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A CASE OF ATYPICAL SCLERODERMA RENAL CRISIS

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ABSTRACT

We present the case of a 63-year-old female diagnosed with atypical SSc in the setting of acute SRC. She was undergoing work-up for progressive dyspnoea in the outpatient setting when she was found to have newly diagnosed restrictive lung pathology and worsening renal function, thus prompting acute hospital admission. Given multisystem involvement of the pulmonary and renal systems, the differential diagnosis included autoimmune and connective tissue disorders. Although serologies were non-specific, renal biopsy confirmed scleroderma renal disease, and she was started on treatment with captopril. This case highlights the importance of clinical judgment and timely diagnosis, even when laboratory data might indicate otherwise.

KEYWORDS

Scleroderma, scleroderma renal crisis, acute hypoxic respiratory failure, pericardial effusion

LEARNING POINTS

- Scleroderma renal crisis (SRC) remains an important cause of morbidity and mortality in systemic sclerosis (SSc), and clinicians should have a high index of suspicion to diagnose it.
- The absence of specific serologic markers makes SSc diagnosis challenging and necessitates reliance on clinical findings and additional diagnostic tools such as imaging studies and tissue sampling.

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterised by skin thickening, vascular abnormalities and visceral organ involvement. While serologic markers aid in diagnosis, there exists a subset of patients who present with characteristic clinical features but lack these typical antibodies. This poses a unique challenge and requires careful clinical evaluation. We present a case of a 63-year-old woman presenting with scleroderma renal crisis (SRC), who was found to have atypical scleroderma.

CASE DESCRIPTION

A 63-year-old female with a past medical history of non-ischaemic cardiomyopathy, type 2 diabetes mellitus, hypertension, dyslipidaemia and bilateral carpal tunnel syndrome presented to the hospital for worsening

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renal function and progressive dyspnoea. Preceding this hospitalisation, the patient was being evaluated for progressive dyspnoea. Computerized tomography (CT) imaging ruled out pulmonary embolism but showed bibasilar consolidation with prominent bilateral axillary lymph nodes, concerning for pneumonia. She completed a course of doxycycline, but her symptoms did not improve. Subsequent pulmonary function tests revealed a severely reduced 'forced expiratory volume in 1 second' test at 45%, with a ratio to forced vital capacity of 82%, total lung capacity of 38% and severely reduced diffusing capacity for carbon monoxide at 25%, consistent with restrictive lung pathology. During this work-up, her creatinine was noted to be 1.78 mg/dl (baseline 0.8–1.0 mg/dl). Despite discontinuation of her sacubitril-valsartan and empagliflozin, repeat testing two weeks later showed worsening creatinine at 4.92 mg/dl and she was recommended for inpatient evaluation.

Upon presentation, she also reported an unintentional 15-pound weight loss, dyspepsia and fatigue. Additionally, she reported tightness and discoloration of bilateral hands without joint swelling or pain. She denied photosensitivity, dry eyes or mouth, abdominal pain or urinary symptoms, but did note a decrease in daily urine output. She denied occupational exposures to dangerous inhalants, and a personal or family history of autoimmune diseases. She was afebrile (37.2°C), hypertensive (200/107 mmHg), tachypnoeic (30/min), without tachycardia (86/min) or desaturation. Physical examination was significant for diffuse end-inspiratory fine crackles without wheezing. Mild finger oedema with early sclerodactyly changes were seen, and digital pitting and tenderness were noted on the right fifth digit. Her hands were cool with dusky discoloration, but her feet were warm without oedema. Admission laboratory investigations are noted in *Table 1*. Ultrasound of the kidneys and bladder was without obstructive uropathy, and a CT scan of the abdomen and pelvis was unremarkable. A high-resolution chest CT (HRCT) scan showed worsening intralobular septal thickening, patchy ground glass opacities in the upper lobes and areas of dense consolidation more prominent in the lower lobes, concerning for interstitial lung disease. Given multisystem involvement of the pulmonary and renal systems, the differential diagnosis included systemic sclerosis, vasculitis, amyloidosis and sarcoidosis. An anti-nuclear antibody (ANA) test returned with a high titre of 1:1280.

During hospitalisation, the patient's blood pressure remained elevated despite aggressive medical management. Within 48 hours, she developed acute hypoxic respiratory failure from flash pulmonary oedema, thought to be provoked by a hypertensive emergency. A transthoracic echocardiogram (TTE) revealed significantly reduced ejection fraction (EF) to 25–30% (a TTE one month previously showed an EF of 40%), global hypokinesis and circumferential pericardial effusion without tamponade physiology. She underwent right heart catheterisation showing right atrial pressure 12 mmHg, pulmonary artery pressure 44/21 mmHg, pulmonary capillary wedge pressure 22 mmHg, thermodilution cardiac output 3.4 l/min, thermodilution cardiac index 2.1 l/min/m^2 and pulmonary vascular resistance of 2.1 Wood units. Her renal dysfunction was out of proportion to the cardiac index and filling pressures, suggesting cardiogenic aetiology alone. She did not have equalisation of chamber pressures to suggest obstructive shock from tamponade. These findings along with clinical examination and elevated ANA titre prompted further autoimmune work-up. She underwent cautious diuresis and quickly weaned back to nasal canula the next day.

Despite respiratory improvement, the patient's urine output continued to decrease, and her creatinine continued to rise, ranging from 5.65–8.46 mg/dl. She subsequently underwent renal biopsy and was initiated on haemodialysis by hospital day 5. The biopsy showed thrombotic microangiopathy (TMA) involving multiple arterioles, normocellular glomerular without specific immunoreactivity, no significant globally sclerosed glomerular and interstitial fibrosis, and mild-to-moderate arterial sclerosis. By this time, her autoimmune serology was non-specific *(Table 2)*. However, her biopsy findings were consistent with scleroderma-associated renal disease. Due to her renal pathology, steroids and mycophenolate mofetil were not initiated. She was started on captopril 25 mg twice daily for SRC which stabilised her blood pressure and improved symptoms. She was discharged to a rehabilitation centre with plans for outpatient haemodialysis and specialist follow-up.

DISCUSSION

Systemic sclerosis (SSc), also known as scleroderma, is an immune-mediated rheumatic disease with high morbidity and mortality[1]. It is associated with chronic inflammatory infiltration in numerous organs – commonly the lungs, heart, kidneys and gastrointestinal tract[2]. Per the 2013 classification criteria for systemic sclerosis by the American College of Rheumatology, our findings on history, physical examination, imaging and kidney biopsy led to a clinical diagnosis of scleroderma, despite the lack of supportive laboratory data[3].

In patients with SSc, a clinically relevant ANA titre of 1:80 or more has been reported in 75–95% of patients, with a sensitivity of 85% and specificity of 54% on immunofluorescence[1]. For anti-centromere (ACA) this has been shown to be 33% sensitive and 99.9% specific, and anti-topoisomerase I (ATA) has a sensitivity of 34% and a specificity of 99.6%. Similarly, anti-RNA polymerase III (anti-RNAP) has a low sensitivity at 10–20% with a high specificity of 98.8%[4]. In our patient, tests for ACA, ATA and anti-RNAP III antibodies were negative, making it a rare presentation of systemic sclerosis with SRC[5].

SRC occurs in about 10% of all patients with scleroderma. Most commonly, it is characterised by malignant hypertension and progressive renal failure. However, about 10% of SRC cases may present with normal blood pressure, known as normotensive renal crisis[6]. Although

Investigation	Value on admission	Value one month prior	Reference range
Sodium (mmol/l)	135	134	136–145
Potassium (mmol/l)	4.0	4.1	3.5–5.1
Blood urea nitrogen (mg/dl)	55	51	7–25
Creatinine (mg/dl)	6.05	2.85	0.6–1.3
BNP (pg/ml)	>5,000	2,844	<80
White blood cell count (103/µl)	7.6	8.1	4.8–10.8
Haemoglobin (g/dl)	9.3	8.7	12–16
Mean corpuscular volume (MCV) (fl)	85.7	84.5	80-99
Mean corpuscular haemoglobin (MCH) (pg)	26.5	26.1	27–34
Mean corpuscular haemoglobin concentration (MCHC) (g/dl)	30.5	31.2	31–37
Reticulocyte distribution width (RDW) (%)	18.5	20.3	11–16
Iron (mcg/dl)	39	25	50–170
Ferritin (ng/ml)	1,018	404	7–271
Total iron binding capacity (TIBC) (ug/dl)	172	196	284–507
Transferrin (mg/dl)	123	140	250–380
COVID-19	Negative	N/A	Negative
Influenza	Negative	N/A	Negative
Respiratory syncytial virus	Negative	N/A	Negative
Urine microscopy	6–10 hyaline casts/LPF, no red blood cells, white blood cells or additional casts.	N/A	0–2/LPF
Urine protein (mg/dl)	100	N/A	Negative
Urine sodium (mmol/l)	96	N/A	No reference range
Urine creatinine (mg/dl)	48.8	N/A	No reference range
Serum protein electrophoresis	IgG 1,885 mg/dl Kappa (K) 211.4 mg/l Lambda (L) 133.5 mg/l K/L ratio 1	N/A	IgG 600–1,540 mg/dl K 3.3–19.4 mg/l L 5.7–26.3 mg/l K/L ratio 0.26–1.65
Blood cultures	Negative	N/A	Negative
Sputum cultures	Negative	N/A	Negative

Table 1. Laboratory investigations.

the pathogenesis of SRC remains unclear, it is thought that intimal proliferation from an endothelial insult leads to luminal narrowing of small renal arteries and arterioles[5]. Common risk factors for renal involvement include diffuse skin disease, use of systemic steroids and the presence of anti-RNAP III[5]. Cases of seronegative SSc may be associated with malignancy, or as paraneoplastic manifestations of secondary malignancies[1,3]. Our patient's serologic and radiographic work-up for malignancy was negative, making this case of further interest.

The pathogenesis of SRC includes activation of renin-angiotensin-aldosterone-system (RAAS)[7]. Since the advent

Investigation	Value on admission	Reference range
C-reactive protein (CRP) (mg/dl)	2.90	<1.00
Erythrocyte sedimentation rate (ESR) (mm/hr)	32	0–30
Anti-nuclear antibody (ANA) titre	1:1,280	<1:40
Anti-centromere B antibody (ACA) (AI)	<1 NEG	<1 NEG
Anti-Scl-70/ATA (anti-topoisomerase I) (AI)	<1 NEG	<1 NEG
Anti-RNA polymerase III (RNAP III) antibody	<20	<20
Anti-SSA (Sjögren's syndrome-related antigen A) (AI)	>8	<1
Anti-SSB (Sjögren's syndrome-related antigen B) (AI)	2.2	<1
Rheumatoid factor (RF) (IU/ml)	32.5	<14.0
Anti-cyclic citrullinated peptide (CCP) antibody (U/ml)	<0.5	<0.5
Anti-neutrophil cytoplasmic antibody) screen (ANCA)	Negative	Negative
Myeloperoxidase (MPO) antibody (AI)	<1	<1
PR-3 (proteinase) antibody (AI)	<1	<1
Anti-polymyositis (PM)/SCL-100 antibody IgG	<20	<20
Anti-Jo1 antibody (SI)	<11	<11
Anti-Mi2 antibody (SI)	<11	<11
Anti-Mda5 (CADM-140) antibody (SI)	<11	<11
Tif-1 gamma (155 kDa) antibody (SI)	<11	<11
Creatine kinase (CK) (IU/l)	122	34–145
C3 complement (mg/dl)	114	89–193
C4 complement (mg/dl)	20.5	15–57
Anti-RNP (ribonucleoprotein) antibody (AI)	<1 NEG	<1 NEG
Anti-dsDNA antibody (IU/ml)	2	<4
Anti-Smith antibody (AI)	<1 NEG	<1 NEG
Anti-fibrillarin (U3 RNP) antibody	Negative	Negative
Cardiolipin IgM and IgG antibody (GPL-U/ml)	<2	<20
Beta-2 glycoprotein IgM and IgG antibody (U/ml)	<2	<20
Lupus anticoagulant	Not detected	Not detected
Anti-PL7 antibody (SI)	<11	<11
Anti-PL2 antibody (SI)	<11	<11
Anti-EJ antibody (SI)	<11	<11
Anti-OJ antibody (SI)	<11	<11
Anti-SRP antibody (SI)	<11	<11
NXP-2 antibody (SI)	<11	<11
Cryoglobulin qualitative	None detected	None detected
Parvovirus B19 IgM	0.2	<0.9
Parvovirus B19 IgG	7.4	<0.9
Angiotensin converting enzyme (ACE) (U/l)	45	9–67
CA (cancer antigen) 125 (U/ml)	25.4	0–35
CA 19-9 (U/ml)	20	<34
Carcinoembryonic antigen (CEA) (ng/ml)	0.3	0–3
Alpha fetoprotein (AFP) tumour marker (ng/ml)	<2	<8.78

Table 2. Autoimmune laboratory investigations.

of angiotensin converting enzyme inhibitors (ACE-I), the prognosis of SRC has improved drastically by reducing the 1-year mortality from 85% to 24%, and they remain the mainstay of treatment[6,7]. A short-acting ACE-I such as captopril is used initially and once blood pressure has stabilised, long-acting ACE-I can be substituted in equivalent doses. Diuretics must be avoided as this may stimulate RAAS further[7]. Although ACE-I have improved outcomes in such patients, they do not have a role in prevention[7]. Continued therapy with ACE-I is recommended as about half of these patients may have renal recovery over 3 to 18 months and may be able to discontinue dialysis[7].

CONCLUSION

This case of severe SRC despite with manifestations including multi-organ systems, illustrates the importance of clinical diagnosis, even when laboratory data might indicate otherwise. The patient underwent HRCT and renal biopsy with findings consistent with scleroderma interstitial lung disease and SRC. It is important for clinicians to promptly recognise atypical scleroderma presentations to make a timely diagnosis and prevent complications.

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