CASE REPORT

Steroid-induced scleroderma renal crisis in an at-risk patient

Sebastian Miguel Toescu,^{1,2} Alex Mansell,^{1,2} Eoin Dinneen,¹ Malcolm Persey²¹Royal Free Hospital, London, London, UK²Department of Rheumatology, Chase Farm Hospital, Enfield, UK**Correspondence to**

Dr Sebastian Miguel Toescu, s.toescu@nhs.net

Accepted 23 October 2014

SUMMARY

Scleroderma renal crisis (SRC) is a major complication of systemic sclerosis (SSc). We present a case of a patient who died of complications attributable to SRC in the context of recently diagnosed SSc. We review the typical clinical and laboratory features of SSc present in our patient and highlight those that identify greater risk of progression to SRC. Particular risk factors for SRC include cutaneous involvement, positive anti-RNA polymerase III antibodies and use of corticosteroids (CS). The authors emphasise the importance of risk evaluation when choosing to use CS in patients with SSc.

BACKGROUND

Scleroderma is a heterogeneous group of autoimmune conditions of uncertain pathological origin broadly linked by the presence of fibrotic skin lesions. It is classified into localised scleroderma and systemic sclerosis (SSc). The latter is again divided into limited (lcSSc) and diffused (dcSSc) forms, with dcSSc carrying a risk of visceral involvement. Scleroderma renal crisis (SRC) is a severe complication of SSc, and constitutes a renal and rheumatological emergency.

SSc is a rare condition, with an estimated incidence of 20 cases per million per year,¹ and SRC is estimated to affect 5–10% of patients with SSc.² Despite the introduction of ACE inhibitors (ACEi) and renal replacement therapy (RRT), mortality remains high, with a 5-year survival rate of only 59%.³ This case is important as we point out the risk factors associated with development of this potentially fatal condition with the aim of alerting a predominantly non-specialist readership to the potential dangers of corticosteroid (CS) use in this patient population.

CASE PRESENTATION

A 76-year-old man with no significant medical history presented to his general practitioner (GP) with peripheral synovitis, Raynaud's phenomenon and thickening of the skin over the fingers. An initial dose of 15 mg prednisolone daily was required to control the symptoms of joint pain and swelling, and serological testing demonstrated positive antinuclear antibodies (1/320) with a speckled pattern and specificity for anti-Scl-70 (anti-topoisomerase) at high titre, consistent with a diagnosis of SSc.

Having weaned his prednisolone to 7.5 mg, some weeks later he began to experience generalised malaise, with shortness of breath and leg swelling. He returned to his GP who increased the

prednisolone dose to 20 mg. Three months after his initial diagnosis of scleroderma, he was admitted to the hospital with dyspnoea and a cough productive of white sputum. On admission, he was noted to be hypertensive at 202/110 mm Hg. Clinically, there was fluid overload with a raised jugular venous pressure, late inspiratory bibasal crepitations and peripheral pitting oedema. Heart sounds were dual and there was no papilloedema on fundoscopy. There was active peripheral synovitis.

INVESTIGATIONS

Blood tests demonstrated an acute kidney injury, with creatinine 413 µmol/L and urea 27.7 mmol/L. Estimated glomerular filtration rate (eGFR) was 13 mL/min/1.73 m², with a baseline eGFR of 71.1 mL/min/1.73 m², equating to a 72% decline. Haemoglobin was 121 g/L, white cell count 15.8×10⁹/L, neutrophils 13.0×10⁹/L, platelets 88×10⁹/L, mean cell volume 87.2 fL, total bilirubin 22 µmol/L and albumin 33 g/L. Blood film analysis showed occasional erythrocyte fragments and lactate dehydrogenase was raised at 599 IU/L. Urinalysis showed 2+ haematuria, 1+ leucocytes and 3+ proteinuria with a protein:creatinine ratio of 100. There was bibasal consolidation, a right-sided pleural effusion on chest radiography and no evidence of pulmonary mass lesions.

A renal biopsy following the acute phase of the crisis demonstrated severe microangiopathic changes, with fibrointimal proliferation with 'onion-skinning' leading to obliteration of the vascular lumen, and myxoid mural degeneration as well as hypertensive vascular damage and glomerular ischaemia (figure 1). There were no immediate or delayed complications as a result of the procedure.

TREATMENT

Treatment with ACEi and intravenous iloprost by infusion was initiated prior to transfer to a specialist renal centre where the patient underwent haemodialysis. He required pharmacological cardioversion with amiodarone following the development of paroxysmal atrial fibrillation, and was later started on digoxin as a rate-controlling agent; his dose of long-acting diltiazem was increased from 90 mg twice daily to 120 mg twice daily, providing an additional antihypertensive effect. A peritoneal dialysis (PD) catheter was placed during his inpatient stay; RRT was still required on discharge and PD was started in the outpatient setting. Initially, a small dose of 2.5 mg ramipril was

CrossMark

To cite: Toescu SM, Mansell A, Dinneen E, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-206675

Figure 1 (A) Collapsed glomerulus (black arrow) with fibrinoid necrosis seen in the wall of the adjacent vessel to the left (H&E stain, $\times 20$). (B) Typical 'onion skinning' representative of fibrointimal proliferation with near obliteration of vascular lumen (Periodic Acid Methenamine Silver (PAMS) stain, $\times 20$). Scale bars 100 μm .

successful in reducing the patient's blood pressure to 156/60 mm Hg, and he was discharged on a maintenance dose of 5 mg twice daily.

OUTCOME AND FOLLOW-UP

Two months after discharge, he developed a community-acquired pneumonia necessitating readmission, and PD peritonitis. He later developed enlarging pleural effusions and pancreatitis with pseudocyst formation, and died of multi-organ failure despite maximal supportive therapy at around 7 months after his initial diagnosis of SSc.

DISCUSSION

SRC is characterised by new onset systemic hypertension ($>150/85$ mm Hg) accompanied by a drop in eGFR of at least 30%. The case presented illustrates several characteristic clinical findings in patients with SRC. There is an acute or subacute decline in renal function, with pulmonary and peripheral oedema arising from water and salt retention. Symptoms ascribable to malignant hypertension such as headache, visual disturbance and encephalopathy may also be present. Urinalysis typically shows only mild haematuria and proteinuria. Haematological findings include microangiopathic haemolytic anaemia and thrombocytopenia. The pathogenesis of SRC remains unclear. Narrowing of renal arteries due to intimal thickening is thought to play a role, leading to hyper-reninaemia, which may drive the systemic hypertension.

In this case, the findings of thrombocytopenia with microscopically viewed corpuscular fragments might prompt consideration of other forms of thrombotic microangiopathy (TMA), such as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome as the pathology underlying the presentation. However, the patient's recent diagnosis with SSc performed the diagnosis of SRC over other forms of TMA far more likely, and the presence of accelerated hypertension would also be in favour of SRC. SSc has been shown to bestow an increased risk of neoplastic disease, particularly lung⁴ and oesophageal⁵ cancer. However, there was no clinical or radiological evidence of malignancy in our patient.

Our patient's gender and advanced age are poor prognostic markers in this case, but beyond this there are several recognised risk factors for development of SRC. A significant factor to be considered is diffuse skin involvement. In a retrospective analysis,⁶ rapidly progressive diffuse skin involvement was found to increase the odds of developing SRC more than twofold, and of those who develop SRC, two-thirds of patients will do so in the first year of their disease,³ as was the case in our patient. Serological testing can also serve as a predictive tool for the development of SRC; the presence of anti-RNA polymerase III is strongly associated with an increased risk of SRC.⁷ Although

not established in this case, this antibody was seen in 59% of patients with SSc with SRC in comparison to just 11.7% in those without SRC in a single-centre retrospective case series.³

The use of CS is a potent risk factor in the development of SRC. Indications for CS use in scleroderma include interstitial lung disease, synovitis, cutaneous disease and the treatment of any overlap syndromes that may occur.⁸ Several studies demonstrate increased odds of developing SRC with recent use of CS,^{3 9 10} with up to 60% of patients with SRC having received CS before presentation.¹¹ Recent, good-quality systematic reviews^{12 13} highlight the risk of SRC with concurrent CS use, whether medium or high doses are employed, or even with the prolonged use of low doses.

The need for CS therapy in scleroderma should be carefully considered and the benefits and risks evaluated on a case-by-case basis. The decline in general health with which our patient presented to his GP was possibly ascribed to scleroderma and this was the rationale for increasing the dose of CS, which ultimately may have contributed to his decline into renal failure. Although scleroderma and its visceral complications will usually be managed in a specialist environment, it is important for a wider audience of doctors to be made aware of the risks of CS use in this disease and to take advice from specialists where necessary. The possibility of alternative immunosuppressants with a steroid-sparing rationale should be considered. This applies to junior doctors working with unselected medical admissions as well as community practitioners caring for patients over a longer timeframe.

When taken together, it can be seen that our patient was particularly at risk of developing SRC, with recognised risk factors of recently increased CS dosing and early diffuse cutaneous disease. Indeed, the risk of SRC in a patient with these two risk factors is double that of patients with SSc without these characteristics.¹² Mortality rates in patients requiring long-term dialysis are significant, and the case presented here is sadly

Learning points

- Scleroderma renal crisis (SRC) is characterised by the development of new onset systemic hypertension ($>150/85$ mm Hg) and a fall in estimated glomerular filtration rate of $>30\%$ in patients with systemic sclerosis (SSc).
- SRC remains potentially fatal despite the introduction of ACE inhibitors and renal replacement therapy.
- Risk factors include diffuse skin involvement, positive anti-RNA polymerase III antibodies and corticosteroid use.
- Non-specialist physicians caring for patients with SSc should be aware of the risks of corticosteroid use in these patients.

typical. Our patient died due to an unfortunate chain of complications that were set in motion by the development of SRC; we wish to emphasise the risks of CS use in patients with SSc, and to raise awareness of this potentially fatal condition.

Contributors AM and MP clinically treated the patient prior to transfer to a specialist unit; SMT wrote the article and performed background literature searches; ED sourced and annotated the pathology slides.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Nikpour M, Stevens WM, Herrick AL, *et al.* Epidemiology of systemic sclerosis. *Best Pract Res Clin Rheumatol* 2010;24:857–69.
- 2 Denton CP, Black CM. Scleroderma—clinical and pathological advances. *Best Pract Res Clin Rheumatol* 2004;18:271–90.
- 3 Penn H, Howie AJ, Kingdon EJ, *et al.* Scleroderma renal crisis: patient characteristics and long-term outcomes. *QJM* 2007;100:485–94.
- 4 Hill CL, Nguyen AM, Roder D, *et al.* Risk of cancer in patients with scleroderma: a population based cohort study. *Ann Rheum Dis* 2003;62:728–31.
- 5 Derk CT, Rasheed M, Artlett CM, *et al.* A cohort study of cancer incidence in systemic sclerosis. *J Rheumatol* 2006;33:113–16.
- 6 Domsic RT, Rodriguez-Reyna T, Lucas M, *et al.* Skin thickness progression rate: a predictor of mortality and early internal organ involvement in diffuse scleroderma. *Ann Rheum Dis* 2011;70:104–9.
- 7 Nikpour M, Hissaria P, Byron J, *et al.* Prevalence, correlates and clinical usefulness of antibodies to RNA polymerase III in systemic sclerosis: a cross-sectional analysis of data from an Australian cohort. *Arthritis Res Ther* 2011;13:R211.
- 8 Alayoud A, Qamouss O, Hamzi A, *et al.* Scleroderma renal crisis precipitated by steroid treatment in systemic lupus erythematosus and scleroderma overlap syndrome. *Arab J Nephrol Transplant* 2012;5:153–7.
- 9 Teixeira L, Mouthon L, Mahr A, *et al.* Mortality and risk factors of scleroderma renal crisis: a French retrospective study of 50 patients. *Ann Rheum Dis* 2008;67:110–16.
- 10 Guillevin L, Bérezné A, Seror R, *et al.* Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. *Rheumatology* 2012; 51:460–7.
- 11 Denton CP, Lapadula G, Mouthon L, *et al.* Renal complications and scleroderma renal crisis. *Rheumatology* 2009;48(Suppl 3):iii32–5.
- 12 Trang G, Steele R, Baron M, *et al.* Corticosteroids and the risk of scleroderma renal crisis: a systematic review. *Rheumatol Int* 2012;32:645–53.
- 13 Iudici M, van der Goes MC, Valentini G, *et al.* Glucocorticoids in systemic sclerosis: weighing the benefits and risks—a systematic review. *Clin Exp Rheumatol* 2013;31 (2 Suppl 76):157–65.

Copyright 2014 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow