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Renal disease in scleroderma: an update on evaluation, risk stratification, pathogenesis and management

Victoria K. Shanmugam and Virginia D. Steen

Division of Rheumatology, Immunology and Allergy, MedStar George-town University Hospital, Washington, DC, USA

Abstract

Purpose of review—Renal disease remains an important cause of morbidity and mortality in scleroderma. The spectrum of renal complications in systemic sclerosis includes scleroderma renal crisis (SRC), normotensive renal crisis, antineutrophil cytoplasmic antibodies-associated glomerulonephritis, penicillamine-associated renal disease, and reduced renal functional reserves manifested by proteinuria, microalbuminuria, or isolated reduction in glomerular filtration rate. The purpose of this review is to provide a concise and up-to-date review of the evaluation, risk stratification, pathogenesis, and management of scleroderma-associated renal disease.

Recent findings—Although SRC survival has significantly improved, mortality of this complication remains high outside of specialized centers. Recent data demonstrate strong associations between anti-RNA polymerase III antibodies and SRC. Subclinical renal impairment affects approximately 50% of scleroderma patients and may be associated with other vascular manifestations. Subclinical renal involvement rarely progresses to end-stage renal failure; however, recent studies suggest it may predict mortality in patients with other vasculopathic manifestations.

Summary—Testing for anti-RNA polymerase III antibodies should be incorporated into clinical care to identify patients at high risk for SRC. Recommendations from European League Against Rheumatism (EULAR), EULAR Scleroderma Trials and Research, and the Scleroderma Clinical Trials Consortium confirm angiotensin-converting enzyme inhibitors as first-line therapy for SRC, and give recommendations for second-line agents.

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Correspondence to Victoria K. Shanmugam, MD, MRCP, Division of Rheumatology, Immunology and Allergy, MedStar Georgetown University Hospital, 3800 Reservoir Road, NW, Washington, DC 20007, USA. Tel: +1 202 444 6200; vks4@gunet.georgetown.edu.

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Keywords

autoantibodies; kidney; renal; scleroderma; scleroderma renal crisis

INTRODUCTION

Scleroderma is a rare multisystem immune disease affecting one to two patients per 100 000 in the United States. It is characterized by immune activation, autoantibody production, fibroblast dysfunction, extracellular matrix deposition, and vasculopathy. Clinically patients with scleroderma are categorized into limited and diffuse subsets on the basis of the extent of skin involvement [1,2]. These clinical phenotypes along with autoantibody profiles are helpful in predicting clinical outcomes [3,4]. Renal disease, particularly scleroderma renal crisis (SRC), adversely correlates with mortality in scleroderma [5–7].

The purpose of this review is to discuss the subtypes of renal involvement in scleroderma (Table 1) and to review the evaluation, risk stratification, pathogenesis, and management of scleroderma-associated renal disease.

SCLERODERMA RENAL CRISIS

SRC remains one of the most feared complications of scleroderma.

Prevalence

Prevalence of SRC is decreasing, perhaps related to aggressive early therapy with angiotensin-converting enzyme inhibitors (ACEi). However, in the United States, SRC affects approximately 10% of patients with diffuse scleroderma [8] and 2% of patients with limited disease. Studies from the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR) database suggest a lower prevalence (5% of diffuse scleroderma and 2% of limited) [9] and a retrospective cohort study [10] from Japan reported a prevalence of 3.2%. Geographic differences in autoantibody profiles, particularly anti-RNA polymerase III anti-bodies likely contribute to these prevalence variations.

Clinical presentation

SRC presents early, with a mean of 3.2 years since onset of disease [8] and, in up to 25% of cases, the diagnosis of scleroderma is made at the time of SRC presentation [11,12]. SRC usually manifests with acute onset of moderate-to-severe ‘accelerated’ hypertension and oliguric renal failure [7,8]. Hyperreninemia, thrombotic microangiopathy, anemia, and congestive heart failure are common, and some patients exhibit hypertensive encephalopathy and retinopathy [7].

In up to 10% of cases, SRC occurs without hypertension, a condition referred to as normotensive SRC. This presentation is associated with prior use of ACEi, calcium channel blockers, and myocardial involvement [7,13]. In some cases, these patients may have actually been relatively hypotensive at baseline such that their blood pressure (BP) elevation, although significant for them as an individual, still falls within the normotensive range.

Pathologic findings and pathogenesis

Pathologically SRC causes a proliferative obliterative vasculopathy with concentric ‘onion skin’ narrowing of arterioles and glomerular ischemia (Fig. 1) [14]. The glomeruli do not show inflammatory changes or immune deposits. These pathologic findings, along with the presence of marked hyperreninemia, suggest that altered perfusion of the juxtaglomerular apparatus triggering renin-driven hypertension may be a driver of SRC. However, autopsy studies demonstrate renal vascular changes in some patients without clinical evidence of SRC. Additionally, some patients have physiologic evidence of episodic renal vasospasm (‘renal Raynaud’s phenomenon’) and, although these changes correlate with baseline and cold-induced renin levels, they do not predict development of SRC [15].

Risk stratification in scleroderma renal crisis

Recent studies suggest several factors that can be helpful to stratify and identify patients at high risk for SRC.

Autoantibody profile—Anti-RNA polymerase III antibodies are seen in 9.4–59% of SRC patients [16, 17■,18, 19■, 20■, 21, 22]. Although anti-RNA polymerase III antibodies are associated with diffuse cutaneous disease, tendon friction rubs, and joint contractures, there is also a strong independent association with SRC [17■,22]. In the Australian Scleroderma Cohort Study, independent of corticosteroid exposure, anti-RNA polymerase III antibodies carried a 25% risk of developing SRC, compared with a 2% risk in the absence of this antibody. Development of an ELISA to detect anti-RNA polymerase III antibodies has helped translate these associations into clinical practice [21].

Other autoantibody profiles are not associated with SRC. Antitopoisomerase I (anti-Scl70) antibody affects 30% of patients with diffuse scleroderma but does not predict SRC [22]. Anticentromere antibodies are negatively associated with SRC, [23■] and anti-U3RNP antibodies are not a risk factor for SRC [24].

Skin involvement and tendon friction rubs—The highest risk group for SRC remains patients with early diffuse scleroderma, with 75–86% of cases occurring during the first 4 years of disease [12,25]. SRC is especially associated with rapidly progressive skin disease [8,11] and tendon friction rubs [26,27].

Corticosteroid exposure—Exposure to corticosteroids (equivalent to 15 mg per day in the preceding 6 months) is well recognized as a risk factor for SRC [28, 29■]. A recent meta-analysis identified 10 patients from 26 studies involving 500 patients exposed to corticosteroids through scleroderma clinical trials [30■]. All patients had either received pulse dose corticosteroids ($n=8$) or medium-dose corticosteroids (15–30 mg per day, $n=2$), equivalent to a rate of SRC of 2% of steroid-exposed patients. This was higher than expected but due to differing inclusion and exclusion criteria for the individual studies, high-risk patients for SRC may have been disproportionately represented, skewing the prevalence data.

Human leukocyte antigen types associated with scleroderma renal crisis—

Nguyen *et al.* [23■■] studied 90 SRC patients from a cohort of 1519 scleroderma cases. Although the population under study had a high prevalence of anti-RNA polymerase III antibodies, this study identified human leukocyte antigen (HLA) DRB1*0407 and HLA-DRB1*1304 as independent risk factors for SRC.

Endothelin pathways in scleroderma renal crisis—Endothelin B receptor polymorphisms are associated with diffuse scleroderma [31] and endothelin-1 and endothelin B receptors are upregulated in renal tissues from SRC cases [32, 33■,34]. A pilot study to investigate the safety of adding a nonselective endothelin-1 receptor antagonist (Bosentan) to ACEi in SRC found that this combination was well tolerated, but there were no significant differences in mortality, rates of dialysis, or renal functional improvement, compared with historical controls. This open-label study [32] was not blinded or randomized, and only six patients were enrolled.

Soluble CD147 in scleroderma renal crisis—CD147 is a glycosylated membrane protein that stimulates matrix metalloproteinase production by stromal cells. In a cohort of 61 Japanese scleroderma patients, serum CD147 levels were significantly higher in SRC patients ($p<0.05$), suggesting promise as a biomarker for SRC [35■■]. However, these findings need to be validated in a larger independent scleroderma population before translation into clinical use.

Magnitude of hypertension—Normotensive SRC is associated with worse outcomes than hypertensive SRC. Multivariate analyses of the SRC population show normotensive renal crisis is an independent predictor of reduced dialysis-free survival [12,13].

Hyperreninemia—Although significant elevations of plasma renin are characteristic of SRC, with levels sometimes reaching 100 times normal [36], the degree of hyper-reninemia does not correlate with outcome in SRC. Lack of timely availability of renin assays limits the usefulness of plasma renin levels in the clinical setting.

Factors not associated with scleroderma renal crisis—Baseline BP, serum creatinine, and presence of proteinuria or hematuria do not predict SRC [8]. There is no association between sex and SRC [11].

Management of scleroderma renal crisis

Evidence-based recommendations from EULAR and EUSTAR included two recommendations pertaining to renal disease in scleroderma: ACEi should be used in the treatment of scleroderma renal crisis and patients on steroids should be carefully monitored for BP and renal function. Several studies [37■■,38■■] have shown strong agreement amongst experts with these recommendations.

ACEi have significantly reduced SRC mortality from 76% at 1 year to less than 15% [39]. Captopril (D3-mercapto-2-methylpropionyl-L-proline) competitively inhibits peptidyl dipeptide hydrolase, blocking conversion of angiotensin I to angiotensin II. It is optimum as first-line therapy due to its short half-life that allows it to be readily titrated. The goal is to

bring the SBP down by 20 mmHg per 24 h and the DBP down by 10 mmHg per 24 h until the BP is within normal limits, while avoiding hypotension. Careful titration of BP is of utmost importance, and many clinicians recommend monitoring in ICU or intermediate care units.

Since the introduction of ACEi, approximately 60% of SRC patients now avoid permanent dialysis. Of patients requiring dialysis, up to 30% have renal functional recovery if ACEi therapy continues concurrently with dialysis [7]. Efficacy of ACEi is dependent on the degree of renal damage at initiation, with greatest likelihood of renal function improvement if therapy is initiated when serum creatinine is less than 4 mg/dl [7,40].

In patients with persistent hypertension despite maximization of ACEi dose, there are no formal studies investigating the next-appropriate agent. Angiotensin II receptor blockers (ARBs) can safely be added once ACEi dose has been maximized, but ARBs alone are insufficient to control SRC without ACEi [41,42]. Recent guidelines from the Canadian Scleroderma Research Group and the Scleroderma Clinical Trials Consortium recommend addition of calcium channel and a antagonists in refractory SRC [37■]. Case reports and small uncontrolled clinical studies [32,43] suggest that endothelin antagonists and direct renin inhibitors may also have a role.

Prognosis and outcome in scleroderma renal crisis

In specialized centers, ACEi have dramatically reduced mortality due to SRC, with data from the Pittsburgh database showing a reduction in mortality from 42 to 4% over a 30-year period [6,44]. However, the overall 5-year mortality from SRC reported in several studies [11,12] in North America, Australia, and Europe remains between 30 and 50%. Recent data from France suggest SRC mortality remains high outside of specialized centers with 1-year mortality rates reported at 29.1% in this cohort [29■].

Retrospective studies [45■] of patients with SRC who require dialysis show that although scleroderma is an independent predictor of mortality in the dialysis population, it is also an independent predictor of renal recovery (hazard ratio 11.1, 95% confidence interval 6.37–19.4). Rates of renal functional recovery reported for the scleroderma population differ geographically, with rates of 10% reported from Australia compared with 34–38% in the United States. Differences in reporting likely contribute to this discrepancy as the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry patients have to be dialysis-dependent for 3 months, so scleroderma patients with early renal functional recovery are excluded [45■]. Even considering these issues, the rates of renal functional recovery reported for the scleroderma population far exceed those reported in other diseases combined (1–2.4%) [46].

The use of renal biopsy to make prognostic recommendations in SRC has been investigated by several groups. A study of 58 biopsies evaluated at the Royal Free Hospital found no association between renal biopsy chronicity index [47] and renal survival [11]. However, a study [48] of 17 biopsies from Pittsburgh found that in addition to vascular thrombosis and glomerular ischemic collapse, elevated peritubular capillary C4d staining (a product of

classical complement degradation associated with antibody-mediated injury and renal allograft failure) was associated with worse outcome.

Role of prophylactic angiotensin-converting enzyme inhibitors and other prophylactic interventions

There are no interventions that prevent SRC, but many clinicians advocate teaching high-risk patients how to self-monitor BP, educating them regarding the importance of seeking care, and discussing the risks of prednisone and other nephrotoxic drugs.

'Prophylactic' ACEi do not reduce the risk of SRC; they are associated with worse outcome and increased likelihood of requiring permanent dialysis [13, 29■]. ARBs have not been studied in the prophylactic setting, but as there are case reports of SRC developing while on ARBs, these agents are likely to be ineffective [11,49].

Renal transplantation in scleroderma renal crisis

Renal transplantation is effective in patients with SRC. Survival for scleroderma patients with end-stage renal failure (ESRF) who undergo transplant is better than those with ESRF awaiting transplant [50]. However, due to the relatively high rates of renal functional recovery, it is usually advised to delay transplantation until patients have been dialysis dependent for at least 2 years. Renal transplant survival rates are similar to those seen in patients undergoing renal transplantation for lupus and other connective tissue diseases. In the ANZDATA registry, renal allograft survival rates in the scleroderma population were 53% for deceased donor allografts, and 100% for live donor allografts [45■].

Scleroderma renal crisis recurrence rates

Recurrence of SRC has been reported but is extremely rare. In patients with SRC who undergo renal transplant, recurrence in the transplanted kidney occurs in less than 5% of cases [51]. Recurrence is more common in patients with early loss of native renal function during the original SRC episode [51].

ANTINEUTROPHIL CYTOPLASMIC ANTIBODIES-ASSOCIATED GLOMERULONEPHRITIS IN SCLERODERMA

Glomerulonephritis associated with myeloperoxidase-specific antineutrophil cytoplasmic antibodies (ANCA) has been reported in scleroderma [52–54].

Epidemiology

In contrast to SRC, this manifestation develops in patients with longstanding limited cutaneous scleroderma. The prevalence is unknown, but approximately 40 cases have been reported in the English language literature.

Clinical presentation

Typically patients present with crescentic glomerulo-nephritis, progressive renal failure, mild hypertension, and proteinuria. Some cases have reported associated pulmonary hemorrhage.

Pathologic features and pathogenesis

Renal biopsy is required to exclude SRC and demonstrates crescentic glomerulonephritis. Although the pathogenesis is unknown, it has been postulated that established scleroderma vasculopathy exacerbates the interaction of ANCA with the endothelium near the vascular pole resulting in neutrophil activation in the glomerulus.

Management

Similarly to ANCA-associated vasculitis in patients without scleroderma, this complication requires therapy with high doses of steroids and immunosuppression. Rituximab has recently been approved by the US Food and Drug Administration for induction therapy in ANCA-associated vasculitis, and there are case reports suggesting efficacy of this drug for ANCA-associated glomerulonephritis in scleroderma [55].

PENICILLAMINE-ASSOCIATED RENAL DISEASE

Although rarely used in scleroderma now, approximately 20% of patients treated with D-Penicillamine develop reversible membranous glomerulonephritis and proteinuria, a complication with approximately 40% mortality [56].

RENAL FUNCTIONAL IMPAIRMENT WITHOUT OTHER MANIFESTATIONS OF RENAL DISEASE IN SCLERODERMA

Histopathologic renal injury is common in scleroderma even without clinically evident SRC [14,15]. Asymptomatic renal functional impairment affects 10–55% of scleroderma patients [7,15,57–59] and comorbidities contributing to renal impairment include congestive heart failure, gastrointestinal involvement, medication exposures, and dehydration. Proteinuria or albuminuria is reported in up to 25% of scleroderma patients, with intermediate-weight proteinuria in 31.3% [60,61]. Intermediate-weight proteinuria is a predictor of glomerular permeability and correlates with gastrointestinal involvement. Although asymptomatic renal changes are typically nonprogressive in scleroderma [7,58], some investigators have suggested that they indicate reduced renal functional reserve [62,63]. Reduced baseline renal functional reserve, measured by intravenous amino acid load test, was associated with significant reduction in mean annual creatinine clearance over the subsequent 5 years [62,63].

Reduced glomerular filtration rate (GFR) correlates with vasculopathic manifestations and prognosis [64–66]. In scleroderma-associated pulmonary hypertension, estimated GFR (eGFR) is a strong predictor of survival, with eGFR less than 60 ml/min per 1.73 m [2] associated with a three-fold increased risk of mortality [65]. The Chronic Kidney Disease Epidemiology Collaboration Equation strongly correlates with measured GFR in scleroderma patients with normal creatinine, suggesting this may be a helpful method for estimating GFR in scleroderma [67].

Renal vascular resistive index is a measure of intrarenal vascular elasticity and complacance assessed using Doppler ultrasound. Resistive index is very sensitive to renal vascular disease and correlates with GFR and digital microvascular damage in scleroderma [68]. The

antioxidant N-acetylcysteine reduces renal resistive index in scleroderma patients with early capillaroscopic changes, but has the opposite effect in patients with late capillaroscopic changes [69]. Identifying patients with early vasculopathy in scleroderma remains an area of active investigation. Soluble CD163, a biomarker for oxidative stress, is elevated in scleroderma and may have promise as a biomarker of renal vascular disease. Although there is no correlation between CD163 levels and skin score, levels correlate with renal artery Doppler pulsatility index ($r=0.534$, $P=0.0009$) [70■]. These observations require further validation in a larger population of scleroderma patients.

CONCLUSION

Renal disease remains an important cause of morbidity and mortality in scleroderma. Although SRC survival has significantly improved, mortality remains high outside of specialized centers. Anti-RNA polymerase III antibodies are a strong predictor for the development of SRC and should be incorporated into clinical care to identify high-risk patients. Recent recommendations from EULAR, EUSTAR, and the Scleroderma Clinical Trials Consortium confirm ACEi remain first-line therapy for SRC.

Subclinical renal impairment affects approximately 50% of scleroderma patients and may be associated with other vascular manifestations. Subclinical renal involvement rarely progresses to ESRF; however, it may predict mortality in patients with other vasculopathic manifestations.

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KEY POINTS

- Anti-RNA polymerase III antibodies are strongly associated with SRC and may be used to identify patients at high risk for SRC.
- ACEi inhibitors are the first-line therapy for SRC, but outside of specialized centers, the mortality of SRC remains high.
- ‘Prophylactic’ ACEi do not reduce the risk of SRC; they are associated with worse outcome and increased likelihood of requiring permanent dialysis.
- Renal transplantation is effective in patients with SRC, but due to the possibility of late renal functional recovery in SRC, it is recommended that transplantation be delayed for 2 years after becoming dialysis dependent.
- Asymptomatic nonprogressive renal impairment is common in scleroderma and correlates with vasculopathic manifestations and prognosis.

FIGURE 1. Renal biopsy from a patient with scleroderma renal crisis. Hematoxylin and eosin stain demonstrates onion skinning concentric narrowing of arterioles and glomerular ischemic changes.

Table 1

Spectrum and associations of renal complications in scleroderma

Renal complication	Associations
Scleroderma renal crisis	Rapidly progressive skin disease
	Tendon friction rubs
	Corticosteroid exposure (15 mg per day in preceding 6 months)
	Anti-RNA polymerase III antibodies
	HLA-DRB1*0407
Normotensive renal crisis	HLA-DRB1*1304
	Prior use of ACEi and calcium channel blockers
	Myocardial involvement
ANCA-associated glomerulonephritis	MPO-ANCA
	Longstanding limited scleroderma
Penicillamine-associated renal disease	20% of patients treated with D-Penicillamine
Proteinuria and microalbuminuria	Reported in 25% of scleroderma patients
Isolated reduction in glomerular filtration rate	Correlates with vasculopathic manifestations and prognosis in scleroderma

ACEi, angiotensin-converting enzyme inhibitors; MPO-ANCA, myeloperoxidase-specific antineutrophil cytoplasmic antibodies.