Interferon-inducible protein 16	Digital ischaemia
Angiotensin II type 1 receptor	Digital ischaemia, pHTN
Endothelin-1 type A receptor	Digital ischaemia, pHTN
Muscarinic-3 receptor	Gastrointestinal
Platelet-derived growth factor receptor	Possibly profibrotic

ILD, interstitial lung disease; pHTN, pulmonary hypertension; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

an acute kidney injury (creatinine 166 µmol/L), with normal haemoglobin (141 g/L) and platelet count (422×10^9/L). CT of the abdomen and pelvis was unremarkable. The patient was managed conservatively with intravenous fluids and continuation of prednisolone at 25 mg daily. A complete autoimmune panel was ordered as outlined in table 2.

Table 2 Autoimmune screen results from initial patient presentation

Antibody	Result
ANA	>1280 (<160), homogeneous pattern
HLA-B27	Negative
Rheumatoid factor	Negative
Anti-CCP	Negative
Anti-dsDNA	Negative
Anti-Smith	Negative
Anti-nucleosome	Negative
Anti-SS-A/SS-B	Negative
Anti-Jo	Negative
Anti-U1RNP	Negative
Anti-Scl-70	**Positive**
Anti-RNA-polymerase III	Negative
Beta-2 glycoprotein	Negative
Anti-cardiolipin	Negative
Serum C3	1.04 g/L (0.90–1.70)
Serum C4	0.17 g/L (0.10–0.40)
Anti-GBM	Negative
Anti-MPO/PR3	Negative
Free light chain kappa/lambda ratio	1.24 (0.26–1.65)
ESR	17 (<21)

ANA, anti-nuclear antibody; anti-CCP, anti-cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate.

Within 48 hours of admission, the patient deteriorated developing hypertensive crisis with oliguric renal failure (creatinine 758 µmol/L), new anaemia (haemoglobin 101 g/L) and thrombocytopenia (platelets 64×10^9/L). Systolic blood pressure was consistently recorded between 220 and 240 mm Hg. Microangiopathic haemolytic anaemia was suspected, confirmed by the presence of schistocytes on blood film, with an undetectable haptoglobin and negative direct antiglobulin test. The primary differential at this time was SRC with secondary thrombotic microangiopathy caused by uncontrolled hypertension. Differentials such as thrombotic thrombocytopenic purpura (TTP) were also considered. The patient was intubated and transferred to the intensive care unit (ICU) following a cluster of tonic–clonic seizures presumed secondary to hypertensive encephalopathy. The patient was commenced on captopril and a nitroprusside infusion for blood pressure control, plasma exchange until TTP was excluded, haemofiltration and levetiracetam for seizure control. Corticosteroids were discontinued due to their recognised effect of precipitating SRC.

With treatment, blood pressure control improved and subsequently the degree of haemolysis. ADAMS-T13 was not suggestive of TTP. CT of the chest revealed bilateral pleural effusions without evidence of fibrotic lung changes. Transthoracic echocardiogram noted elevated pulmonary arterial pressures (50–55 mm Hg); however, in the setting of pulmonary congestion, this was thought to be wedge driven. Scleroderma-related antibodies were positive for anti-topoisomerase-1 as seen in table 2. The remainder of the autoimmune and vasculitis screen was negative including RNA-polymerase III. The diagnosis of diffuse SSc was based on the presence of sclerodactyly, with skin thickening extending proximal to the metacarpophalangeal joints. Supportive clinical features included telangiectasia, Raynaud's phenomenon, scleroderma-related antibodies and corticosteroid-induced hypertensive crisis. The modified Rodnan Skin Score at this time was 19/51.

The patient transitioned to intermittent haemodialysis via Permcath and underwent renal biopsy. Histopathology showed accelerated hypertensive endothelial injury and ischaemic glomerulopathy, with sclerosis to 2/20 glomeruli. Over the following 2 months, the patient's urine output improved, and with consistent blood pressure control, the patient was successfully weaned from renal replacement therapy.

In the weeks that followed cessation of haemodialysis, the patient re-presented with worsening dyspnoea and was found to have a new pericardial effusion thought to be a cardiac manifestation of SSc. Corticosteroid therapy was re-initiated, which achieved resolution of the effusion. Unfortunately, this again triggered SRC. The patient was transferred to a quaternary hospital ICU for rheumatology review and haemofiltration to manage acute renal failure and fluid overload. Repeat CT of the chest showed no evidence of ILD; however, pulmonary function testing showed a severely reduced diffusion capacity of 35% consistent with pulmonary vascular disease. Repeat transthoracic echocardiogram showed persistently elevated pulmonary artery pressure with severe tricuspid regurgitation. Once euvolemic, type 1 non-wedge-driven pHTN was confirmed on right heart catheterisation. Sildenafil was commenced with good response, with bosentan discontinued due to adverse effects. A timeline of key investigations is outlined in table 3.

Table 3 Timeline of pertinent results over multiple presentations with scleroderma renal crisis

Investigations	Initial presentation	First episode of renal crisis	Initial discharge	Re-presentation with renal crisis
Haemoglobin (g/L)	141	101	101	88
Platelets ($\times 10^9$/L)	422	64	420	267
Urea (mmol/L)	11.6	30.2	23.5	44.3
Creatinine (µmol/L)	166	758	298	593
eGFR (mL/min/1.72 m^2)	33	<5	15	7
C reactive protein (mg/L)	11.9	15.4	11.7	13.5
White cell count ($\times 10^9$/L)	13.1	37.9	12.8	21.0
Haptoglobin (g/L)	–	<0.01	1.22	–
Direct anti-globulin test	–	Negative	–	–
Blood cultures	No growth	No growth	–	No growth

eGFR, estimated glomerular filtration rate.

The patient remained oliguric and dialysis dependent via newly formed arteriovenous fistula with ACE inhibitor therapy continued. Renal transplantation currently is not a viable consideration due to progression of pHTN and intolerance of corticosteroids.

The patient continued to experience refractory nausea and abdominal discomfort. Coeliac serology was unremarkable. The patient underwent endoscopy, followed by Barium swallow and gastric emptying study. Barium swallow identified oesophageal dysmotility likely secondary to SSc, with significant impact on quality of life and management decisions. In the setting of recurrent aspiration events, initiation of immunosuppression has been delayed and the patient remains off disease-modifying therapy.

Given the complexity of the case with multiple systems affected, the patient will be followed up by several specialty units including nephrology, rheumatology, respiratory and gastroenterology. Future management decisions will require a multidisciplinary approach.

DISCUSSION

SRC represents the most striking and well-studied renal manifestation of SSc.[11] Renal manifestations are common in SSc with up to 50% of patients having clinical markers of renal dysfunction such as proteinuria or elevated creatinine, and up to 80% of patients having occult renal pathology on autopsy.[11] SRC is less common, occurring in approximately 10% of patients with diffuse SSc, and just 1%–2% of limited SSc.[10 11] Rapidly progressive skin thickening and positive RNA-polymerase III antibodies are the strongest risk factors for development of renal crisis.[10 11] Exposure to corticosteroids at >15 mg per day in the preceding 6 months is a major recognised risk factor.[12] Patients with antibodies to topoisomerase-1 without RNA-polymerase III tend to develop renal crisis later in the disease course.[11] Approximately 40% of patients with SRC require renal replacement therapy.[13] Prognosis remains poor despite the early introduction of ACE inhibitor therapy, with a 5-year survival rate of 65%.[10] Renal transplantation remains difficult given the risk of corticosteroid and ciclosporin-induced renal failure.[11]

A variety of autoimmune conditions have been reported following infection with COVID-19 including systemic lupus erythematosus, large and small vessel vasculitis, rheumatoid arthritis, inflammatory myopathy, polyarteritis nodosa, Graves' disease, acute inflammatory demyelinating polyradiculoneuropathy and immune thrombocytopenic purpura.[14–17] Post-viral autoimmunity is hypothesised to occur through multiple mechanisms including molecular mimicry and reactive epitope spreading.[18] Viral uptake by cells triggers pyroptosis, leading to the release of damage-associated molecular patterns.[15] Cytokine recruitment and excessive NETosis lead to immune dysregulation with altered tolerance to self-antigens triggering the production of cross-reactive antibodies and subsequent autoimmune disease.[15 19 20]

While autoimmune disease post-COVID-19 is increasingly recognised, early diagnosis remains challenging. This lies in the shared symptomatology and serology of multisystem autoimmune disease with the post-COVID-19 syndrome colloquially termed 'long COVID'.[21] Symptoms and signs such as lethargy, fevers, arthralgias, cognitive fatigue and cutaneous manifestations are difficult to distinguish in aetiology.[19] Serological investigations add to the challenge for clinicians with positive antibodies reported during and post-COVID-19 including ANA, anti-neutrophil cytoplasmic antibodies, anti-CCP, anti-cardiolipin, anti-beta-2-glycoprotein, anti-SSA/Ro and anti-endoglin.[15 19] Antibodies can be transiently elevated during and post-COVID-19, with some studies showing persistence of antibodies at 12 months.[22] It is unclear whether these antibodies represent a virally triggered autoinflammatory processes, early autoimmune disease or may have been present preceding COVID-19. What we do know is the complexity of the shared symptomatology and serology challenge clinicians to distinguish autoimmune disease from post-COVID-19 syndrome. These challenges could lead to delayed diagnosis and treatment, resulting in increased healthcare burden, and increased morbidity and mortality for patients.

Learning points

- Systemic sclerosis is a complex multisystem connective tissue disease presenting with fibrosis of the skin and internal organs.
- Corticosteroid therapy is not without risk in rheumatological conditions and is a recognised trigger for scleroderma renal crisis and should be used with caution in all cases of systemic sclerosis regardless of antibody status.
- The symptomatology and serology observed with COVID-19 infection challenge clinicians to diagnose autoimmune diseases that can have significant impact on morbidity and mortality for patients.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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