

## Case report

# Scleroderma renal crisis as an initial presentation of systemic sclerosis: a case report and review of the literature

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### ABSTRACT

*Scleroderma renal crisis (SRC) is a life-threatening complication of systemic sclerosis (SSc) that is characterised by new-onset malignant hypertension and progressive acute renal failure, often with associated microangiopathic haemolytic anaemia and thrombocytopenia. SRC was at one time almost uniformly fatal, with death often occurring within a few weeks. With the development of angiotensin-converting-enzyme inhibitors (ACE-I), survival has improved dramatically, but death rates still remain unacceptably high. About 20% of SRC cases occur prior to making a diagnosis of SSc and, in some cases, there is no evidence of skin sclerosis at the time that SRC develops. In this report, we present a case in which a patient developed SRC prior to being diagnosed with scleroderma. Additionally, we review the pathogenesis, presenting signs and symptoms, management and prognosis of SRC.*

### Case report

A 60-year-old Hispanic female with a long-standing history of Sjögren's syndrome and cutaneous vasculitis, characterised by tender, erythematous, ulcerating nodules involving the extremities, initially presented to the Emergency Room with a 3-week history of epigastric pain, nausea, vomiting and diarrhoea. As an outpatient, she had been taking 15 mg of prednisone daily for her vasculitis and lisinopril 2.5 mg daily. Upon presentation, her blood pressure was 178/85 mmHg, her creatinine was 1.4 mg/dL (increased from her baseline of 0.7 mg/dL) and her platelet count was 143K/ul. She was admitted for further evaluation.

Over the next two days, the patient remained persistently hypertensive and her creatinine continued to rise. Her platelet count and haemoglobin dropped

precipitously. An evaluation for haemolysis revealed an elevated serum lactate dehydrogenase which rose to 1155 U/L and an undetectably low haptoglobin. Peripheral smear showed schistocytes with evidence of microangiopathic haemolytic anaemia (MAHA). The patient was thought to have thrombotic thrombocytopenic purpura (TTP) with MAHA and treated with methylprednisolone 1g IV daily for 3 days and plasmapheresis. ADAMTS13 level was ordered.

Over the next several days, despite treatment for TTP, the patient's condition continued to worsen. Her platelet count fell to 43 k/uL and her haemoglobin dropped to 6.2 g/dL, her creatinine rose to 4.1 mg/dL and she developed pulmonary oedema. At that point she was started on haemodialysis. Her ADAMTS13 activity level was 43%, which, in combination with her intact mental status and lack of improvement with treatment, brought the diagnosis of TTP into question. Given her history of Sjögren's syndrome and cutaneous vasculitis, as well as her clinical picture of hypertension, acute renal failure, thrombocytopenia and MAHA, the diagnosis of scleroderma renal crisis (SRC) was considered and a rheumatology consultation was requested. The patient was noted to have 3+ sclerodactyly and loss of digital pulp. Serologic studies revealed a positive ANA (speckled pattern, titer 1:5120) and a positive scl-70 antibody at 90 U/mL. Anti-glomerular basement membrane, anti-neutrophil cytoplasmic and anti-RNA III polymerase antibodies were negative.

Based on these findings, the patient was started on treatment for SRC with captopril. After 3 days of treatment, her blood pressure remained uncontrolled and valsartan was added. Over the next week, her blood pressure, anaemia and thrombocytopenia gradually improved.

Competing interests: none declared.

Her platelet count increased to 105 k/uL and she was able to safely undergo a renal biopsy to clarify her diagnosis. Light microscopy showed marked edematous intimal expansion of the interlobular arteries with skeins of fibrinoid material and interstitial fibrosis. The glomeruli were normocellular but appeared ischaemic and markedly congested. The diagnosis reported was "thrombotic microangiopathy consistent with scleroderma renal crisis."

The patient's hypertension remained controlled with captopril and valsartan and her thrombocytopenia and MAHA resolved. She was then discharged from the hospital but has remained dialysis-dependent over the following 3 years.

## Literature review

### Introduction

Systemic sclerosis (SSc) is a multisystem connective tissue disease characterised by immune system activation, microvascular injury and widespread fibrosis of skin and internal organs (1). It primarily affects the skin, heart, lungs, kidneys and gastrointestinal tract and exists in both diffuse (dcSSc) and limited forms (lcSSc).

Scleroderma renal crisis (SRC) is a life-threatening complication of SSc that was first characterised by Moore and Sheehan in 1952 as malignant hypertension and acute renal failure (2), often with associated thrombotic microangiopathy. While SRC remains a very serious complication of SSc, it was at one time almost uniformly fatal, with death often occurring within a few weeks. With the development and usage of angiotensin-converting-enzyme inhibitors (ACE-I) in the late 1970s, 1-year survival from SRC improved dramatically, from 18% to 76% (3). However, early diagnosis and treatment remain critical to improving outcome.

### Epidemiology

SSc has an estimated prevalence of 276 cases per million persons in the US (4), and SRC has been found to affect 3–13% of all SSc patients (5–8). Studies have shown that SRC primarily affects Caucasians (92–94%) and females (75–80%), with a mean age of 50 years at the onset (9–11).

### Risk factors

Certain risk factors for SRC have been identified. Patients with early, diffuse SSc (disease duration <4 years) have been found to be at greatest risk of developing SRC (11). A retrospective case series of 110 patients with SRC showed that only 2% with lcSSc *versus* 12% with dcSSc developed SRC. Also, 66% developed renal crisis within the first year of SSc diagnosis. In fact, in 22% of the patients, renal crisis was the initial presenting feature, occurring before the diagnosis of SSc was made (5). Additional risk factors include: rapidly progressive skin thickening, new cardiac events such as pericardial effusions and congestive heart failure, new anaemia (9), presence of anti-RNA polymerase antibodies and use of corticosteroid therapy (>15 mg prednisone/day) (10).

### Pathogenesis

Although incompletely understood, the pathogenesis of SRC appears to result from an initial trigger of vascular endothelial injury resulting in increased permeability and intimal oedema. This results in a cascade of events as the sub-endothelial connective tissue is exposed to circulating elements in the blood, causing activation of the coagulation cascade and thrombosis. Additionally, the connective tissue reacts to the injury, resulting in fibroblastic and non-fibroblastic stromal proliferation. These events (oedema, thrombosis and stromal proliferation) result in narrowing of renal arterial vessels and decreased renal perfusion with subsequent hyperplasia of the juxtaglomerular apparatus and increased renin release. The increase in renin causes accelerated hypertension and further renal injury (12–16). SRC patients often have markedly elevated renin levels, and hypertension has been shown to improve dramatically after nephrectomy, likely because of the resultant fall in renin production (16).

Over-expression of endothelin-1 (ET-1) and its receptor, endothelin-B, has also been implicated in the pathogenesis of SRC. ET-1 is produced by endothelial and smooth muscle cells and acts as a potent vasoconstrictor. Increased expression of ET-1 and its receptors has been demonstrated in the renal arterioles and

arteries of SRC patients. In the future, ET-1 receptor blockade may serve as an alternative therapy for SRC (17, 18).

Corticosteroid use has been associated with SRC in multiple studies (8, 10, 19–21). One retrospective study of 50 SRC patients demonstrated that 60% had been exposed to corticosteroids prior to SRC onset, with an odds ratio of 24.1 for developing SRC associated with corticosteroid exposure in the preceding 3-month period (19). Steen *et al.* report a case-controlled study of 110 SSc patients in which 36% of SSc patients receiving steroids (at least 15 mg of prednisone/day) developed SRC *versus* 12% not receiving steroids (10). A recent systematic review also supported the association between the use of medium and high dose corticosteroids and the development of SRC (21). However, this relationship was not found in the review of 110 SRC patients by Penn *et al.* (5). A systematic review by Iudici *et al.* found that a beneficial role of low to medium dose corticosteroids in SSc is limited, although they could be used in certain situations (*i.e.* for treatment of interstitial lung disease, diffuse cutaneous disease or myositis) (22). Immunosuppressive agents such as methotrexate, azathioprine or cyclophosphamide may be used to minimise corticosteroid exposure (10). When corticosteroids are needed, the lowest possible dose should be used and patients should be closely monitored with regular blood pressure checks and serum creatinine levels to allow for early detection of SRC (23).

### Presentation

SRC typically presents as a new onset of significant systemic hypertension and acute renal failure. Approximately 10% of patients may be normotensive but almost invariably have an increase in blood pressure above their baseline (6, 19). Additionally, about 60% of patients will also present with MAHA and 50% with thrombocytopenia. Symptoms may include hypertensive encephalopathy with confusion, fatigue, lethargy, headache, visual changes and seizures. Severe cases can lead to cerebral haemorrhage, coma and death. Patients may also suffer from congestive heart failure, pericardial effusions, pericardi-

tis, arrhythmias and pulmonary haemorrhage (5, 6). In some cases, there is no evidence of skin sclerosis when SRC develops (known as systemic sclerosis sine scleroderma). However, skin thickening often develops within the next few months with eventual progression to diffuse SSc (24-26).

Although uncommon, there have been several reports of systemic vasculitis (including antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) and mixed cryoglobulinemia vasculitis) developing in patients with SSc. It is important to be aware of this potential overlap as renal vasculitis may be confused with SRC and proper diagnosis is critical to allow for appropriate and timely treatment. Vasculitis should be considered in SSc patients with acute renal failure, especially with features not typical of SRC. Such features include: renal failure late in disease (mean of 8-9 years after SSc develops), normotensive renal failure, absence of MAHA and thrombocytopenia, presence of significant hematuria and/or proteinuria and positive testing for perinuclear ANCA and anti-myeloperoxidase antibodies. Anti-Scl-70 antibodies have also been found to occur much more commonly in patients with AAV-SSc overlap than those with SSc alone (27-29).

#### *Laboratory findings*

Typical laboratory abnormalities found in patients with SRC include: elevated serum creatinine (present in 90-96% of cases), hyperreninaemia, and MAHA (45-60% of cases) with associated thrombocytopenia, schistocytes in peripheral smear, elevated serum LDH and decreased haptoglobin (5, 11). The degree of thrombocytopenia is usually moderate ( $>50,000/\text{mm}^3$ ) and platelet counts return to baseline once blood pressure is controlled (24). Urinalysis may show evidence of mild proteinuria and haematuria with granular casts on microscopy (5, 15, 24).

Antinuclear antibodies (ANAs) have been found in virtually all patients with SSc. An ANA speckled pattern has been found in 60% of SRC patients and is associated with development of SRC (5). Anti-RNA polymerase III antibodies are also strongly associated. One study

of 252 SSc patients found that 24% with this antibody developed SRC (30). RNA polymerase antibodies have been reported in 25-59% of SRC patients (5, 31-33). Anti-centromere, anti-topoisomerase I and anti-U3 RNP autoantibodies have not been found to correlate with SRC development (5, 32-34).

#### *Biopsy findings*

Although biopsy is not always necessary, findings are specific to SRC and can be used to confirm the diagnosis. Microscopic examination reveals a picture of a thrombotic microangiopathic process affecting small vessels (12, 24, 35). Larger arteries are often normal. Early changes include accumulation of mucin in the arcuate and interlobular arteries with mucoid intimal thickening and fibrinoid necrosis of the arterioles (14). Later changes include hypertensive vascular damage, glomerular ischemia and thrombosis with vascular occlusion and fibrosis. The classic "onion skin lesion" results from proliferation of the vascular intimal cells which causes narrowing of the vessel lumen. Chronic changes including glomerulosclerosis and ischaemic glomerular collapse can occur. Additionally, hyperplasia of the juxtaglomerular apparatus from increased renin production has been found in 12% of cases (13). In advanced stages of the disease, histologic findings may be non-specific (12).

#### *Treatment*

The mainstay of treatment for SRC is with ACE-Is. ACE-I therapy should be started as soon as possible and continued even if serum creatinine continues to rise. Prompt, aggressive treatment greatly reduces the need for dialysis (11). Use of ACE-I prophylactically has not been found to prevent development of SRC (5, 19, 20). Angiotensin-receptor blockers theoretically should also be beneficial, but currently clinical experiences have been inconsistent (24, 36, 37). Additionally, calcium-channel blockers (CCBs), alpha-blockers (36, 38) and nitrates can be used when blood pressure remains uncontrolled despite maximal ACE-I therapy. A recently reported retrospective case series of 410 SSc patients found that those taking

CCBs had a greatly reduced risk of developing SRC. This suggests that CCBs may be useful as a "background" therapy for SSc, although further studies are needed (7). Possible future therapies include continuous low-dose prostacyclin, direct renin inhibitors and endothelin receptor antagonists. Case reports and a recent pilot study have shown some success with endothelin receptor blockade; however, formal trials are needed (18, 36, 39, 40).

Despite maximal medical therapy, dialysis is required in up to half of SRC patients (11). Fifty percent of those patients initially requiring dialysis are able to be weaned off within 2 years. For patients requiring dialysis beyond 2 years, renal transplant should be considered, as this has shown to improve long-term outcomes (5). Unfortunately, graft survival is typically lower in SSc patients than in transplant patients in the general population (41). This reduced graft survival may be secondary to recurrence of SRC and the systemic nature of SSc.

#### *Prognosis*

While prognosis for SRC was at one time dismal, with the advent of ACE-I, it improved dramatically. However, despite maximal therapy with ACE-I, other antihypertensive medications and dialysis, the mortality rate remains high. Studies have found that 36-38% of patients recovered without dialysis, 23% required temporary dialysis and 39-41% had poor outcomes (death or permanent dialysis) (5, 11). 1- and 5-year survival rates have been reported to be between 78-82% and 59-69%, respectively (5, 19).

Certain factors have been identified as poor prognostic indicators in multiple studies. Normal or mildly elevated blood pressure at presentation is associated with a higher mortality (5, 6, 19). This may be a result of delayed diagnosis with ongoing subclinical kidney injury. Additionally, it may be that normotensive patients have a less renin-angiotensin-aldosterone system-dependent process occurring and therefore, may be less responsive to ACE-Is (5). Additional factors associated with a poorer outcome include: male sex, older age ( $>55$  years old), higher initial serum creati-

nine (greater than 3.0 mg/dL), MAHA and thrombocytopenia (5, 11, 19).

Biopsy findings have been studied to determine whether they could provide further information regarding patient prognosis. Acute vascular changes and the extent of vascular injury were found to be most indicative of a poor outcome (5, 13).

## Discussion

In the case described in this report, the patient developed SRC prior to being diagnosed with scleroderma. Because she did not have known SSc when she presented with renal failure and MAHA, there was a delay in the diagnosis and treatment of her SRC. While the patient was fortunate to survive her illness, she unfortunately remained dialysis-dependent. Initiation of an ACE-I earlier in her disease course may have improved her outcome. This case serves as an important reminder to clinicians that SRC can develop in patients with little to no skin involvement and may be the initial presenting feature of the disease. In patients with new onset refractory hypertension, renal failure and MAHA, it is important to perform a thorough physical examination as subtle findings (*i.e.* early sclerodactyly) may provide clues that scleroderma is the underlying aetiology. Early detection and treatment of this disease is critical for renal recovery and patient survival.

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