

Chapter

Renal Involvement in Systemic Sclerosis

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Abstract

Scleroderma renal crisis (SRC) is classical renal disease in systemic sclerosis (SSc). SRC is a relatively rare manifestation, approximately in 5% of patients. In terms of severity, manifestation in the form of SRC is the most common cause of acute organ failure. In SSc patients, SRC is defined as a new onset of accelerated arterial hypertension and rapidly progressive anuric or oliguric renal failure. SRC is primarily vascular injury with increased activity of the renin-angiotensin activity. These events lead to release or activation of cytokines and growth factors that result in the typical proliferative vascular lesions. Successful approach is routine use of angiotensin-converting enzyme inhibitors in the treatment of SRC (except prevention) and other advances in renal replacement therapy in SSc management. It is crucial to detect manifestations of SRC early and to manage appropriately in collaboration with intensive care medicine, cardiologists, and nephrologists. In contrast to SRC, clinical presentation of interstitial renal disease is poor, often without evidence of renal abnormality. Interestingly, other renal manifestations are glomerulonephritis and vasculitis. These manifestations are associated with overlapping mechanisms. The objective of this chapter is to focus on actual knowledge about the renal involvement in SSc and current treatment principles and possibilities.

Keywords: kidney, systemic sclerosis, scleroderma renal crisis, glomerulonephritis, diagnosis, management

1. Introduction

Systemic sclerosis (SSc) leads to morbidity and mortality through a combination of inflammation, fibrosis, and vascular damage leading to internal organ complications affecting the heart, lung, bowel, and kidneys. In SSc, we observe kidney involvement as three main clinical situations described below.

Most often, SSc causes a range of renal manifestations, which occur in both subsets of the disease: limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) subsets.

As overlaps are often seen in connective tissue diseases, SSc should be associated with other immunological features of renal disease findings typical for systemic lupus erythematosus (as lupus glomerulonephritis) and ANCA-associated vasculitis/glomerulonephritis.

Scleroderma renal crisis (SRC) is a dramatic and classical scleroderma manifestation, historically known as dominant cause of scleroderma-related death. Currently, the leading causes of death in scleroderma are pulmonary fibrosis and pulmonary arterial hypertension [1]. Regardless, one-year SRC outcomes remain poor, with over 30% mortality and 25% of patients remaining dialysis-dependent.

To make the summary complete, possible drug-related adverse events including from toxic renal involvement to renal acute renal failure must be mentioned.

2. Scleroderma renal crisis

2.1 Epidemiology

SRC occurs usually in early dcSSc (11%), as compared to patients with lcSSc (4%) [2, 3]. SRC is more common in rapidly progressing disease, SRC was previously reported up to 25% of SSc, but over time, it was found that incidence of renal crisis appeared to have decreased since improvement of early diagnostics [1].

Historically, study of Steen and Medsger [4] presented change of mortality causes during 1972–2002 years. This study showed that SRC as the cause decreased from 42 to 6% of SSc-related deaths, while the proportion of other causes of death increased: pulmonary fibrosis rose from 6 to 33% and pulmonary arterial hypertension from 22 to 28%. Large data were obtained prospectively followed in the EULAR Scleroderma Trials and Research (EUSTAR) cohort. The EUSTAR database was inaugurated in June 2004 and represents a multinational, prospective, and open SSc cohort [5]. According to EUSTAR data, SSc-related deaths include pulmonary fibrosis 19%, pulmonary arterial hypertension 14%, arrhythmia 6%, heart failure 7%, and SRC 4%. Non-SSc-related deaths in total 4% include infection 13%, malignancy 13%, and cardiovascular 12%. Renal causes accounted for the death of 10 patients (4%), all due to renal crisis. Renal crisis was fatal in 16% of all patients experiencing renal crisis [5].

2.2 Pathogenesis of scleroderma renal crisis

Pathogenesis is characterized by series of insults (**Figure 1**):

- *Changes in intima and endothelium*: Initially, there is injury to the endothelial cells with intimal thickening and proliferation in the arcuate and interlobular arteries [6].
- *Absence of inflammation*: There is a notable absence of inflammatory cells (lymphocytes and monocytes) in the renal vasculature [6].
- *Vascular injury*: Platelet factors are released causing increased vascular permeability, fibrin deposition, and collagen formation, which lead to further luminal narrowing [6].
- *Renal ischemia*: Narrowed renal arterioles decrease renal cortical blood flow [6].
- *Activation of renin*: Renal ischemia and episodic renal vasospasm “renal Raynaud phenomenon” contribute to decrease of blood flow. Decreased renal blood flow causes hyperplasia of the juxtaglomerular apparatus and release of renin [6].
- *Secondary small vessel changes*: endothelial injury is associated with thrombus formation. Intravascular thrombi and mucoid intimal edema may be seen in renal histology. Small vessel thrombi are more abundant than glomerular

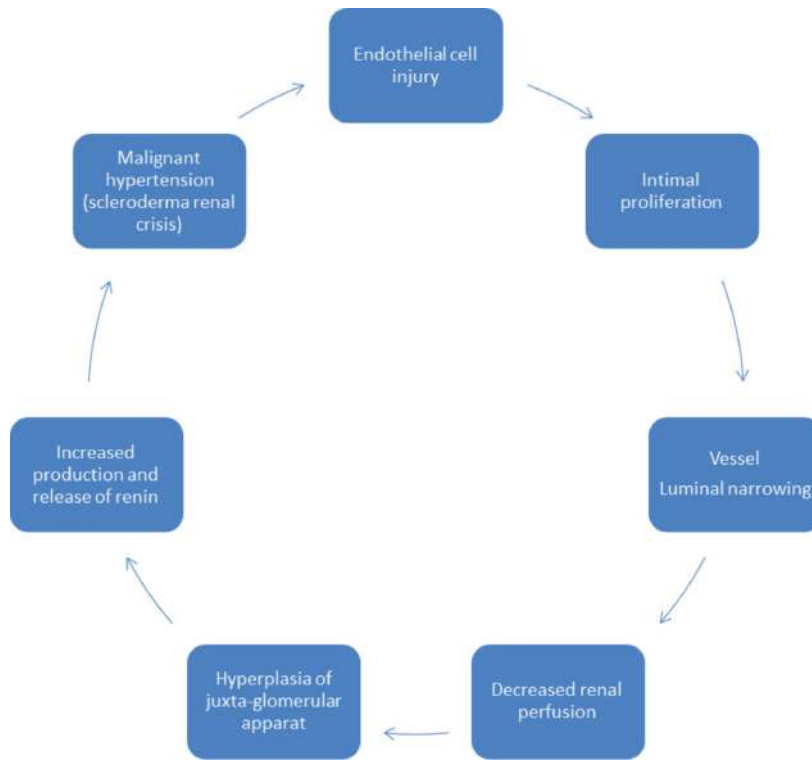


Figure 1.
The mechanisms in the pathogenesis of SRC. Adapted from Steen et al. [8].

thrombi (unlike the pathology seen in hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura) [7].

2.3 Renal histopathology

Histopathological findings of SRC are more frequently manifested by severe involvement of small arteries and arterioles. Early vascular changes are characterized by intimal accumulation of myxoid material in the interlobular and arcuate arteries, which results in severe luminal narrowing (**Figure 2**). Sometimes microthrombi are developed in the affected vessels and fragmented red blood cells can be

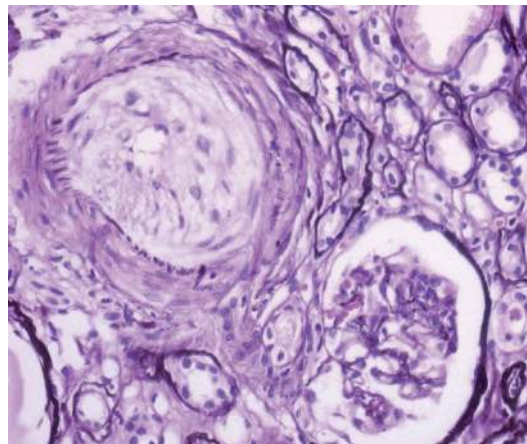


Figure 2.
Early vascular changes are characterized by intimal accumulation of pale myxoid material in the small artery, which results in severe luminal narrowing (Methenamine-silver stain).

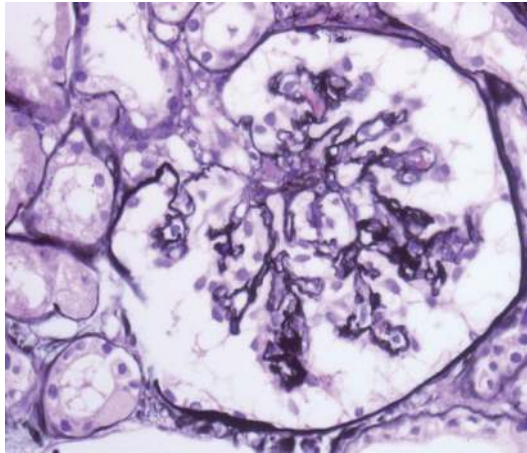


Figure 3.
Two types of glomerular injury associated with scleroderma renal crisis. Ischemic collapse of glomerulus with wrinkling of glomerular basement membrane corresponds to arterial stenosis.

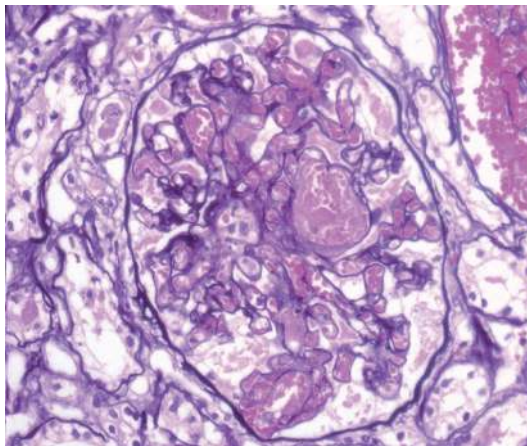


Figure 4.
Two types of glomerular injury associated with scleroderma renal crisis. Thrombotic microangiopathy with occlusion of outgoing arteriole is characterized by the congestion and hemorrhagic necrosis of the tuft (Methenamine-silver stain).

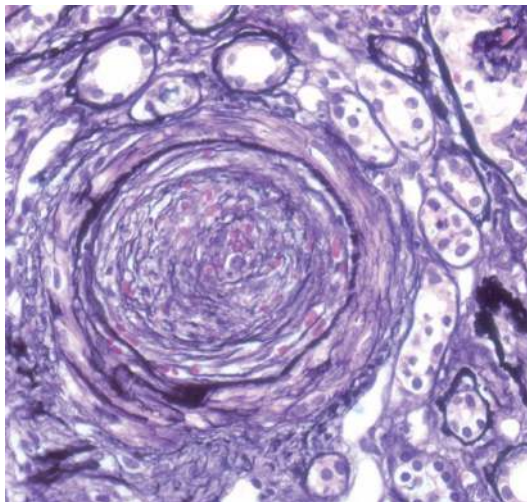


Figure 5.
Prominent intimal concentric lamination within an interlobular artery (arterial onion skin lesion) with irreversible reduction of the arterial lumen (Methenamine-silver stain).

seen in vessel wall. Microthrombi in arterioles can also progress to the glomeruli. When the arterioles incoming to glomeruli are predominantly affected, the morphological features in glomeruli are characterized by ischemia with wrinkling of glomerular basement membrane and ischemic collapses of glomeruli (**Figure 3**). When microthrombi are developed mainly in outgoing arterioles, the corresponding pathology is severe congestion and hemorrhagic necrosis of the tufts (**Figure 4**).

Later arterial injury is characterized by change of edematous mucoid intima to the concentric lamination and so called onion skin lesion (**Figure 5**) with significant luminal reduction. In glomeruli, the lesion is represented by double contouring of glomerular basement membrane (as a result of prolonged or repeated endothelial injury) and segmental or global sclerotic lesions.

Because blood supply in the kidney is represented by end vessels without collaterals, each area of kidney tissue after arterial luminal narrowing must suffer from severe ischemia or even tissue necrosis. In histopathology, pronounced ischemia leads to tubular injury in the interstium and tubular atrophy with interstitial fibrosis in the course of time.

Since none of these findings are specific for SRC, the pathological diagnosis must be supported by appropriate clinical and serological data [9].

Histopathology: with courtesy of Eva Honsová, MD., PhD. Department of Pathology IKEM, Prague.

2.4 Definition, diagnosis, and classification

SRC is defined as new onset of accelerated arterial hypertension and rapidly progressive oliguric renal failure during the course of SSc. There are differences between the criteria used to *define SRC* [1]. Occasionally, more modest elevations in blood pressure and renal dysfunction and at times normotensive presentations were found [9, 10]. The diagnosis is complicated in the case of malignant hypertension with absence of kidney impairment.

SRC was defined in a minority of studies and criteria were heterogeneous [10]. It is a problem to establish criteria for SRC, because the clinical spectrum of SRC is broad, ranging from accelerated hypertension to normotensive patients 7% [10]. Arterial hypertension is a typical symptom in SRC accompanied by classical complications such as hypertensive encephalopathy, retinopathy, congestive heart failure, hemolysis, etc. Diagnosis of SRC in patients without pre-existing SSc diagnosis and in normotensive SRC patients is difficult, mainly in the absence of renal biopsy [10, 11].

Only one study up to now has partially validated criteria for SRC (**Table 1**) [8]. It was proposed by experts in 2003. It included items for systolic and diastolic blood pressure, serum creatinine, proteinuria, hematuria, microangiopathic hemolytic anemia, and renal histopathology. These are known as the Ancona criteria for SRC [8].

Recently, the Scleroderma Clinical Trials Consortium (SCTC) and Scleroderma Renal Crisis Working Group generate a core set of items to develop classification criteria for SRC using Delphi methodology. The final core set of items to develop classification criteria for SRC contains domains: blood pressure arise, kidney impairment, hematological changes, thrombotic microangiopathy, and organ dysfunction. A consensus definition of SRC is urgently needed to standardize data collection on SRC [9].

Novel concepts of SRC classification included the stratification of SRC:

- *definite SRC*: defined as at least two of: new onset hypertension, microangiopathic hemolytic anemia (MAHA), and rising creatinine
- *subacute forms of SRC*: such as hypertension, renal insufficiency, and renal sediment changes in the absence of microangiopathic hemolytic anemia [9, 10]

<p>SRC is defined as following, requiring both:</p> <p>A new onset of blood pressure >150/85 mm Hg obtained at least twice over a consecutive 24-hour period. This blood pressure is chosen because it is defined by the New York Heart Association as significant hypertension.</p> <p>Decrease in the renal function as defined by a decrement of at least 10% in the estimated GFR (eGFR) or GFR of <90 (mL/min/1.73 m². When possible, a repeat serum creatinine and recalculation of the GFR should be obtained to corroborate the initial results.</p> <p>In order to corroborate further the occurrence of acute renal crisis, it would be desirable to have any of the following, if available:</p> <ul style="list-style-type: none"> • new onset of urinary red blood cells (excluding other causes) • flash pulmonary edema • oliguria or anuria • microangiopathic hemolytic anemia on blood smear • retinopathy typical of acute hypertensive crisis • renal biopsy with typical features including onion skin proliferation within the walls of internal arteries and arterioles, fibrinoid necrosis, and glomerular shrinkage <p>Notes</p> <ul style="list-style-type: none"> • Cases of typical SRC histological appearance have been associated with scleroderma in the absence of hypertension; these cases of normotensive SRC are reported to have a particularly poor outcome, and their precise relationship to the more typical hypertensive SRC is not known. Normotensive SRC was observed in glucocorticoid scleroderma users. • Up to one fifth of cases of SRC with hypertension have been identified as the presenting feature of systemic sclerosis, and so, in these cases, pre-existing diagnosis of systemic sclerosis will not be present. <p><i>SRC, scleroderma renal crisis; GFR, glomerular filtration rate.</i></p>

Table 1.
Clinical criteria for definition of scleroderma renal crisis [1].

New concept also includes the addition of ACE inhibitor responsiveness as a characteristic of hypertension (in *probable SRC*) and the addition of more specific time frames for measurement of blood pressure (taken twice, 2 hours apart, within 3 days of first event-associated observation) [10].

In addition to heterogeneity and rarity, the absence of a gold standard and classification criteria are important challenges for research on SRC. The development of new criteria is important to improve the definition of normotensive SRC. In this case, performing kidney biopsy and examination of biomarkers (including anti-RNA III polymerase) are important and promising.

2.5 Role of kidney biopsy in diagnosis of scleroderma renal crisis

Kidney biopsy is not mandatory for diagnosis of SRC. In patients at risk of SRC with its typical clinical presentation, kidney biopsy is usually not performed. However, it should be considered in all patients with atypical presentation and findings, especially in normotensive patients, patients with ANCA positivity, severe proteinuria, and nephrotic syndrome.

In most patients, we cannot perform kidney biopsy immediately as severe hypertension and frequently present thrombocytopenia significantly increase the risk of bleeding. Biopsy is usually performed within a few days after blood pressure correction and is done with reasonably low risk in patients with blood pressure below 160/90 mmHg and thrombocyte count above $100 \times 10^9/l$.

2.6 Predictive and risk factors

Identification of SRC predictive factors (before the development of SRC) is essential (**Table 2**). The vast majority of SRC cases (75–80%) occur in patients with diffuse skin involvement, i.e., skin scleroderma proximal to knee and elbow (dcSSc patients), and rapid progression of skin thickening has been shown to be associated with the development of SRC [12]. Arthritis, palpable tendon friction rubs, swollen fingers, and distal parts of hands are routine syndrome in patients with early dcSSc [13]. Tendon friction rubs were confirmed to be an independent predictor of SRC (HR: 2.33) [14].

SRC starts early, most often less than 4 years after the first SSc symptom, although SRC patients have minimal or even no skin changes at the time of the diagnosis of SRC. Males are proportionately more frequently affected than females [15].

On the other hand, patients previously called as CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly and Telangiectasia) rarely develop SRC. These patients are subgroup of lcSSc fundamentally [12].

When talking about risk factors of death, a history of renal crisis (HR 2.89), presence of proteinuria (HR 3.09), elevated acute phase reactants (HR 1.79), elevated creatine kinase (HR 1.73), and muscle weakness (HR 1.55) were associated with decreased survival [5, 16]. On the other hand, since the introduction of ACE inhibitors, renal crisis appears to have become an increasingly less frequent terminal event [4]. In EUSTAR cohort, except one individual, all patients dying from renal crisis were on an ACE inhibitor at the time of death. Prednisone equivalents above 15 mg daily have been implicated in exacerbating SRC [5].

Several retrospective studies suggest that glucocorticoids are associated with a higher risk of SRC. Blood pressure and renal function should be carefully monitored in patients with SSc treated with glucocorticoids [17]. Evidence regarding the impact of steroid use on the development of SRC comes mainly from retrospective studies, most of which showed significant association between steroid exposure and the occurrence of SRC [11, 15, 18–22].

A retrospective analysis including 140 patients with SRC showed that high doses of steroids (prednisone ≥ 30 mg/day) were used frequently in patients with SSc with normotensive SRC (64%) as compared with those with hypertensive SRC (16%) suggesting an association between the use of high-dose steroids and the risk of normotensive SRC, which is associated with worse prognosis [11].

Glucocorticoids are routinely used for the management of interstitial lung disease, puffy fingers, and skin involvement. These indications are not recommended (because of insufficient evidence of efficacy); however, the experts recognize their use in everyday practice in the management of inflammatory manifestations such as musculoskeletal involvement (arthritis, tendonitis, myositis—in overlap with idiopathic inflammatory myopathies), pericarditis, pleuritis (in overlap with SLE), nonspecific symptoms such as skin itching/burning, fatigue, and appetite (with empiric basis) [17, 23]. Considering the potential risk of SRC associated with steroid use, the experts recommend that patients with SSc treated with steroids should be carefully monitored with respect to the development of SRC [17].

It can be summarized that glucocorticoids have a very narrow or no therapeutic opportunity in SSc.

SRC patient-specific characteristics
Race—black Gender—male sex
SSc characteristics
Short course of SSc Diffuse cutaneous systemic sclerosis Modified Rodnan skin score (>14 or 20) Musculoskeletal contractures Tendon friction rubs Pitting scars on finger tips Cardiopulmonary manifestation <i>Heart failure</i> <i>Pericarditis</i> <i>FVC <75% expected value</i> <i>DLCO low/decrease</i> Muscle involvement <i>Muscle weakness</i> <i>Higher creatine kinase level</i> <i>Myalgias or myopathy</i> Arthritis/Arthralgias
Genetics and biomarkers
Anti-RNA polymerase III presence Anti-RNA polymerase I/II/III presence ELISA anti-RNA polymerase III ≥ 157 IU Anti-centromere absence Anti-nRNP presence ANA speckled immunofluorescence lipocalin-2 high levels [24] sCD147 high levels [25] angiogenin high levels endothelin-1 high levels HLA-DRB1*0407 HLA-DRB1*1304
Risk factors developed during SSc
Skin changes acceleration Hemoglobin, thrombocyte decrease Cardiac involvement—new <i>Pericarditis</i> <i>Congestive heart failure</i>
Drugs
Cocaine [26] Glucocorticoid treatment Cyclosporine A Absence of calcium channel blocker
Factors without evidence of SRC risk
Previous blood pressure arise Abnormal dip-stick and light proteinuria Chronic elevation of serum creatinine Presence of antibodies: anti-topoisomerase, anti-centromere
<i>SRC, scleroderma renal crisis; SSc, systemic sclerosis; FVC, forced lung vital capacity; DLCO, diffusing capacity for carbon monoxide; RNA, ribonucleic acid; ELISA, enzyme-linked immunosorbent assay; nRNP, nucleic ribonucleic protein; ANA, antinuclear antibodies; HLA, human leucocyte antigen.</i>

Table 2. Clinical and laboratory predictors of scleroderma renal crisis and worse outcome. Adapted from Bose et al. [6].

2.7 Clinical manifestation of scleroderma renal crisis

2.7.1 Early symptoms

Sometimes SRC symptoms are nonspecific, for example, fatigue or not feeling well. Typically, patients complain of severe headache, blurred vision, or other encephalopathic symptoms with the onset of accelerated hypertension. Seizures may be also an early finding [1].

2.7.2 Blood pressure

Most patients have striking increase of blood pressure at the onset of SRC. Above 90% patients have blood pressure levels >150/90 mm Hg, 30% have diastolic pressure >120 mm Hg, and <10% of SSc have a normal blood pressure. In addition to thinking about absolute values, clinically important risk factors arise of 30 mmHg systolic and 20 mmHg diastolic blood pressure (repeatedly measured) [1].

2.7.3 Kidney injury, *conditio sine qua non*

Acute kidney injury is defined as any of the following: increase in serum creatinine by >26.5 $\mu\text{mol/L}$ (> 0.3 mg/dl) within 48 hours; increase in serum creatinine to >1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, and urine volume <0.5 ml/kg/h for 6 hours. This is the definition of acute kidney injury from the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [27].

2.7.4 Cardiopulmonary system

Patients with SRC often present with congestive heart failure presented as dyspnea, paroxysmal nocturnal dyspnea or pulmonary edema, serious ventricular arrhythmias, cardiac arrest, or large pericardial effusion [11]. Interestingly, this is primarily owing to the stress of hypertension on the heart, effects of hyperreninemia, and fluid overload secondary to oliguric renal failure. Some patients have primary scleroderma myocardial involvement contributing to these consecutive insults [1].

Acute pericarditis is diagnosed if the patient has at least 2 of the 4 following criteria: (1) pericarditis chest pain; (2) pericardial rub; (3) new widespread ST-elevation or PR depression on electrocardiogram; (4) pericardial effusion (new or worsening) on cardiac echocardiography [1].

Pulmonary hemorrhage is a rare life-threatening status, which has occurred in several of SRC patients [10]. Etiopathogenesis is associated with pulmonary edema and hemorrhagic diathesis. In differential diagnosis, diffuse alveolar hemorrhagia and acute renal failure were rarely observed in cases of ANCA systemic vasculitis and SSc overlaps [28].

2.7.5 Target organ dysfunction

Typically, hypertensive retinopathy (hemorrhages, hard and soft (cotton wool) exudates, and/or disc edema, not attributable to other causes), confirmed by an ophthalmologist, is observed. Hypertensive encephalopathy is characterized by headache, altered mental status, seizures, visual disturbances, and/or other focal or diffuse neurologic signs not attributable to other causes. Acute congestive heart

failure is characterized by typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema) [1, 6].

2.8 Laboratory findings

2.8.1 Autoantibodies

Antinuclear antibodies (ANA) are hallmark of connective tissue diseases. In case of Raynaud phenomenon, puffy fingers, nailfold capillaroscopy finding with typical microvascular changes, and ANA can alert to the very early diagnosis of SSc and may determine etiology of malignant hypertension. ANA are seen in 95% of SSc.

The presence of scleroderma-specific antibodies may confirm SSc diagnosis, anti-topoisomerase I predicts diffuse SSc, but only 10% of SRC has anti-topoisomerase I positivity [6, 29] (**Figure 6**).

Anti-RNA polymerase III is a scleroderma-specific antibody and is seen only in diffuse scleroderma. About 24–33% of these patients develop SRC [30–32]. It was showed that anti-RNA polymerase is strongly associated with SRC, OR 6.4 [33]. This statement is valid with the exception of geographical variability. For example, the difference in prevalence of autoantibodies among SRC patients between the Italian and other population might originate from the lower prevalence of anti-RNA polymerase III among Italians [34]. Anti-RNA polymerase III is associated with worse prognosis of SRC including Dialysis, persistence on dialysis, and survival [1].

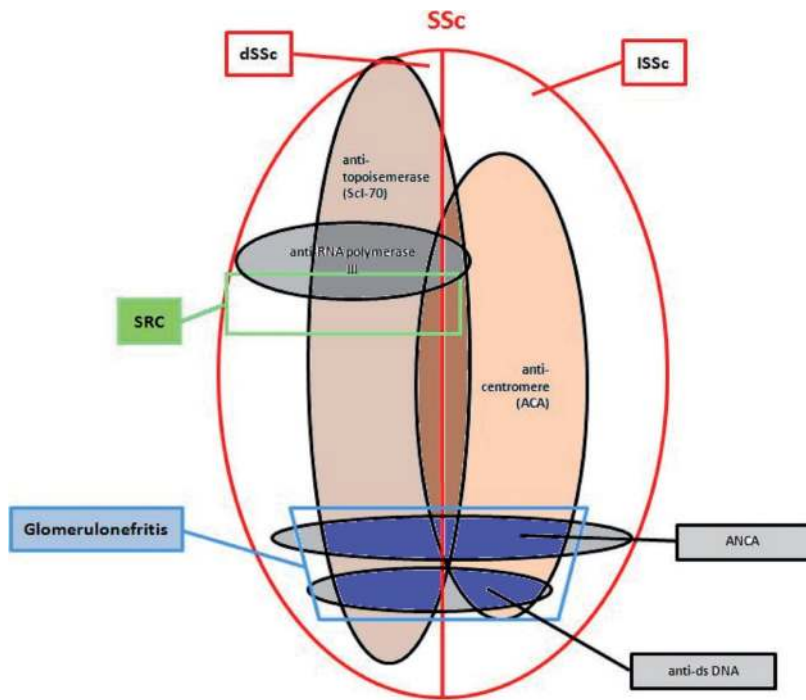


Figure 6.

Diagram showing subsets of systemic sclerosis associated with kidney involvement stratified by antibodies. Colored areas represent approximated proportion in patients. Adapted from Kuwana M and Medsger A [35]. SSc, systemic sclerosis; SRC, dSSc, diffuse cutaneous systemic sclerosis; lSSc, limited cutaneous systemic sclerosis; scleroderma renal crisis; anti-RNA polymerase III, anti-ribonucleic acid polymerase III antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; anti-ds DNA, antibodies against double-stranded (ds) DNA.

2.8.2 Microangiopathic hemolytic anemia and thrombocytopenia

SRC is a disease characterized by thrombotic microangiopathy with typical blood laboratory findings—new or worsening anemia, presence of schistocytes or other red blood cell fragments in peripheral blood smear, and thrombocytopenia <100.000, confirmed by manual smear. Typical features are laboratory evidence of hemolysis, including elevated lactate dehydrogenase, reticulocytosis, and/or low/absent haptoglobin and negative direct anti-globulin test. In differential diagnosis, other types of thrombotic microangiopathies need to be excluded (see **Table 3**). In some cases, thrombotic thrombocytopenic purpura has been reported in scleroderma patients, but it is unclear whether it was an isolated coexisting disease or a different interpretation of SRC [1, 6, 36].

2.9 Differential diagnosis of scleroderma renal crisis

The most common differential diagnoses are

- anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis,
- lupus nephritis, and
- diseases associated with thrombotic microangiopathy (**Table 4**).

Thrombotic thrombocytopenic purpura (TTP) /hemolytic-uremic syndrome (HUS)/disseminated intravascular coagulation (DIC)/heparin-induced thrombocytopenia (HIT)/ pre-eclampsia or HELLP syndrome refers to an acronym used to describe the clinical condition that leads to hemolysis, elevated liver enzymes, and low platelets/catastrophic antiphospholipid syndrome (CAPS), etc. [37].

Other differential diagnoses reported included membranous and membranoproliferative nephropathies, other vasculitis (including polyarteritis nodosa, mixed cryoglobulinemia, and Goodpasture syndrome), drug-induced nephropathies (due to D-penicillamine or cyclosporin A), oxalate nephropathy, renal artery stenosis, and pre-renal causes (e.g., sepsis and dehydration) [10].

2.10 Management of scleroderma renal crisis

2.10.1 Prevention

Despite significant decrease in incidence of SRC, no reliable preventive measures were identified. To decrease the risk of SRC development, we have to identify patients at high risk. Risk factors are discussed above (see chapter “Predictive and Risk Factors”), and we should take special caution in patients with dSS in the early stages of the disease (less than 5 years from diagnosis) with rapid progression of skin thickening, palpable tendon friction rubs, and anti-RNAP III antibodies [39]. Clinically, most important modifiable factor seems to be glucocorticoid treatment. Doses as high as 15 mg of prednisone are associated with increased incidence of SRC in several studies (see below).

Patients at risk should have their blood pressure controlled well. However, ACE inhibitors that are recommended for SRC treatment have not been shown to have protective effect before SRC onset and do not improve outcome of SRC [18, 19]. On the other hand, there are some reports of negative impact of ACE inhibitors on worse outcome of SRC, if ACE inhibitors were used in prevention of SRC [1, 40].

History and condition	Scleroderma renal crisis	CAPS	TTP-HUS	HELLP syndrome	Sepsis	DIC	HIT
Previous history	Systemic sclerosis	APS/SLE/malignancy/ pregnancy	Malignancy/ non	pregnancy	infection	Infection/ malignancy	Heparin exposure
Thrombosis	Small vessels	Large/small vessels	Small vessels	Small vessels	Large/small vessels	Small vessels	Large/small vessels
Hemolytic anemia	+	-/+	++	+	-/+	-/+	—
Schistocytes	+	-/+	++	+	-/+	-/+	—
Fibrinogen	Normal/high	Normal/high	Normal/high	Normal/high	Normal/low	Normal/low	Normal/high
Typical antibodies	anti-RNA polymerase III	aPL	ADAMTS13	None	None	None	Anti-PF-4

TTP, thrombotic thrombocytopenic purpura; HUS, hemolytic uremic syndrome; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes and low platelets syndrome; HIT, heparin-induced thrombocytopenia; APS, antiphospholipid syndrome; CAPS, catastrophic antiphospholipid syndrome; SLE, systemic lupus erythematosus; aPL, antiphospholipid antibodies; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; PF-4, platelet factor 4.

Table 3. Differential diagnosis of thrombotic microangiopathies from the view of scleroderma renal crisis. Adapted from Cervera et al. [37].

Event	Differences from SRC
Essential hypertension	Without acute renal failure
ANCA-associated glomerulonephritis	ANCA positivity, significant Proteinuria, hematuria [38]
Overlaps with connective tissue disease with glomerulonephritis (SLE)	Anti-dsDNA positivity, other CTD-specific antibodies
Renal artery stenosis	Absence of systemic symptoms
Thrombotic microangiopathies	
<i>Pre-eclampsia</i>	<i>Pregnancy</i>
<i>Hemolytic uremic syndrome</i>	<i>Shigella toxin</i>
<i>Thrombocytic thrombocytopenic purpura</i>	<i>ADAMTS13 antibody</i>
<i>Catastrophic antiphospholipid syndrome</i>	<i>Antiphospholipid antibodies</i>
<i>Heparin-induced thrombocytopenia</i>	<i>Heparin treatment</i>

Other conditions: membranous nephropathy, drug-induced nephropathies (e.g., cyclosporin A), other vasculitis (e.g., polyarteritis nodosa, mixed cryoglobulinemia, and Goodpasture syndrome), oxalate nephropathy, membranoproliferative nephropathy, pre-renal causes (e.g., sepsis, dehydration, and cardiac or pulmonary vascular involvement), and isolated renal abnormalities. SRC, scleroderma renal crisis; ANCA, antibodies against neutrophils; SLE, systemic lupus erythematosus; CTD, connective tissue diseases; ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.

Table 4.
 Differential diagnosis of scleroderma renal crisis. Adapted from Bose et al. [6].

Therefore, other antihypertensive drugs should be used to treat primary hypertension in these patients. Calcium channel blockers are a preferred option, as these drugs are effective in controlling blood pressure and a positive vasodilatory effect [41].

2.10.2 Early diagnosis

Early diagnosis and treatment can significantly improve prognosis of the patients. Patients at risk should be instructed to monitor blood pressure at home at least twice a week. They should report sudden increase in blood pressure and blood pressure above 140/90 mmHg. These patients should have their blood pressure quickly normalized and should be evaluated for possible SRC development (evaluation of kidney function, presence of MAHA, etc.).

2.10.3 Treatment of scleroderma renal crisis

Current treatment of SSc focuses on broad-spectrum immunosuppression or organ-based therapy for separate manifestations such as lung fibrosis, skin and gastrointestinal involvement, pulmonary or systemic hypertension, and kidney impairment [1]. The treatment of SRC is based on three main principles: causal treatment with ACE inhibitors, methods of renal function replacement, and plasma exchange in some patients. For organ complications, supportive treatment is used. SRC without treatment is often lethal. SRC patients should be treated immediately and aggressively with hospitalization and under careful control (**Figure 7**) [1]. It is advisable to admit patients with symptomatic hypertension to intensive care units.

2.10.3.1 Angiotensin-converting enzyme inhibitors

The key to improved outcome is treatment with ACE inhibitors. It should be initiated as soon as possible. Captopril is the preferred option. It has been used in

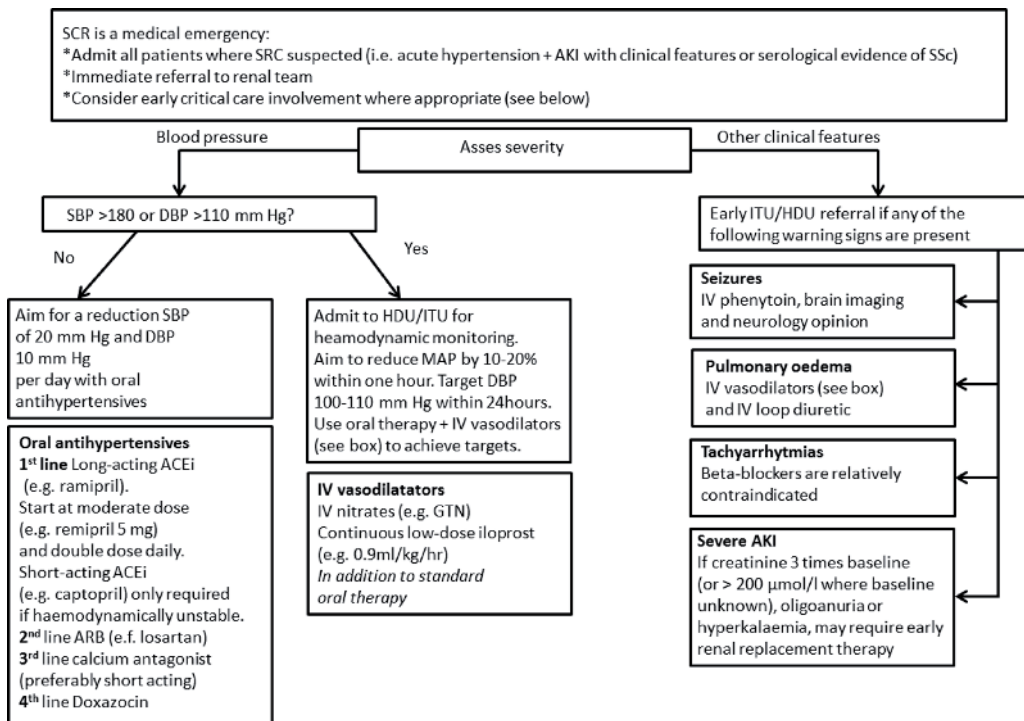


Figure 7. Management of scleroderma renal crisis, adapted from Lynch et al. [50]. ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ARB, angiotensin receptor blocker; DBP, diastolic blood pressure; HDU, high dependency unit; ITU, intensive therapy unit; MAP, mean arterial pressure; SBP, systolic blood pressure.

most studies and its short-acting character enables good titration at the start of the treatment. It is usually necessary to use very high doses. Blood pressure should be brought back to normal levels within 2–4 days.

ACE inhibitors have complex effect and decrease blood pressure and plasma renin activity. The dramatic response to therapeutic inhibition of the renin-angiotensin system in SRC implicates renin overproduction as a central part of the pathogenesis of SRC [1, 42].

Several cohort studies showed benefit in survival with the use of ACE inhibitors in patients with SRC. The experts recommend immediate use of ACE inhibitors in the treatment of SRC [11, 17–19, 29, 43–48]. Prospective analysis of 108 patients with SRC has suggested that patients on ACE inhibitors (captopril in 47 and enalapril in 8) had a significantly better 1 year survival rate (76%) and 5 years (66%) compared to patients without ACE inhibitors (15% at one and 10% at 5 years, respectively). Treatment with ACE inhibitors was significantly associated with better survival in SRC, after adjustment for age and blood pressure ($p < 0.001$) [29, 49, 50]. Two recent retrospective studies including 91 and 110 patients with SRC, respectively, the majority of whom (91 and 98% respectively) were treated with ACE inhibitors and/or angiotensin receptor antagonists (ARA), reported survival rates from 71–82% at 1 year, 59–60% at 5 years, and 42–47% at 10 years [19, 47]. Other anti-hypertensive agents may be considered for management of refractory hypertension in conjunction with an ACE inhibitor in SRC, including ARA, calcium channel blockers, doxazosin, and clonidine [1, 49]. Beta-blockers are not appropriate, as they affect peripheral circulation.

It can be summarized that survival benefit was shown with the use of ACE inhibitors in patients with SRC. Experts recommend immediate use of ACE inhibitors in the treatment of SRC [17].

2.10.3.2 Acute kidney injury

A patient with SRC is, from a definition, the one with acute kidney injury and should be managed in cooperation with a nephrologist. Thus, recommendation for acute kidney injury should be applied including regular monitoring of kidney function, minimization of nephrotoxic medication, etc. During first days of SRC treatment, serum creatinine levels usually increase. This is an anticipated decrease in glomerular filtration that should not discourage us from intensive blood pressure control [27].

Renal replacement therapy should be initiated if necessary. Both hemodialysis and peritoneal dialysis are possible alternatives. However, hemodialysis is a preferred option. ACE inhibitor treatment should continue long term, even in patients on chronic renal replacement therapy, especially in patients with possible recovery of renal function.

In chronic hemodialysis patients, kidney transplantation has to be considered. There are two particular details in SSc patients that should be discussed: first, there is a possibility of late recovery of kidney function and, second, there is historically reported bad outcome of transplanted SSc patients. Indeed, patients with SRC may recover renal function up to 3 years after the crisis, most often within 12–18 months [50]. Thus, many authors recommend that decision to transplant should not be made before 2 years after SRC onset [17]. Patients after SRC on hemodialysis treatment should therefore be regularly checked for signs of recovery of kidney function. But in general, postponing kidney transplant in hemodialysis patients could worsen their prognosis. It seems prudent that in patients without significant residual renal function, without signs of kidney recovery and unfavorable findings on kidney biopsy (if done) such as vascular thrombosis and glomerular ischemic collapse, we consider kidney transplant in 6 months from SRC [51].

Older studies reported bad outcome of SSc patients after kidney transplant compared to patients with other causes of kidney failure. However, recent studies have shown excellent patient and graft survival [52].

Generally, on the other hand, long-term dialysis increases the risk of death. Independent of the underlying disease, dialysis increases the risk of infection (in patients undergoing peritoneal dialysis) and, over the long term, enhances the risk of vascular calcification and atherosclerosis. In patients on chronic dialysis, kidney transplantation has to be considered [53].

In a series of 260 SSc patients who underwent renal transplantation in the United States, their 5-year graft-survival rate was 56.7% [53]. In that study, the risk of SRC recurrence was higher for patients with early renal insufficiency following SRC onset. Recurrent SRC in the allograft may be predicted by the same previously described risk factors [53–55].

For those with recurrent SRC, the time of onset following transplantation is not known. Recurrence usually happens within the first few months to the first 1–2 years after transplantation [53, 54].

Kidney transplantation should therefore be considered in all SSc patients with the need of renal replacement therapy. What has not changed over the last decade is that only small percentage of patients with SSc is transplanted due to severe extrarenal disease. Thorough work-up before enrolling a patient on waiting list is warranted.

Both recurrence of SRC after kidney transplantation and graft loss due to SRC recurrence have been reported. Recurrence rate is fortunately low (8.8%) and patients after kidney transplant should be monitored similarly to patients with SSc at high risk of SRC development [52].

Immunosuppression given to SSc patients after kidney transplant alters the course of the disease. Most of the patients after kidney transplant have stable disease or even improve symptoms. Regarding immunosuppressive regimens after kidney transplant, it is difficult to make any evidence-based conclusions. Most patients were treated with high-dose steroids at the time of transplantation followed by long-term low doses in combination with calcineurin inhibitors and mycophenolate mofetil. A significant number of patients were weaned from steroids with reasonable outcome, but recommendations cannot be made due to limited number of patients [52].

2.10.3.3 Plasma exchange

Plasma exchange, which has been proposed for thrombotic microangiopathy, has not demonstrated efficacy and should not be prescribed, with the exception of the rare SRC patients who might develop thrombotic microangiopathy associated with anti-ADAMTS-13 antibodies [54]. There are no clinical trial data for use of plasma exchange in SRC.

3. Nonscleroderma renal crisis involvement of kidney in systemic sclerosis

3.1 Interstitial kidney changes/disease

Clinically relevant renal involvement (non-SRC) in SSc is uncommon [55]. Asymptomatic and slowly progressive renal involvement is present in 60–80% of SSc patients. In more than half of asymptomatic SSc patients, renal function demonstrates clinical markers of renal damage (proteinuria, elevation of serum creatinine, hypertension, etc.) [32, 56–58]. These patients presented with evidence of underlying chronic renal disease but without confounding illnesses such as diabetes or hypertension existing prior to the onset of their SSc. Histological findings showed expressions of fibrillar collagens. In some SSc cases, drug exposure may explain interstitial kidney changes [6]. It is unclear whether SSc cases are more susceptible to this, but interstitial nephritis remains an important differential diagnosis.

3.2 Glomerulonephritis

Glomerulonephritis occurs in the context of overlap connective tissue disease or systemic vasculitis. In other words, SSc should be associated with other immunopathological diseases presented by glomerulonephritis, mainly systemic lupus erythematosus and ANCA-associated glomerulonephritis [59].

Circulating antimyeloperoxidase antibodies have been reported in several patients with dcSSc associated with necrotizing and crescentic glomerulonephritis [1, 58]. A study of 81 SSc patients with renal impairment found 2 patients with lcSSc with perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) along with circulating IgG and IgM antimyeloperoxidase antibodies. After screening for ANCA in SSc by indirect immunofluorescence, the levels of IgM and IgG anti-MPO antibodies in 8 patients (8%) with SSc were determined by ELISA [60]. In conclusion, the presence of ANCA in SSc patients should predict ANCA-associated vasculitis. The treatment of these associated glomerulonephritis is managed according to the principles of treatment of the overlapping renal diseases (**Figure 8**).

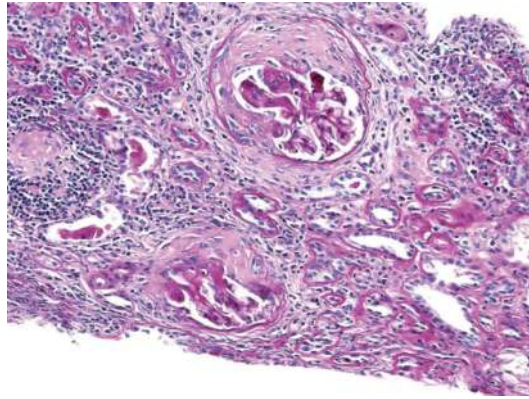


Figure 8.

Normotensive patient with systemic sclerosis and acute renal failure underwent renal biopsy. End-stage kidney disease: crescentic glomerulonephritis showing fibrous crescents. A mixed mononuclear cell infiltrate and considerable tubular loss are shown. Hematoxylin-eosin staining, magnification 200 times. Courtesy of Miroslav Podhola, MD., PhD., Department of Pathology, Faculty of Medicine in Hradec Kralove, Charles University.

4. Conclusion

SRC is a rare manifestation with dramatic clinical picture and high morbidity and mortality. Current strategies to reduce the associated morbidity and mortality include identification of at-risk patients to aid early diagnosis. Caution should be exercised in diagnosis of SSc cases with serological features of renal disease including anti-RNA polymerase III autoantibodies, for non-SRC renal disease SLE serology and ANCA positivity. ACE inhibitor therapy should be lifelong in all SRC patients. Prompt initiation of ACE inhibitors stays a key point in SRC therapy. New therapeutic possibilities are needed.

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