Scleroderma renal crisis: patient characteristics and long-term outcomes

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Summary

Background: Scleroderma renal crisis (SRC) is an important complication of systemic sclerosis, causing acute renal failure, and usually hypertension.

Aims: To review the clinical and pathological features of SRC, and correlate them with renal outcomes and mortality.

Design: Retrospective case series.

Methods: We identified 110 cases of SRC managed at a single centre between 1990 and 2005.

Results: SRC occurred in 5% of scleroderma cases under follow-up. Cases were predominantly female (81%), with diffuse cutaneous disease (78%). RNA polymerase antibodies were found in 59% of cases tested. Almost all (108/110) received treatment with ACE inhibitors (ACEIs). Dialysis was not required in 36%, was required temporarily (for up to 3 years) in 23%, was required permanently in 41%. Patients not on dialysis showed improvement in estimated glomerular filtration rate after SRC (mean change +23 ml/min over 3 years). Poor renal outcome was associated with lower blood pressure at presentation, and with higher age in those requiring dialysis. Steroid use, microangiopathic haemolytic anaemia, and antibody profile were not related to renal outcome. In the 58 renal biopsies available for clinical correlation, acute changes of mucoid intimal thickening in arteries and fibrinoid necrosis in arterioles were associated with a poorer renal outcome. Mortality was high (59% survival at 5 years), and was higher in men.

Discussion: Despite the efficacy of ACEIs in managing SRC, the poor long-term outcome warrants evaluation for additional treatments for this devastating complication of systemic sclerosis.

Introduction

Systemic sclerosis is a heterogeneous autoimmune rheumatic disease of uncertain aetiology, characterized by inflammation and fibrosis in the skin and other organs, and vascular abnormalities, including Raynaud’s phenomenon. It has a female predominance, and typically presents between 30 and 60 years of age, without major geographical variation. Cases are classified into two major subsets distinguished by the extent of skin involvement—limited cutaneous systemic sclerosis (lcSSc), and diffuse cutaneous systemic sclerosis (dcSSc)—with distinct differences in outcome.
Scleroderma renal crisis (SRC) is a complication of systemic sclerosis that was first reported in 1863.² It typically causes accelerated phase hypertension and acute renal failure. SRC had a high mortality until the advent of treatment with angiotensin-converting-enzyme inhibitors (ACEIs), following which mortality fell appreciably (from 85% at 1 year, to 24% at 1 year in a single centre³). SRC is more common in patients with the diffuse subset of the disease.

Other clinical features of SRC⁴ include hypertensive retinopathy in the majority of patients, and encephalopathy, which can cause seizures. Pulmonary oedema is common, and reflects the large afterload and oliguria, inducing salt and water retention. Pericarditis, myocarditis and arrhythmias may supervene, and may be associated with a poorer prognosis.⁵ Urinalysis commonly demonstrates proteinuria (which is non-nephrotic range) and haematuria; granular casts are often seen on microscopy.

Changes that can be seen in the circulation include high levels of renin, which mediates the hypertension (evidenced by the remission of the hypertension on nephrectomy⁶). Other circulatory changes include microangiopathic haemolytic anaemia (MAHA). Markers of endothelial cell perturbation have been observed, including high levels of soluble adhesion molecules in the circulation (VCAM-1, ICAM-1 and E-selectin).⁷

Biopsies taken from kidneys of affected patients initially show accumulation of mucin in interlobular arteries, and fibrinoid necrosis of arterioles (indistinguishable from changes of accelerated hypertension).⁸ Immunohistochemical staining has confirmed the upregulation of the endothelin axis, including endothelin-1 (ET-1) and endothelin B receptors.⁹

Risk factors proposed for renal crisis include anaemia,¹⁰ new cardiac events,¹¹ steroid use (>15 mg prednisolone/day),¹² cyclosporin therapy,¹³ diffuse skin disease,⁸,¹⁴ rapidly progressive skin disease,¹⁵ high skin score,¹¹ large joint contractures,¹¹ presence of anti-RNA-polymerase antibody,¹⁴ and <4 years since scleroderma onset.¹⁶ These risk factors may relate to disease severity, rather than having a causative role in pathogenesis of the renal crisis.

Data from the high dose versus low dose D-penicillamine trial¹¹ showed a persistently high mortality and morbidity from this disease, with 9/18 patients with renal crisis dying at a mean of 0.9 years after presentation with renal crisis. These patients were, due to the nature of the trial, a group with diffuse disease of recent onset (mean duration 0.8 years); 13% of patients enrolled developed renal crisis. There is an excess mortality associated with scleroderma (standardized mortality ratio estimated at 4¹⁵), and studies of SRC have shown appreciable early rates of mortality.⁴,⁵,¹¹ In this study, we report a large single-centre series of confirmed SRC, and review patient characteristics and outcomes. The relationship between biopsy features and outcome is examined.

**Methods**

Cases with SRC were identified from databases held by the departments of Rheumatology, Nephrology, and Pathology, using the criteria in Table 1. Patient records at the study centre were analysed using data gathered during routine clinical practice from patients attending the Royal Free Hospital Centre for Rheumatology. The observations

| Renal crisis classification |

In the presence of limited or diffuse cutaneous systemic sclerosis:

1. A new onset of blood pressure >150/85 mmHg obtained at least twice over a 24-h period. This blood pressure is chosen because it is that defined by the New York Heart Association as significant hypertension.
2. A documented decrease in the renal function as defined by a decrement of at least 30% in the calculated glomerular filtration rate (eGFR). When possible, a repeat serum creatinine concentration and recalculation of the eGFR should be obtained to corroborate the initial results.

To corroborate further the occurrence of acute renal crisis, it would be desirable to have any of the following, if available:
- Microangiopathic haemolytic anaemia on blood smear
- Retinopathy typical of acute hypertensive crisis
- New onset of urinary RBCs (excluding other causes)
- Flash pulmonary oedema
- Oliguria or anuria
- Renal biopsy showing characteristic changes

Renal biopsy showing an alternative cause excludes the case from classification as SRC.
included in this study relate to the period between 1990 and 2005.

Patients were treated with the aim of reducing systolic blood pressure by 20 mmHg/day, as previously described. Presenting blood pressure was taken as the first recorded blood pressure of the hospital admission. Scleroderma was classified according to the preliminary ACR criteria. eGFR was calculated using the MDRD formula as previously validated in SSc. Where relevant, characteristics of the SRC group were compared with those of the whole group of scleroderma patients (n=1997) followed-up at the Royal Free Hospital over the same period, which included the SRC patients. Statistical analyses used Minitab 14.

Antinuclear antibody (ANA) analysis was performed on HEP-2 cells. Patients with positive antibodies to extractable nuclear antigens (ENA) were classified by the type of ENA. Patients with a positive ANA and negative ENA were classified into those showing a speckled pattern (‘ANA—speckled’) (reported as fine speckled, or fine speckled and nucleolar) vs. ‘ANA—other’ for the rest. This was to define as far as possible patients with RNA polymerase antibodies, which typically have these appearances on immunostaining, and are ENA-negative. RNA polymerase antibodies were verified by a radioimmunoprecipitation assay or by ELISA (INOVA, San Diego) in 56/66. Early cases often had only a positive ANA recorded without specifying the pattern. These cases were all classified as ‘ANA—other’. Hence the observed prevalence of speckled antibodies may be underestimated in both the SRC and the other scleroderma groups.

Pathological analysis of renal biopsies was performed by one of the authors, who was blinded to the outcomes. The amount of chronic damage was measured as the index of chronic damage, as described previously. Parts of cortex with chronic damage were outlined on digital images, their area was measured by image analysis, and the total was expressed as a percentage of the cortical area. Acute changes were defined as either or both of mucoid intimal thickening in interlobular arteries and fibrinoid necrosis in arterioles. Chronic changes were chronic intimal thickening in arteries and hyalinosis in arterioles.

**Results**

We identified 110 patients who fulfilled the criteria for SRC, of whom 58 had undergone a renal biopsy at the time of SRC. Among patients excluded from analysis were three patients who had episodes of accelerated hypertension in the context of scleroderma without renal failure, and two patients with hypertension and acute renal failure, but who had disorders other than scleroderma on renal biopsy. In total, 447 years of patient follow-up were available: median 1132 days, range 5–5349. The mean age at diagnosis of SRC was 50.7 years (range 24–80) and 79% were female, compared to 81% of the RFH group, which consisted of 1997 patients.

**Characteristics of patients before SRC**

Of 110 SRC patients, 24 (22%) had lcSSc, and 86 (78%) dcSSc. This compared with our overall database population over the period of observation of 706 (35%) with dcSSc, and 1291 (65%) with lcSSc. The frequency of SRC was therefore 2% in lcSSc and 12% in dcSSc in this centre (χ² = 91, p < 0.001). The odds ratio for SRC in dcSSc vs. lcSSc was 7.2 (95% CI 4.5–11.4, p < 0.001). SRC was thus significantly more common in patients with dcSSc, although more than a fifth of our cases occurred in the limited subset. The antibody profiles of patients with lcSSc included 11 with fine-speckled ANA, six with anti-topoisomerase antibody (Scl-70), and three with non-specific ANA.

The median duration of SSc at the time of SRC was 7.5 months (range 0–200); 69 (66%) had SRC within 1 year of the diagnosis of scleroderma. SRC was the presenting feature of SSc in 23/105 (22%). Cases with SRC late in the course of their disease were more likely to have lcSSc (SRC occurred >2 years after diagnosis in 70% of lcSSc vs. 16% of dcSSc; χ² p < 0.001).

Full data on medication prior to SRC were available for 64 patients; 38 (59%) were treated with steroids within 1 month of developing SRC, and 25 (39%) were taking disease-modifying drugs, including 5 patients treated with antithymocyte globulin and steroid, 4 with cyclosporin, 4 with azathioprine, 3 with interferon-α, 2 with D-penicillamine, 2 with cyclophosphamide, 2 with methotrexate, 1 with anti-transforming-factor-β antibody, 1 with mycophenolate mofetil and 1 with danazole for idiopathic thrombocytopenic purpura.

Data on use of angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin type II receptor blockers prior to SRC were available for 68 patients; 18 were on ACEIs prior to diagnosis of SRC, and two on angiotensin type II receptor blockers. Most patients were on sub-maximal doses of these agents, for treatment of Raynaud’s phenomenon.

Table 2 shows a comparison of antibody profiles in SRC cases and scleroderma patients without SRC. The RNA polymerase antibody assay is relatively
The prevalence of RNA polymerase antibodies in SRC was 59% of the 95 tested for this antibody. Of 61 patients with fine speckled ANA and negative ENA tested for RNA polymerase antibodies, 56 were positive. Consistent with this, there was an association between a fine speckled pattern of ANA with negative ENA (ANA—speckled) and SRC (OR 10.9; \( p < 0.001 \)). Anti-centromere antibody (strongly associated with lcSSc) was significantly under-represented.

The data needed to calculate the pre-SRC MDRD eGFR (taken between 2 and 24 months prior to SRC) were available for 63 patients. There was significant renal impairment in this group, with a mean eGFR of 77 ml/min, SD 20. One patient had pre-existing renal impairment due to nephrolithiasis.

**Characteristics of patients at SRC presentation**

Blood pressure at presentation was available for 72 patients. The mean BP was 193/114 mmHg. Patients with systolic BP of <150 mmHg at presentation had hypertension (>150/85) later in the course of their disease. Serum creatinine concentration at presentation was available for 76 cases. The median creatinine concentration was 200 μmol/l (IQR 142–284, range 77–1123); three were in the normal reference range. A minority (\( n = 14 \)) presented with creatinine >400 μmol/l. A blood film report was available for 54 patients, of whom 52% had evidence of red cell fragments. Thrombocytopenia was found in 50% of the 50 patients with documented platelet counts, including 10 patients in whom a blood film did not demonstrate fragments. Altogether, 38/64 (59%) patients had evidence of thrombotic microangiopathy on a blood film. Echocardiographic data were available in 45 patients; 14 (31%) had evidence of reduced left ventricular ejection fraction (≤55%).

Two patients were not treated with ACEIs at diagnosis: one who was pregnant (treated with methyldopa and a beta-blocker), and one who was treated at home by her family physician during the crisis with a beta-blocker and a calcium antagonist. All other patients were commenced on ACEIs. Intravenous prostacyclin analogues or iloprost were also used commonly (in at least 46 patients) at the time of SRC, but dose and duration of prostanoid use were variable, and data often incomplete.

**Outcome of SRC**

Information on renal replacement therapy was available for 106 patients; 38 (36%) did not require dialysis at SRC (‘no dialysis’ group). Of these, only three were subsequently given dialysis: one who had a nephrectomy for renal cell carcinoma 10 years after SRC, one with deteriorating renal function who started dialysis 7 years after SRC, and one who required dialysis 8 years after SRC. Twenty-four patients (23%) were given dialysis at presentation subsequently recovered sufficient renal function to discontinue dialysis (‘dialysis and recovery’ group). Two of these required dialysis again: one had 13 months of dialysis, came off dialysis for 6 months, and then restarted dialysis, the other had 18 months of dialysis, and at 7 years after presentation with SRC required a 10-day period of dialysis during an intercurrent illness. Forty-four patients (42%) were either given dialysis at presentation and did not recover renal function

<p>| Table 2 Antibody status in SRC and non-SRC SSC patients with odds ratios. RNA polymerase antibodies are associated with increased risk of SRC. |</p>
<table>
<thead>
<tr>
<th>All SRC</th>
<th>All non-SRC</th>
<th>Odds ratio (95%CI)</th>
<th>( p^{**} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA—Speckled</td>
<td>66 (60%)</td>
<td>183 (12.1%)</td>
<td>10.9 (7.3–16.5)</td>
</tr>
<tr>
<td>RNA polymerase*</td>
<td>56 (59%)</td>
<td>54 (11.7%)</td>
<td>NA</td>
</tr>
<tr>
<td>ANA negative</td>
<td>3 (2.7%)</td>
<td>14 (0.9%)</td>
<td>3.0 (0.92–10.0)</td>
</tr>
<tr>
<td>PMScl</td>
<td>5 (4.5%)</td>
<td>47 (3.1%)</td>
<td>(0.6–3.2)</td>
</tr>
<tr>
<td>Scl 70</td>
<td>19 (17.2%)</td>
<td>286 (18.9%)</td>
<td>0.90 (0.54–1.50)</td>
</tr>
<tr>
<td>nRNP</td>
<td>2 (1.8%)</td>
<td>116 (7.6%)</td>
<td>0.22 (0.06–0.83)</td>
</tr>
<tr>
<td>ACA</td>
<td>2 (1.8%)</td>
<td>438 (28.9%)</td>
<td>0.05 (0.01–0.17)</td>
</tr>
<tr>
<td>Other</td>
<td>13 (12%)</td>
<td>432 (28.5%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>110 (100%)</td>
<td>1516 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

*RNA polymerase only tested in 96 SRC serum, and ‘All non-SRC’ is based on findings in 735 SSC patients. **Fishers exact test.
of dialysis and died \((n = 3)\) (‘dialysis without recovery’ group). Nineteen patients died on dialysis, and three had a renal transplant (these were categorized as ‘dialysis without recovery’, one of whom died in the peri-operative period.

Serum creatinine concentration at presentation was lowest in the ‘no dialysis’ group (mean 198 µmol/l). The ‘dialysis and recovery’ group presented with a higher creatinine concentration than the ‘dialysis without recovery’ group (376 vs. 287 µmol/l, respectively, ANOVA \(p = 0.028\)). Higher blood pressure at presentation was associated with a better outcome (Figure 1). Mean blood pressure was 205/121 mmHg in the ‘no dialysis’ group, 196/113 mmHg in the ‘dialysis and recovery’ group, and 172/103 mmHg in the ‘dialysis without recovery’ group (for both systolic and diastolic blood pressure, \(p < 0.05\), ANOVA test). Low LVEF at SRC was not associated with requiring permanent dialysis (OR 0.45, 95%CI 0.11–2.2, Fisher’s exact test \(p = 0.18\)) nor with death (\(\chi^2\) \(p = 0.35\)).

There were significant differences in age at SRC between the groups of different renal outcomes: mean age was 49 years in the ‘no dialysis’ group, 44 years in the ‘dialysis and recovery’ group, and 54 years in the ‘dialysis without recovery’ group (ANOVA test \(p < 0.002\)). Older patients were no more likely to require dialysis, but were less likely to recover renal function if dialysis was required. There was no correlation between age and systolic or diastolic blood pressures at presentation (\(p = 0.34\) and \(p = 0.14\), respectively).

There was no significant correlation between renal outcome and pre-SRC eGFR. There was no significant correlation between presence of MAHA and renal outcome. In the ‘no dialysis’ group, 18/28 (64%) were taking steroids at crisis vs. 24/52 (46%) of those dialysed, but there was no correlation between steroid use and renal outcome (ANOVA \(p < 0.2\), although ascertainment was incomplete. There was no difference between those treated with prostanoids and those not treated or for whom data was unavailable (ANOVA \(p = 0.30\)). The use of angiotensin II receptor blockers or ACEIs prior to SRC was associated with a trend towards requiring long-term dialysis, but this did not reach significance (OR 2.5, 95%CI 0.85–7.9, \(p = 0.16\); Table 3).

### Renal recovery

The median time to renal recovery (discontinuing dialysis) after SRC was 11 months, range 1–34 months. Renal recovery after 24 months was uncommon, and did not occur more than three years after SRC. Overall, 63% of patients required dialysis at presentation of SRC, and 33% of survivors were still on dialysis at 5 years.

Follow-up eGFR was calculated in patients not on dialysis. Measuring the yearly change in eGFR after SRC in non-dialysed patients showed an improvement in renal function continuing for at least 3 years (means in ml/min/year: year 1, 17.5; year 2, 2.8; year 3, 2.7; year 4, 2.4) (Figure 2).

###Deaths

Forty-four patients died after SRC (Figure 3). Survival was 82% at 1 year, 74% at 2 years, 71% at 3 years, 59% at 5 years, and 47% at 10 years. Deaths were most common in the ‘dialysis without recovery’ group. The ‘dialysis and recovery’ group had the best prognosis (log rank test \(p < 0.001\); Figure 4).

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**Figure 1.** Presenting diastolic blood pressure in SRC related to different renal outcomes. Higher BP was associated with better renal outcomes.

**Table 3** Pre-SRC use of angiotensin-converting-enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ATII), and renal outcome

<table>
<thead>
<tr>
<th>Renal outcome</th>
<th>No dialysis</th>
<th>Dialysis and recovery</th>
<th>Dialysis without recovery</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI/ATII</td>
<td>7 (35%)</td>
<td>3 (15%)</td>
<td>10 (50%)</td>
<td>20</td>
</tr>
<tr>
<td>No ACEI/ATII</td>
<td>20 (42%)</td>
<td>14 (29%)</td>
<td>14 (29%)</td>
<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>17</td>
<td>24</td>
<td>68</td>
</tr>
<tr>
<td>Odds ratio (95%CI)</td>
<td>0.75 (0.26–2.2)</td>
<td>0.43 (0.12–1.6)</td>
<td>2.5 (0.85–7.0)</td>
<td></td>
</tr>
<tr>
<td>(p^*)</td>
<td>0.78</td>
<td>0.36</td>
<td>0.16</td>
<td></td>
</tr>
</tbody>
</table>

*Fishers exact test.
There was no correlation between age at SRC and death ($p=0.27$), nor between subset of scleroderma and death ($\chi^2 0.45, p=0.75$). No antibody profile was significantly associated with mortality. Prognosis was worse in males: 10-year survival 17%, vs. 50% in females (log rank test $p=0.025$).

**Pathological findings**

The index of chronic damage was measured in 58 biopsies. The median index was 32% (IQR 16–51%). The index did not correlate with age or duration of scleroderma at SRC. The mean index was higher in the ‘no dialysis’ group compared with dialysed patients (44% vs. 29%, t test $p=0.028$). There was no significant difference in the index between the ‘dialysis and recovery’ group and the ‘dialysis without recovery’ group (26% and 31%, respectively). When the index was stratified into values of 0–19%, 20–39%, 40–59%, and >59%, renal survival was independent of the index (log rank test $p=0.75$).

Acute or acute and chronic changes were present in 36 biopsies, and chronic changes only in 16 (six biopsies contained no assessable blood vessels). The presence of acute changes, whether or not there were also chronic changes, correlated with poorer renal outcome: 48% of patients with acute changes required permanent dialysis, vs. 13% with chronic changes only (OR 6.6, 95%CI 1.3–33, Fisher’s exact test $p=0.025$; Table 4).

Patients with acute changes had a lower mean index of chronic damage (29%) than those...
without (49%). They had similar eGFRs before SRC (75 ml/min and 70 ml/min, respectively), but those with acute changes had higher serum creatinine at presentation (mean 288 and 186 μmol/l, respectively, t-test \( p = 0.021 \)). There was no correlation between the presence of acute changes and blood pressure, MAHA, type of scleroderma, or antibody status. In the ‘dialysis and recovery’ group, the rate of renal recovery was similar for those with acute changes and those without (cumulative change in eGFR at 3 years +20.8 and +17.1 ml/min, respectively). Despite the differences in renal outcome, mortality in those with acute changes was similar to those without (10-year survival 47% in those with acute changes vs. 43% in those without; log rank test \( p = 0.88 \)).

**Discussion**

This study confirms that patients with early dcSSc are at highest risk of developing SRC. A small number of patients presented with SRC later, particularly patients with lcSSc. Anti-RNA polymerase antibodies were a significant risk factor for SRC. The presence of fine speckled ANA with no other characterized antibodies is the typical pattern of RNA polymerase antibodies, and may be of help in characterizing the antibody profile in centres where a RNA polymerase antibody ELISA is not available. The prevalence of RNA polymerase antibody positivity in SSC has been estimated at 11.7% in this centre after assaying 735 patients serum, which correlates well with the 12.1% prevalence of fine speckled ANA in the whole group. Anti-topoisomerase-1 antibodies are not associated with increased risk of developing renal crisis in this SRC group, despite the association with diffuse skin disease. 88% of the SRC group had one of the characteristic auto-antibodies associated with SSC, which is consistent with the proportion found in patients with SSC as a whole (81%).

A small but significant proportion of SRC occurred in patients with limited disease. This is in keeping with estimates from previous studies, although it is possible that fewer cases with limited skin disease reach a tertiary care centre. These patients rarely carry anti-centromere antibody, but had a high proportion of fine-speckled ANA and topoisomerase-1 antibody.

More than a fifth of patients with SRC did not carry a diagnosis of SSC at presentation. This emphasizes the importance of early recognition of SSC, as it is clearly central to making the diagnosis of SRC, especially in those presenting with relatively modest rises in blood pressures and/or creatinine.

The role for medication in precipitating SRC has been reported previously, and may reflect disease severity or a causal role. The prevalence of steroid use in this group (59%) was similar to those in other reports. Steroid use was not associated with poorer outcomes. It has previously been suggested that prednisolone dose should not exceed 10 mg/day, where possible.

**Renal outcomes**

Of those patients requiring dialysis at onset, 35% were able to discontinue it. The eGFR of patients not on dialysis improved for at least 3 years after SRC, reflecting a slow recovery process that is likely to include vascular remodelling. This slow and prolonged improvement may also explain the low rate of renal failure later in the course of these patients. Only 7% of SRC cases who required and came off dialysis subsequently required renal replacement therapy.

The association between blood pressure and prognosis (both mortality and renal outcome) has been noted before in one study, and prominently in the reports of normotensive renal crisis. The present study excluded patients who were not hypertensive; despite this, higher BP at presentation was associated with a better outcome. The basis for

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**Table 4 Renal outcomes and acute changes on biopsy: acute changes are associated with poorer renal outcomes**

<table>
<thead>
<tr>
<th>Renal outcome...</th>
<th>No dialysis</th>
<th>Dialysis and recovery</th>
<th>Dialysis without recovery</th>
<th>Unknown outcome</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any acute changes</td>
<td>9 (25%)</td>
<td>9 (25%)</td>
<td>17 (47%)</td>
<td>1 (3%)</td>
<td>36 (100%)</td>
</tr>
<tr>
<td>Chronic changes only</td>
<td>11 (68%)</td>
<td>3 (19%)</td>
<td>2 (13%)</td>
<td>0</td>
<td>16 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>12</td>
<td>19</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>Odds ratio (95%CI)</td>
<td>0.15 (0.04–0.57)</td>
<td>1.5 (0.35–6.5)</td>
<td>6.6 (1.3–33)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>( p^* )</td>
<td>0.009</td>
<td>0.45</td>
<td>0.025</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Fishers exact test.
poorer outcome in those with lower blood pressure at presentation is unclear. An attractive hypothesis is that the hypotensive patients have cardiac involvement, although the analysis of echocardiographic data for SRC cases did not demonstrate a correlation between BP and left ventricular ejection fraction (LVEF), or renal outcome and LVEF. Low ejection fractions are common at presentation, and typically resolve as the SRC is treated and the vascular resistance falls. A further hypothesis would be that those presenting late with SRC have lower blood pressure; however, patients with relatively low blood pressure did not present in established renal failure more commonly than those with relatively high blood pressure in this study, in contrast to a previous report. It may be that in normotensive cases the disorder is less renin-angiotensin-dependent, causing less hypertension and less response to ACEI therapy. The pathogenesis of SRC involves endothelial activation, and this results in the production of multiple vasoactive mediators (including endothelin-1), which may be pathogenic.

MAHA has been associated with more severe hypertension and a higher frequency and degree of renal dysfunction in accelerated hypertension. In this study, there was no difference in blood pressure or outcome between those with MAHA and those without it. Other groups have reported a correlation between MAHA and good outcome, and a higher rate of MAHA in normotensive renal crisis.

In the present study, use of ACEIs prior to SRC was not associated with benefit, but a trend towards poorer renal outcome. The use of ACEIs in patients at risk of SRC has not previously been shown to be beneficial or harmful. The high vs. low dose D-penicillamine study found similar rates of ACEI use in patients with SRC compared with those without SRC, although the numbers were small. The case-control study performed by Steen and Medsger also analysed ACEI use in patients prior to SRC, but there were insufficient numbers to demonstrate a significant effect. There may be confounding factors influencing this trend: for example, patients with more severe Raynaud's phenomenon may be more likely to have been given ACEI, which may be independently associated with SRC. It still leaves the important question of whether ACEI may prevent SRC unanswered, but does suggest that a prospective study would be needed to find whether routine use of ACEIs in patients at risk of SRC is beneficial (prevents SRC), or might be harmful (results in a less favourable renal outcome).

Pathological findings

Pathological findings in renal biopsies were of prognostic significance, as well as of diagnostic use. Acute changes were associated with an increased requirement for dialysis, and failure to recover renal function. These changes occurred independently of the blood pressure, and reflected the degree of vascular damage occurring in the kidney. This affected renal prognosis, with half of those with acute changes requiring permanent dialysis, compared to 13% of those without. Acute changes were associated with a lower index of chronic damage, better pre-SRC renal function, and higher creatinine at presentation. Pre-existing chronic damage may be in some way protective against the acute changes, and may explain why poor renal function prior to the SRC does not seem to give a worse renal outcome.

The index of chronic damage did not correlate with renal prognosis in SRC. This finding is unusual: the index correlates with prognosis in a wide range of renal diseases, including lupus nephritis, IgA nephropathy, and others. This difference is probably due to the predominantly acute vascular nature of the injury, with the possibility of renal recovery (which is not seen in the diseases for which the index correlates well with survival).

Mortality

Although improvement in survival in SSC has been demonstrated in recent studies, the prognosis for patients with SRC remains poor (5-year survival of a dcSSc patient group from our same centre was 77%, compared with 59% in these patients). Survival after SRC is comparable with that of pulmonary hypertension in scleroderma (71% survival at 2 years), and is less favourable than for other organ-based complications such as pulmonary fibrosis in systemic sclerosis.

The poor prognosis of patients with SRC and ESRF has been well described, and transplantation improves long-term outcomes in terms of mortality. Suggestions that transplantation may reduce the progression of scleroderma are likely to be confounded by a variety of factors, including the tendency of the skin disease to improve with time, and the effect of immunosuppression on the disease. The improvement in renal function after SRC suggests that any decision for transplantation should be deferred for up to 2 years, to allow a chance of recovery of intrinsic renal function. Patients must be selected for transplantation with great care, given the co-morbidities common in this group of patients. It is unusual for SRC to recur
in transplant. One report suggested a rate of 5%, with cases occurring within two years of transplantation.\textsuperscript{36}

Patients who underwent temporary dialysis had the best prognosis of all three groups of renal outcomes. Dialysis has been considered beneficial for scleroderma skin disease, although the basis for this is unclear.\textsuperscript{35} However, it seems that it is more likely that the younger age of these patients (mean 44 years old) was at least a strong confounder, and may explain why they had a lower mortality than those who did not require dialysis at all (mean 49 years old). The poorer prognosis of males with SSC has also been noted previously,\textsuperscript{37} but the cause for such a difference remains unclear.

In this large series of SRC patients, higher blood pressure at presentation and younger age were associated with better renal outcome. Surprisingly, chronic damage on renal biopsy was not predictive of renal outcome, whereas acute changes were associated with poor renal outcome. In those that recovered, improvement in renal function continued over several years after SRC. Mortality and morbidity of SRC were high, despite routine ACEI treatment. New strategies for therapy in addition to ACEIs need to be explored for this life-threatening condition.

References


with systemic sclerosis and p-antineutrophil cytoplasmic autoantibodies which developed into Paget’s disease of bone after immunosuppressive therapy. *Rheumatology (Oxford)* 1999; **38**:190–1.


