Normotensive Scleroderma Renal Crisis

Dear Editor,

Scleroderma renal crisis (SRC) is an uncommon complication of systemic sclerosis that presents with malignant hypertension and oliguric renal failure. However, 10% of SRC cases are normotensive,¹ which are typically associated with prior use of angiotensin converting enzyme inhibitors (ACE-I), calcium channel blockers and in patients with myocardial involvement.¹ For some patients with normotensive SRC, initial blood pressure is relatively higher compared to baseline levels, although these levels could fall well within the normal limits of blood pressure. A high index of suspicion is therefore necessary to identify high-risk patients who may benefit from early treatment.

Case Presentation

A 66-year-old Chinese man presented to the Emergency Department with vomiting and non-bloody diarrhoea for two days. Blood pressure was 127/77 mm Hg and heart rate was 70 beats per minute. His baseline blood pressure was 106/57 mmHg.

He was diagnosed with diffuse cutaneous systemic sclerosis 3 months earlier following an initial presentation of rapidly worsening diffuse cutaneous thickening, Raynaud phenomenon and gastroesophageal reflux. His medications included oral nifedipine, omeprazole and domperidone. Two weeks prior to his current presentation, he received oral prednisolone and intravenous cyclophosphamide 700 mg for non-specific interstitial pneumonitis.

Antinuclear screen was reported as positive but its titre and staining pattern was not performed. Anti-Ro and anti-La were positive. Anti-RNA polymerase III antibody and anti-ds DNA were negative.

Transthoracic echocardiogram (ECG) showed grade 1 left ventricle diastolic dysfunction and pulmonary hypertension with estimated pulmonary artery systolic pressure of 41 mmHg. Otherwise, heart valves and ventricular function were normal. Left ventricle ejection fraction was 60%. There were no regional wall motion abnormalities. Dobutamine stress ECG was negative for inducible ischaemia. ECG showed normal sinus rhythm.

He was treated for infective gastroenteritis with ceftriaxone and metronidazole. His vomiting and diarrhoea resolved within a day. However, his acute kidney injury worsened over the next few days despite adequate hydration (Fig. 1) and he became oliguric. His baseline creatinine was 84 umol/L. He did not consume any non-steroidal anti-inflammatory agents or other nephrotoxic medications prior to admission. Other than gastroenteritis which resolved rapidly, there was no other sources of sepsis. C-reactive protein was 4.2 mg/L and procalcitonin was 0.59 ug/L. Ultrasound of the kidneys showed normal sized kidneys and no hydronephrosis. Doppler renal artery was not performed. Urinalysis showed 5 red blood cells per ul but no white cells or casts were seen. Urine protein creatinine ratio was 0.99. Creatine kinase was 179 U/L.

He also developed features of microangiopathic haemolytic anaemia (MAHA) and thrombocytopaenia but his average blood pressure remained normal (Fig. 1). Lactate dehydrogenase was 1254 U/L and haptoglobin was less than 4mg/dL. Prothrombin time and activated thromboplastin time were normal. Numerous fragmented red blood cells were seen on peripheral blood film. Dengue serology was negative. Anti-cardiolipin IgM and IgG were negative.

The differential diagnoses were diarrhoeaassociated haemolytic uraemic syndrome, thrombotic thrombocytopaenic purpura and normotensive SRC. There were no features of fever or neurological symptoms to favour thrombotic thrombocytopenic purpura. ADAMTS-13 was not performed. Overall, it was difficult to differentiate between these diagnoses. In view of the clinical picture of rapidly developing scleroderma and recent initiation of high-dose prednisolone, SRC was highly suspected.

On day 5 of admission, the patient was started on continuous renal replacement therapy in view of uraemia and acidosis. He was also started on captopril and prednisolone was decreased from 30 mg to 20 mg daily. Renal biopsy on day 8 of admission showed florid acute on chronic thrombotic microangiopathy (TMA) characterized by arteriolar fibrin thrombi associated with mild mural thickening and focal hyperplastic sclerosis (Fig. 2). The glomeruli demonstrated endothelial cell swelling, prominent ischaemic wrinkling of capillary walls and double-contoured capillary loops. Acute tubular injury was present. There were no crescents or immune deposits.

Seven sessions of plasma exchange, each comprising 1 plasma volume replacement with 5% albumin and fresh



Fig. 1. Trends of average blood pressure, serum creatinine and platelet count.



Fig. 2. A: Interlobular artery shows mucoid intimal thickening (asterisk). Fibrin thrombi in preglomerular arteriole and glomerular capillaries (arrows). H&E, original magnification x200. B: Same microscopic focus showing lack of much fibrosis in the thickened, swollen intimal layer. Fibrin thrombi are trichrome red. Combined silver-masson trichrome stain, original magnification x200.

frozen plasma, were performed on alternate days. Iloprost (a synthetic prostacyclin analogue) was given as a slow intravenous infusion of a total 40.32 mcg over 6 hours per day for 3 days.²

Although the patient's platelet counts and lactate dehydrogenase (LDH) normalised, his acute kidney injury persisted and he continued to require dialysis. Due to his deconditioning, he required rehabilitation. One month later, he developed a sudden cardiorespiratory arrest. ECG showed new left bundle branch block. Cardiac enzymes were raised. The cause of collapse was presumed to be acute coronary syndrome. Due to prolonged downtime of 50 minutes, patient developed severe hypoxic ischaemic encephalopathy and progressively deteriorated and passed away.

Discussion

SRC, an uncommon complication of systemic sclerosis, typically presents early with a mean of 3.2 years¹ following the onset of disease. Risk factors include the presence of anti-RNA polymerase III antibody, rapidly progressive skin disease, high-dose corticosteroid exposure, human leukocyte antigen (HLA) DRB1*0407 and HLA-DRB1*1304 and high serum CD 147 levels.¹

Clinical features of MAHA and thrombocytopaenia affects 60% and 50% of SRC patients, respectively.³ Mild proteinuria and microscopic haematuria and cardiac complications such as congestive cardiac failure, pericardial effusions and arrhythmias are also observed.¹ SRC is likely triggered by endothelial injury leading to intimal proliferation and obliterative vasculopathy. Altered perfusion to the juxtaglomerular apparatus leads to hyperreninaemia that worsens vasoconstriction and renal ischaemia. Some patients have physiologic evidence of episodic renal vasospasm (renal Raynaud's phenomenon).¹ Pathologic features include TMA changes in small arcuate and interlobular arteries and glomeruli, concentric onionskin narrowing of arterioles and glomerular ischaemia.²

European League against Rheumatism recommends ACEI as the first-line treatment in SRC and that patients started on steroids should be carefully monitored for the development of SRC.¹ ACEI have significantly reduced SRC mortality from 76% to less than 15% within the first year.⁴ However,

temporary dialysis is still needed in 23% of SRC patients and permanent dialysis in 41% of SRC patients.³

Early initiation of ACEI is associated with better likelihood of renal recovery.⁴ However, caution is still needed to avoid hypotension that will reduce renal perfusion leading to acute tubular necrosis. Our patient belongs to the rare cohort of SRC who are normotensive. Normotensive SRC has a higher mortality and poorer renal outcome compared to hypertensive SRC,⁵ in part explained by a delay in diagnosis and a greater likelihood of myocardial involvement.

Prophylactic ACEI does not reduce risk of SRC.¹ But clinicians can teach patients to monitor blood pressure (BP) and seek early attention when BP suddenly goes higher than baseline especially following initiation of corticosteroids.⁶

The most well recognised cardiac complication of SSc is pulmonary hypertension. In contrast, fibrosis of myocardium and conduction system are underdiagnosed and occurs in 25% of patients. They result in systolic and diastolic dysfunction and conduction abnormalities. Patients with cardiomyopathy and ventricular arrhythmias are at high risk of sudden death.⁷

In summary, SRC can present with normal blood pressure. A high index of suspicion is needed to avoid delay in diagnosis and starting ACEI. Delay in treatment portends worse prognosis in overall survival and renal recovery.

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