CASE REPORT

Mistaken identity: normotensive scleroderma renal crisis

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SUMMARY

A patient presented with neuromuscular, respiratory and cardiac symptoms and was initially diagnosed with amyotrophic lateral sclerosis (ALS), myocardial ischaemia and pneumonia. He developed unexplained progressive kidney failure over the ensuing week, and his kidney biopsy showed thrombotic microangiopathy that led to the correct diagnosis of normotensive scleroderma renal crisis. His clinical presentation and course were consistent with systemic sclerosis and normotensive scleroderma renal crisis. He was treated with an ACE inhibitor (ACEi) and haemodialysis with significant functional improvement over the next 3 months to his prior baseline with the exception of kidney failure. This case highlights a diagnostic challenge requiring astute history and physical examination skills, and the value of a kidney biopsy in providing the final diagnosis.

BACKGROUND

Systemic sclerosis (SSc; scleroderma) is a rare multi-system connective tissue disease of unknown aetiology affecting 1–2 in 100 000 individuals in the USA per year¹ increasing their mortality about 5–8 fold.² It is characterised by immune activation, fibrosis and vascular dysfunction. Systemic manifestations of SSc include skin thickening, oesophageal dysmotility, pulmonary fibrosis and arterial hypertension. Renal abnormalities such as azotemia, proteinuria and hypertension occur in 45–60% of patients with SSc.^{3–4} About 10% of patients develop a rapidly progressive oliguric renal failure known as scleroderma renal crisis (SRC).^{5–6} In 90% of these patients, SRC is preceded by or associated with accelerated arterial hypertension with a blood pressure (BP) greater than 150/90 mm Hg,⁵ but the remaining 10% are normotensive (diastolic BP ≤90 mm Hg) at presentation. Normotensive SRC has a poorer prognosis than hypertensive SRC, possibly due to delayed diagnosis and alternate pathological mechanisms that are less responsive to current SRC therapies. Owing to its rarity, a common presentation of this disease could be mistaken for a variety of other diseases. Hence, the practitioner must remain attentive to the clinical course, including systemic signs and symptoms, in order to appropriately diagnose and promptly treat this highly morbid disease.

CASE PRESENTATION

A 57-year-old man with a history of alcohol abuse and no other known medical diagnoses was admitted with 4 months of dysphagia, 40-pound weight loss, symptoms of Raynaud's phenomenon,

progressive weakness and lower extremity paresthesias that rendered him bedbound. On examination, he appeared cachectic, with mild bilateral deltoid weakness and intrinsic hand muscle weakness. Proximal lower limb strength was only antigravity bilaterally and he was not able to dorsiflex either foot or walk. Initial reflexes were 2+ in the upper extremities and patellar tendons, but absent in the Achilles tendons. Vibratory sense was diminished in the toes. Diagnostic investigation revealed leukocytosis, a pulmonary infiltrate on chest X-ray (CXR) and oesophageal dysmotility on swallow studies leading to a diagnosis of aspiration pneumonia. Specific workup for his weakness included electromyography and nerve conduction studies which revealed a diffuse motor neuronopathy, consistent with motor neuron disease. Additionally, an axonal sensorimotor polyneuropathy was found, and attributed to prior alcohol abuse. Cerebrospinal fluid analysis and MRI of the brain and spine were unremarkable. Infectious, rheumatological and neoplastic laboratory evaluation was only significant for elevated erythrocyte sedimentation rate and C reactive protein and a positive antineutrophil antibody (ANA) 1:160 titre, nucleolar pattern (table 1).

A differential for subacute sensory-motor neuropathy was considered, and included benign fasciculations, thyrotoxic myopathy, cervical spondylosis, paraneoplastic diseases related to haematological and solid malignancies, Guillain-Barre syndrome and subacute neuropathies associated with systemic disorders, such as Churg-Strauss syndrome, or autoimmune-induced motor neuron diseases (ie, myasthenia gravis). Based on this evaluation, EMG findings consistent with motor neuron disease and progressive weakness in the setting of preserved reflexes, he was diagnosed with amyotrophic lateral sclerosis (ALS) and he was discharged to a nursing facility.

The patient presented to another hospital 5 months later with acute on chronic dyspnoea with chronic lower extremity weakness and swelling. He was febrile, tachypnoeic, tachycardic, briefly hypertensive and hypoxic (temperature 100.9°F, RR 36, oxygen saturation spO₂ 92%, HR 150, BP 180/130). Apart from his BP on presentation, his BP remained low to normal throughout his hospitalisation with an average of 141/77 (SD systolic/diastolic BP=12/7). Serum troponins and creatinine (Cr) were elevated (troponin T 0.4 ng/mL (<0.1 ng/mL), Cr 4.6 mg/dL (0.5–1 mg/dL)) and urine protein: Cr ratio was elevated (0.6). He was treated empirically for non-ST elevation myocardial infarction, pulmonary oedema, aspiration

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Table 1 Patient specialty labs: first and second hospitalisations

	Reference range	Admit #1: July 2010	Admit #2: December 2010
Erythrocyte sedimentation rate	0–15 mm/h	103	
C reactive protein	<0.5 mg/dL	3.6	
Antinuclear antibody titre and pattern	<1:40	1:160 nucleolar	1:320 nucleolar
ANCA screen	Qualitative	Negative	
SCL-70 antibody	Negative		Negative
Antiphospholipid Ab	Negative		Negative
Double-stranded DNA antibody	0–200 IU/mL	54	94
RNA polymerase III AB, IgG	<20.0 U		2.4
C3 complement	90–180 mg/dL	158	
C4 complement	16–47 mg/dL	25	
Total complement (Ch50)	31–60 U/mL	59	
Cryoglobulin quantitation	0.0–0.0%	0.0	
Smooth muscle Ab.	<1:40	<1:40	
SSA antibody	<19 units	8	
SSB antibody	<19 units	5	
IgM, serum	60–263 mg/dL	58	
IgA, serum	68–378 mg/dL	514	
IgG, serum	694–1618 mg/dL	1379	
IgG subclass 1	240–1118 mg/dL	908	
IgG subclass 2	124–549 mg/dL	527	
IgG subclass 3	21–134 mg/dL	88	
IgG subclass 4	7–89 mg/dL	152	
Immunoglobulin E	0–100 IU/mL	234	313

The bold typeface characters in Table 1 signify results outside the specified reference ranges.

pneumonia and a possible pulmonary embolus with intravenous heparin, nitroglycerin, furosemide and antibiotics and then transferred to our hospital for continued care.

On arrival to our hospital, he was haemodynamically stable (temperature 98.2°F, RR 20, spO₂ 97% (2 L nasal cannula), HR 93, BP 149/71). Examination revealed thickened skin with sclerodactyly, telangiectasias, signs of Raynaud's phenomenon, diffuse muscle atrophy and weakness and depressed reflexes in the lower extremities. In addition, a pericardial friction rub was noted on cardiac examination.

INVESTIGATIONS

A cardiac nuclear perfusion scan to workup his shortness of breath and elevated troponins revealed perfusion defects consistent with an old infarct, without ischaemia. Echocardiography showed a moderate left ventricular hypertrophy, ejection fraction 69%, a pericardial effusion without tamponade physiology, moderate-sized pleural effusions and no regional wall motion abnormalities or pulmonary hypertension. Chest X-ray showed vascular congestion, pleural effusions and infiltrates. He was treated with antibiotics and diuretics for healthcare-associated pneumonia and congestive heart failure (CHF).

The patient's kidney injury progressed despite normal haemodynamic function. Urinalysis revealed proteinuria, without cells or casts. Renal anatomy and haemodynamics were normal on ultrasonography. A kidney biopsy was performed because of the rapidly progressive injury, and it revealed severe arterial intimal thickening with fragmented erythrocytes in arteriolar walls, consistent with thrombotic microangiopathy (figure 1). The glomerular basement membranes were thickened and wrinkled, consistent with ischaemia. These histological findings support the diagnosis of normotensive scleroderma renal crisis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of normotensive SRC includes haemolytic uraemic syndrome/thrombotic thrombocytopenic purpura, renal artery stenosis, antineutrophil cytoplasmic antibody-mediated glomerulonephritis and D-penicillamine exposure (table 2).

The cardiopulmonary features of normotensive SRC can be interpreted as being due to the far more common aetiologies of myocardial ischaemia, pulmonary oedema or aspiration pneumonia, as occurred in our patient. Myocardial ischaemia is more commonly diagnosed in patients with SSc, although not substantiated with intraluminal coronary obstructions or wall motion abnormalities.⁷ Similarly, our patient had positive serial troponins on admission, but did not have ECG and echocardiogram changes consistent with cardiac ischaemia. Critically appraising the patient's symptoms and signs over time within the wider scope of the differential diagnoses helped to differentiate the aetiology of his condition from ischaemic cardiac myopathy, congestive heart failure, healthcare-associated pneumonia and ALS.

TREATMENT

Captopril was started for management of SRC and haemodialysis was initiated for hypervolemia on the 11th day of hospitalisation. Further laboratory testing including hepatitis B and C, fungal serologies, antiphospholipid antibody and RNA polymerase III antibody were all negative (table 1).

OUTCOME AND FOLLOW-UP

The neurology service removed the ALS diagnosis because of the improvement in strength over subsequent weeks, and suggested repeating the patient's electromyography, but the patient refused. The patient's motor neuron disease was, in retrospect,

Figure 1 Light and electron microscopy from kidney biopsy. The glomeruli appeared ischaemic, but not globally sclerotic (A and B). Severe arterial and arteriolar intimal thickening with intimal fragmented erythrocytes, along with microangiopathy, were noted. Mild-to-moderate arteriosclerosis is present. There was no evidence of interstitial inflammation or fibrosis or tubular atrophy. The glomeruli were negative for immune deposits with all stains (IgG, IgA, IgM, C3, C1q, albumin, fibrinogen, κ and λ light chains; data not shown). Ultrastructural evaluation by electron microscopy revealed diffuse epithelial foot process effacement, and thickened and wrinkled glomerular basement membranes, indicating ischaemia (C). Electron dense deposits were absent.

attributed to an autoimmune neuropathy associated with the scleroderma. His prior cardiopulmonary symptoms were ascribed to systemic manifestations of systemic sclerosis.

Over the following 18 months, the patient's swallowing, lung function, limb strength and functional status markedly improved. At present, he remains on dialysis and captopril and is being evaluated for a kidney transplant.

DISCUSSION

Normotensive scleroderma renal crisis comprises a distinct subset of SRC, wherein patients are normotensive throughout the course of stable illness and hence require a high level of suspicion to diagnose (table 2). There are few case reports/series on this entity, the largest being of 11 patients in 1989.⁸ This case report highlights the importance of a comprehensive history and

Table 2 Common characteristics of normotensive and hypertensive SRC

	Normotensive SRC	Hypertensive SRC
Primary mechanism of renal ischaemia	Non-renin-mediated endothelin-mediated, extrarenal factors—that is, cardiac decompensation	Renin-mediated
Renal histology		
Thrombotic microangiopathy, intimal proliferation with:	Acute infarcts	Glomerular sclerosis and intimal fibrosis
Risk factors and clinical features		
Age (years)	55	50
Sex (% female)	68	75
Blood pressure (mean)	119/71	184/108
Anaemia (microangiopathic haemolysis)	+++	+
Thrombocytopenia	+++	+
Antecedent steroid use	++	++
Differential diagnosis		
► Renal artery stenosis		
► Haemolytic uraemic syndrome (HUS)/thrombotic thrombocytopenic purpura (TTP)		
► Crescentic GN (ie, ANCA-mediated glomerulonephritis, anti-GBM GN, immune-complex-related GN)		
► D-penicillamine exposure		
Survival at 6 months (%)	14	81

ANCA, antineutrophil cytoplasmic antibody; HUS, haemolytic uraemic syndrome; TTP, thrombotic thrombocytopenic purpura; SRC, scleroderma renal crisis.

physical examination, since common symptoms and signs can represent a rare disease presenting in a usual fashion.

The pathogenesis of SRC is not fully understood, and genetic and environmental factors likely play a role. Endothelial wall injury leads to intimal proliferation, subsequent narrowing of arterioles and formation of microthrombi. In addition to structural changes, episodic vasospasm, or 'renal Raynaud's phenomenon', contributes to renal hypoperfusion, increasing renin release and juxtaglomerular hyperplasia.^{5–9} Hyper-reninemia perpetuates vasoconstriction and worsening renal ischaemia which also contributes to accelerated hypertension in hypertensive SRC. While these postulated mechanisms help explain the pathogenesis of hypertensive SRC, the pathogenesis of normotensive SRC is less clear. Endothelin-1, a potent vasoconstrictor peptide is a contributor in the setting of decreased cardiac output and microangiopathic haemolytic anaemia.^{5–10–11} Despite immunological pathways contributing to SSc, lymphocytes and other inflammatory cells are characteristically absent on histology. This distinction helps to differentiate normotensive SRC from vasculitis.

Certain signs and symptoms of SRC could point clinicians to early recognition and treatment of SRC. Patients with diffuse cutaneous SSc, proximal and/or truncal skin thickening, rapid progression of skin thickening and presence of large joint contractures are at greatest risk for SRC. Approximately 12–25% of such patients with SSc develop SRC, with 75–86% cases seen within 4 years.¹² New cardiac events (eg, CHF, pericarditis, asymptomatic pericardial effusion, arrhythmias) and/or new-onset microangiopathic haemolytic anaemia can also antedate SRC.¹ Our patient developed symptoms of CHF and a pericardial friction rub, which did not resolve with dialysis, arguing for SSc-related cardiac involvement rather than uraemic pericarditis. While our patient was anaemic, he had no haemolysis or thrombocytopenia on the peripheral blood smear. In addition, the presence of specific autoantibodies are risk factors.¹³ Patients with elevated soluble CD147 levels, a glycosylated membrane protein that belongs to the immunoglobulin superfamily, have an increased risk of SRC compared with those with normal levels (13% vs 0%; $p < 0.05$).¹⁴

Recipients of corticosteroids are at a higher risk of SRC; the OR of SRC after corticosteroid exposure in the preceding 1 or 3 months is 24 and 17, respectively.¹⁵ A causal relationship has not been established, but it has been hypothesised that corticosteroids inhibit prostacyclin and increase ACE activity.¹⁵ Interestingly, prior hypertension, abnormal urinalysis, previous acute or chronic kidney disease and pathological abnormalities in renal vessels are not predictive of SRC. No difference has been demonstrated in the demographics, clinical manifestations, disease duration or the extent and rapidity of cutaneous involvement between normotensive and hypertensive SRC.

Scleroderma renal crisis can have an insidious course except when hypertension or its complications declare it. Progressive renal failure with markedly elevated plasma renin activity (usually 10×, occasionally 100× normal) is universal in SRC, and may remain despite successful treatment of hypertension, especially in normotensive SRC. During the acute phase of SRC, urinalysis frequently shows non-nephrotic proteinuria, microscopic haematuria and granular casts.⁵ Our patient presented with trace proteinuria that progressed to 1 g at the time kidney biopsy revealed fused foot processes. Foot process effacement has never been reported in the setting of SSc. We hypothesise that this unique histological finding reflects endothelin-1-derived podocyte injury, without cytoskeletal rearrangement.¹⁶ Our patient was diagnosed with normotensive

SRC as his BP remained consistently <150/90 mm Hg immediately preceding and during SRC, with recurrent hypotensive episodes. The period of hypertension at admission was attributed to cardiopulmonary response, which resolved with directed therapy.

The introduction of ACE inhibitor (ACEi) in 1979 revolutionised the treatment of SRC. Prior to it, SRC was highly fatal, with <10% 3-month survival rates.³ By inhibiting the renin-angiotensin system and preventing degradation of vasodilatory bradykinin, ACEi slows renal deterioration in the majority of patients with SRC, and reverses acute kidney injury in a small proportion.¹⁷ This benefit is not attributed solely to reduction of BP, as it is also seen in normotensive SRC.⁸ There are no specific guidelines for using captopril in normotensive patients with SSc. We recommend monitoring their BP for an increase above their baseline, monitoring their urine for protein and their Cr and initiating captopril at the tolerated dose that keeps the BP at baseline.

ACEi therapy in patients with SRC should be continued even if the Cr level continues to rise, BP is normalised or the patient is on dialysis, as it potentiates improvement in renal-related functions after renal crisis.^{5–18} Angiotensin receptor blockers (ARBs) have been tried in a small number of patients and are less effective than ACEi in managing SRC, possibly because of the lack of bradykinin effect from ARBs.⁵ Alternative therapies for refractory SRC have been studied, including endothelin receptor antagonists,¹⁹ prostacyclin agonists, calcium channel blockers and statins with variable results.¹¹ Prophylactic ACEi use remains controversial; while there are no specific studies for pre-emptive ACEi in preventing SRC, pre-emptive ACEi has not been found to prevent future vascular complications of SSc.²⁰ A recent observational study of patients with SSc found that dihydropyridine calcium channel blockers could have a role in preventing the development of SRC.²¹ Renal transplantation is recommended in patients who require dialysis for ≥ 2 years, as SRC recurrence is uncommon (5%) in transplant recipients.²²

Despite benefits of ACEi in normotensive SRC, the prognosis is poorer than with hypertensive SRC. Helfrich *et al*⁸ reported only 13% survival at 1 year in patients with normotensive SRC, as compared with 35% in hypertensive SRC. Limiting analysis to patients treated with ACEi, short-term survival was 50% in normotensive SRC, as opposed to 67% in hypertensive SRC. Penn *et al*⁸ also reported a worse prognosis in patients with SRC and lower BP at presentation.

Most case reports of normotensive SRC result in a fatal outcome, yet our patient is still alive 3 years after diagnosis.^{23–26} Poor outcomes in normotensive SRC have been attributed to delayed recognition, and therefore, therapy. Moreover, non-renin-mediated mechanisms of normotensive SRC are thought to render it less responsive to ACEi therapy.

Learning points

- ▶ Normotensive scleroderma renal crisis (SRC) is a rare, severe complication of systemic sclerosis with a poorer prognosis than hypertensive SRC.
- ▶ Heightened awareness of comprehensive signs and symptoms can lead to a prompt diagnosis and intervention.
- ▶ Early initiation of ACEi therapy is of paramount importance to improve morbidity and mortality in the management of patients with normotensive SRC irrespective of their blood pressure.

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