Chapter 2
Scleroderma Renal Crisis

Marie Hudson, Cybele Ghossein, and John Varga

Introduction

The kidneys can be affected in patients with systemic sclerosis (SSc) in multiple ways. While renal involvement can be indolent and relatively benign, scleroderma renal crisis (SRC), the most dramatic form of renal involvement that occurs in up to 10% of patients with diffuse cutaneous SSc, commonly has an abrupt onset and progressive course, and is associated with poor outcomes and high mortality.

Case #1 Classic Case of SRC

Diane is a 55-year old woman who developed Raynaud's phenomenon and puffy fingers approximately 2 years ago. At

M. Hudson (✉)
Jewish General Hospital, Lady Davis Institute, McGill University, Montreal, QC, Canada
e-mail: marie.hudson@mcgill.ca

C. Ghossein · J. Varga
Scleroderma Program, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
e-mail: Cybele.ghossein@nm.org; j-varga@northwestern.edu

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that time, she was found to have a high titre speckled ANA and positive anti-RNA polymerase III antibodies. Her baseline blood pressure was normal (130/70 mmHg) as was her creatinine (75 umol/L or 0.85 mg/dL). She noted progressive thickening of her skin involving the fingers, hands, forearms, face, chest, thighs and feet. A diagnosis of SSc was made, and her modified Rodnan skin score (MRSS) was 23. Treatment with mycophenolate (1 gm bid) was initiated. Three months prior to her admission, she complained of joint pain, and was started on low-dose prednisone (7.5 mg/day). She presented to the clinic without an appointment complaining of general unwellness and shortness of breath over the last 2 weeks. In the clinic, her blood pressure was 180/90 mmHg. Blood tests were remarkable for new anemia (hemoglobin 95 g/L) and an elevated creatinine (145 umol/L or 1.64 mg/dL). How should this patient be managed?

Scleroderma renal crisis (SRC) is characterized by new onset malignant hypertension and acute kidney injury. Risk factors for SRC include early SSc (less than 5 years), rapidly progressive skin disease and the presence of anti-RNA polymerase III antibody. When anti-RNA polymerase III testing is not available, a speckled, and at times nucleolar, immunofluorescence staining pattern in the absence of other known fine specificities may be a clue. Other risk factors for SRC include male sex, tendon friction rubs and exposure to nephrotoxic drugs, including non-steroidal anti-inflammatory drugs and calcineurin inhibitors. Exposure to glucocorticoids, even at low doses, is commonly reported as a risk factor [1]. Whether the association of SRC and glucocorticoid exposure is causal or instead represents the presence of active disease remains uncertain; nevertheless, glucocorticoids remain relatively contra-indicated in SSc patients with risk factors for SRC. It is interesting to note that the conditioning regimen used in most autologous hematopoietic stem cell transplant (AHSCT) protocols includes high-dose glucocorticoids,

prompting the *prophylactic* use of ACE inhibitors in this setting. Although AHSCT might be a possible risk factor for SRC, the role of prophylactic ACE inhibitors in this setting remains uncertain.

Patients presenting with signs and symptoms of SRC should be immediately referred to a monitored setting (such as an emergency room or an intensive care unit) for continuous blood pressure monitoring, and assessed for evidence of acute kidney injury (AKI). The Kidney Disease Improving Global Outcomes (KDIGO) definition of AKI is as follows [2]:

- Increase in serum creatinine by >26.5 umol/L (> 0.3 mg/dL) within 48 h.
- Increase in serum creatinine to >1.5 times baseline, known or presumed to have occurred within the prior 7 days.
- Urine volume < 0.5 mL/kg/h for 6 h.

Evaluation

Urinalysis and urine microscopy are essential to rule out alternative explanations for new onset hypertension and AKI. In particular, hematuria, dysmorphic red blood cells and casts could suggest vasculitis or glomerulonephritis. Target organ dysfunction could manifest as encephalopathy, seizures, heart failure, pericardial effusion and retinopathy. A cardiac echocardiogram and ophthalmoscopic exam, the latter preferably performed by an ophthalmologist, are therefore also part of the basic work up. Appropriate testing for thrombotic microangiopathy should be performed.

The indications for kidney biopsy (Fig. 2.1) in an SSc patient presenting with classic hypertensive SRC remain uncertain. Although kidney biopsy for SRC may be useful prognostically [3], this must be balanced with the risks of

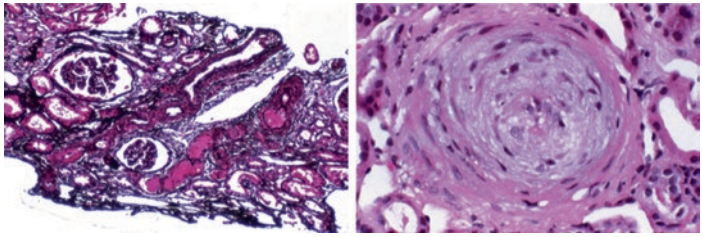

FIGURE 2.1 Renal biopsy findings of SRC

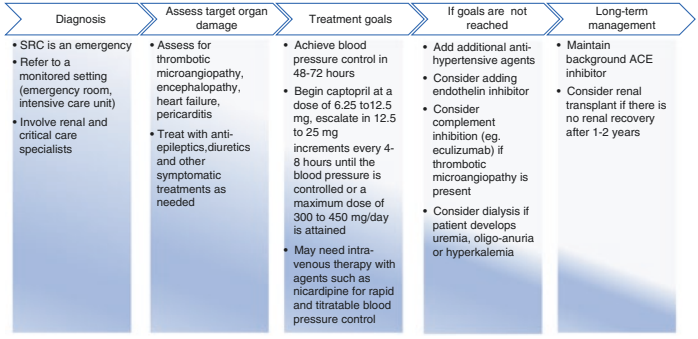

FIGURE 2.2 Management of scleroderma renal crisis

bleeding in the setting of uncontrolled hypertension and anemia. Unexplained AKI in a normotensive SSc patient, however, is an indication for a kidney biopsy. Approximately 10% of cases of SRC are not associated with hypertension.

Management (Fig. 2.2)

Initial management for suspected SRC consists of ACE inhibition using a short-acting agent such as captopril. If the patient is unable to take oral medications, intravenous enalaprilat could be used, although it is not preferred because of a

long duration of action (up to 36 h). In our experience, combination therapy with intravenous nicardipine is helpful to control blood pressure as the dose of oral ACE inhibitor is titrated to maximal tolerated dose. There are no standard guidelines on the target for blood pressure control; however, restoring the patient's baseline blood pressure should be the goal. Of note, since hypertension in SRC is acute, commonly used targets for controlling chronic hypertension are not applicable. In fact, in SRC, we generally aim to normalize the blood pressure rapidly (over 2–3 days) with the goal of preserving renal function.

It is not unusual to note a rise in creatinine as ACE inhibitors are up-titrated. This increase can reflect hemodynamic changes as a result of ACE inhibition, as well as worsening SRC or an alternative cause of AKI. We recommend a coordinated team approach with rheumatologists and nephrologists in the management of SRC.

If blood pressure goals are not achieved with ACE inhibitors and calcium channel blockers, additional antihypertensive medication should be added. Although angiotensin receptor blockers (ARB) might be expected to be effective in patients with SRC, there are multiple caveats. First, they have not been adequately evaluated as monotherapy in this setting. Second, they should not replace ACE inhibitors because, unlike ACE inhibitors, they do not inhibit the degradation of bradykinin, which are potent vasodilators. Third, studies in other diseases have suggested that patients treated with both an ACE inhibitor and ARB are at higher risk of adverse events compared with those treated with only one agent. Endothelin inhibitors have been used in the setting of SRC, although results with bosentan, a non-selective endothelin-1 receptor antagonist, have so far been disappointing [4]. There is an ongoing trial with zibotentan, a selective endothelin-A antagonist (NCT02047708). Since SRC can be associated with a thrombotic microangiopathy and in view of recent evidence of the potential role of complement activation in other thrombotic microangiopathies

such as atypical hemolytic uremic syndrome, the complement inhibitor eculizumab has been used in some cases of SRC [5]; however the proper role of anti-complement therapy in the treatment of SRC remains to be established. Although there are theoretical advantages for using direct renin antagonists, the published evidence remains sparse. Beta blockers should be avoided because of the risk of reducing cardiac output and triggering "renal" Raynaud's.

Patients with SRC require close monitoring for blood pressure, creatinine and urine output until blood pressure is adequately controlled, kidney function stabilizes, and signs of microangiopathy and target organ dysfunction resolve. Improvement in renal function can continue for up to 1–2 years following an episode of SRC. Hence, decisions regarding kidney transplantation should be deferred until that time.

Life-long use of ACE inhibitors after SRC is usually recommended, even in the absence of hypertension. However, the data on the use of ACE inhibition post-transplant is sparse and insufficient to make a reliable recommendation.

Case #2 Isolated Systemic Hypertension

Jay is a 55-year old African-American man with a 2-year history of Raynaud's phenomenon, sclerodactyly, gastroesophageal reflux and a positive anti-centromere antibody. His only medication is a proton pump inhibitor. At his yearly appointment, he reported feeling well, but was noted to have newly elevated blood pressure (150/90). Laboratory investigations including hemoglobin, platelets and creatinine (90 umol/L or 1.02 mg/dL) were all normal and not changed from his baseline. How should newly diagnosed isolated hypertension be managed in this patient with limited cutaneous SSc?

SSc patients presenting with hypertension need to be carefully assessed and risk stratified. Although this patient has some risk factors for SRC (male sex and relatively early disease), his limited cutaneous involvement and serology (anti-centromere antibody) put him at low risk. In particular, anti-centromere antibody positivity appears to be "protective" for SRC. Nevertheless, a thorough work up, including evaluation of family history of hypertensive disease, urinalysis and investigation for hemolysis, are indicated for this patient. Creatinine should be monitored. If hypertension persists, without evidence of AKI or other signs and symptoms of SRC, we would diagnose essential hypertension. Of note, a recent study suggested that hypertension (as well as proteinuria and chronic kidney disease) at the time of SSc diagnosis may be risk factors for SRC [6]. Thus, continued vigilance is warranted over time.

Treatment of essential hypertension in SSc remains a challenge. The obvious dilemma is whether new "isolated" hypertension in a patient with SSc could in fact herald the onset of SRC, and whether initiating treatment with an ACE inhibitor could abort a crisis. However, while definitive answers are lacking, some studies suggested that exposure to ACE inhibitors in SSc prior to SRC may not be protective, and may in fact be harmful [7]. We therefore recommend a calcium channel blocker (which may also have benefit on Raynaud's phenomenon) for patients with SSc and new onset isolated hypertension. We also recommend avoiding beta-blockers, which may worsen Raynaud's and exacerbate "renal" Raynaud's, and diuretics, because fluid shifts have been proposed as potential triggers for SRC.

Some advocate the use of ACE inhibitors in early SSc to prophylax against SRC (Fig. 2.3). There is no data at this time to support the role of prophylactic ACE inhibition for SSc patients without indications for ACE inhibition (eg. hypertension or chronic kidney disease with proteinuria [which is not uncommon in SSc] [8]). Therefore, we do not recommend prophylactic ACE inhibitors at this time.

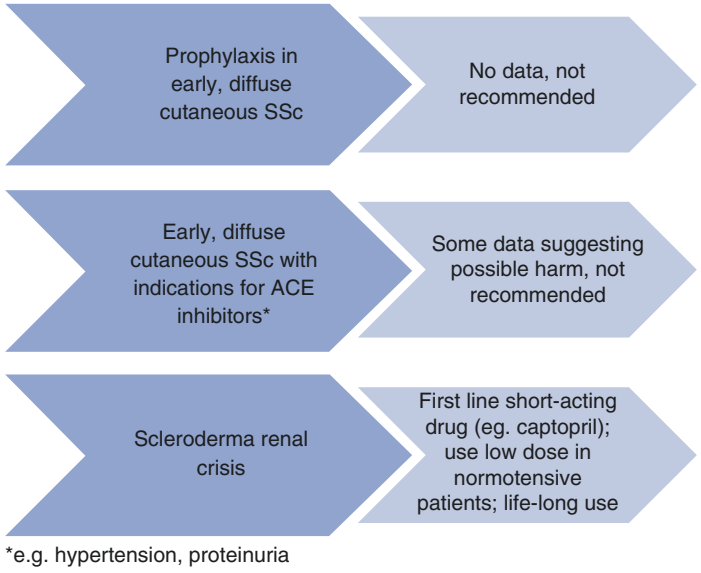

Figure 2.3 ACE inhibitors in systemic sclerosis

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References

1. DeMarco PJ, Weisman MH, Seibold JR, Furst DE, Wong WK, Hurwitz EL, et al. Predictors and outcomes of scleroderma renal crisis: the high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. Arthritis Rheum. 2002;46(11):2983–9.
2. Kellum J, Lameire N, Aspelin P, Barsoum R, Burdmann E, Goldstein S. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int. 2012;2(1):1–138.
3. Batal I, Domsic RT, Shafer A, Medsger TA Jr, Kiss LP, Randhawa P, et al. Renal biopsy findings predicting outcome in scleroderma renal crisis. Hum Pathol. 2009;40(3):332–40.

4. Bérezné A, Hendy A, Karras A, Marie I, Huart A, Ficheux M, et al. Bosentan in scleroderma renal crisis: a National Open Label Prospective Study [abtract]. Arthr Rheumatol. 2017;69 (suppl 10).
5. Thomas CP, Nester CM, Phan AC, Sharma M, Steele AL, Lenert PS. Eculizumab for rescue of thrombotic microangiopathy in PM-Scl antibody-positive autoimmune overlap syndrome. Clin Kidney J. 2015;8(6):698–701.
6. Gordon SM, Stitt RS, Nee R, Bailey WT, Little DJ, Knight KR, et al. Risk factors for future scleroderma renal crisis at systemic sclerosis diagnosis. J Rheumatol. 2019;46(1):85–92.
7. Hudson M, Baron M, Tatibouet S, Furst DE, Khanna D. International scleroderma renal crisis study I. exposure to ACE inhibitors prior to the onset of scleroderma renal crisis-results from the international scleroderma renal crisis survey. Semin Arthritis Rheum. 2014;43(5):666–72.
8. Steen VD, Syzd A, Johnson JP, Greenberg A, Medsger TA Jr. Kidney disease other than renal crisis in patients with diffuse scleroderma. J Rheumatol. 2005;32(4):649–55.