Kidney involvement in systemic sclerosis

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Abstract

Kidney involvement in systemic sclerosis (SSc) is primarily manifested by scleroderma renal crisis (SRC). More than 30 years ago, it was the main cause of death in these patients. The use of ACE inhibitors has modified the prognosis and nowadays SRC has become a much more easily treatable complication of SSc. Furthermore, although there are still many patients who do not survive this complication, the early diagnosis and prompt therapy of SRC can have an excellent outcome. Renal abnormalities independent of SRC are possible but are attributed to different pathogenetic mechanisms. Further understanding of pathogenesis of SRC may lead to additional improvement in the therapy of this serious complication.

Introduction

The manifestation of accelerated arterial hypertension and/or rapid progressive failure of the renal function of filtering (oliguria) are highly suggestive of scleroderma renal crisis (SRC). Renal biopsy is not very specific and not always useful for diagnostic purposes. Indeed, the histological assessment of bilateral stenosis of infrarenal arteriole is indistinguishable from that of other thrombotic vascular disorders (malignant arteriolar nephroangiosclerosis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, radiation nephritis, chronic rejection response, antiphospholipid syndrome). However, in case of doubtful association of the clinical picture with SRC, it could be useful to turn to a renal biopsy as soon as possible so as to increase the chances of reversibility of the clinical situation. Data from autopsy reports reveal renal involvement in 60-80% of patients with scleroderma, most of them female. On the other hand, only a minimal part of them clinically show and acute or subacute kidney involvement (<5%). In clinical practice, 50% of patients show minimal signs or kidney involvement (slight increase in proteinuria, slight or no increase in arterial tension, slight increase in creatininemia). SRC usually occurs in the early years of the disease (within 4-5 years from the onset of the first extra-Raynaud’s symptoms). The advent of ACE inhibitors has reduced the mortality from this complication. Renal insufficiency is one of the causes of death from systemic sclerosis, although much less frequent than cardiac or pulmonary decease. Patients with low arterial tension during early SRC and patients on dialysis and elderly patients on dialysis have the poorer renal outcome. The mortality rate in SRC, which is higher in males, is nonetheless high (life expectancy within 5 years is 59%). Studies on immunocytochemistry have shown the activation of the endothelin axis, including the endothelin receptors type A and B. It is likely that following the beginning of the prophylactic therapy with ACE inhibitors and the early use of Iloprost and endothelin-1 (ET-1) inhibitors the risk of SRC onset can be progressively reduced. The first case of SRC was described in 1863.

Risk factors

Black patients with recent cardiac and diffuse and progressive cutaneous involvement and those with anemia, as well as patients on higher cortisol doses (<15 mg a day of prednisone) and anti-RNA polymerase III (anti-RNAP) are potentially more affected. Approximately 50-59% of patients with SRC show positive anti-polymerase III antibodies. The association with anti-centromeres (2%) and anti-topoisomerases I (9%) is less evident. In 78% of cases, SRC is associated with disturbances of cutaneous involvement. The simultaneous occurrence of diffuse renal involvement and anti-RNA polymerase III significantly increases the risk of SRC. The occurrence of anti-topoisomerases and, even more, of anti-centromeres has a protective role. The early 1990s anti-polymerase III antibodies determined by the immunoprecipitation technique were associated with the diagnosis of systemic sclerosis (SSc). More recently, since the introduction of the ELISA method for their determination, their role has been gradually associated with peculiar clinical characteristics and complications of systemic sclerosis. Apparently, these antibodies seem to play a prognostic, rather than pathogenetic, role. They appear early, with considerable intra- and inter-patient variability. The prevalence of anti-polymerase III
may differ in relation to the examined cohorts and from country to country: pp to 9.4% in France, 12% in Great Britain, 6% in Japan, 19.4% in Canada, and 25% in America.\textsuperscript{10-14} The main clinical correlations of anti-RNAPs include the diffuse cutaneous involvement, and therefore a major skin score (mRSS); the synovitic, tendinous and myositis involvement; SRC and the development of tumors.\textsuperscript{15} It should be emphasized that the anti-RNA polymerase III positive population with scleroderma makes use of a higher daily dose of cortisone due to the clinical profile more oriented towards synovitis and myositis and the independent role of cortisone in causing a higher SRC risk is known.\textsuperscript{16} Nevertheless, anti-RNA polymerase II remains an independent risk factor for this clinical complication. Finally, lung tumors, melanomas, non-melanoma cutaneous tumors, colon cancer and lymphomas are the main malignancies - a six-fold higher risk - found in patients with an anti-RNA polymerase III positive clinical subset. Genetically, the HLA DRB1*0407 (Odds Ratio 3.21) and *1304 (Odds Ratio 4.51) alleles are the main genetic risk factors for the SRC development.\textsuperscript{7} On the other hand, DQB1*0301 and DQA1 0501 alleles seem to correlate with the susceptibility to the scleroderma onset in a more general sense and regardless of ethnicity; whereas DRB1*0802, together with DQA1*0501, seem to be predictive of mortality in a general sense.\textsuperscript{17,18}

**Pathogenesis**

The pathogenesis of renal events in SSc is not yet completely understood. As for other organs, the endotheliopathy is the *primus movens*, as it causes intimal thickening and proliferation, especially of the interlobular and arcuate arteries (Figure 1).

In these areas, the endothelial aggregability and adhesiveness of blood platelets occurs easily in the beginning with consequent release of platelet and endothelial factors [thromboxane, platelet derived growth factor (PDGF) and endothelin-1] causing an hypertrophic and hyperplastic effect on the arterial layers of the vascular walls, a chemotaxis and proliferation of fibroblasts on the spot with deposit and stratification of fibrin and collagen with consequent narrowing of the vascular lumen and renal hypoperfusion (primary pathogenetic mechanism), especially at the cortical level (area designed to the reception of bloodstream of involved vessels). Lymphomonocytes cells are little present at the histopathological examination of these arteries, probable sign of their secondary pathogenetic role. A renal Raynaud’s phenomenon has been demonstrated by Cannon \textit{et al.}\textsuperscript{19} in patients with scleroderma with significant reduction of renal cortical blood flow after immersion of hands in cold water. The study by Cannon and colleagues documented that patients with SRC had a reduction in renal cortical blood flow; on the contrary, patients with normal, or only slightly reduced, renal function had a regular or only slightly reduced cortical flow. Renal hypoperfusion, as a result of both vasoospasm and structural alteration, leads to an excessive release of renin due to the hyperplasia of the juxtaglomerular apparatus.\textsuperscript{20} The activation of the renin-angiotensin system has an important pathogenetic role in SRC activating a vicious circle that perpetuates the same renal crisis leading to a worsening of the infrarenal vasoconstriction, a systemic arterial hypertension, and a further worsening of renal ischemia due to the vascular spasm, which is

![Figure 1. Affected arterial blood vessels in scleroderma renal crisis.](image-url)
the main cause of SRC. In fact, cardiac dysfunctions causing renal hyperperfusion, such as cardiac decompensation, arrhythmia and significant effusion, may sometimes precede SRC. Hormonal changes in pregnancy have been reported to cause SRC, even though on a less solid pathogenetic basis. A prolonged dehydration can cause SRC similarly to some hypo-perfondant drugs on a vasospastic basis such as cocaine, cyclosporin, and tacrolimus. Other drugs that can reduce renal perfusion with different mechanisms - such as ACE inhibitors, NSAIDs, due to a local reduction of prostaglandins having vasodilatory action, and calcium antagonists - do not seem to increase the risk of activating SRC. In fact, calcium antagonists seem to have a protective role against its progression. On the contrary, a dose of prednisone higher than 15 mg/day seems to play a highly predisposing role in the SRC onset if used for a period of at least six months. The role of ET-1, which is overexpressed in the pathological tissues of patients with SRC, is unknown. It should be emphasized that infrarenal vascular alterations and hyperreninemia have also been found in scleroderma patients without SRC and that patients without hyperreninemia do not develop SRC. Therefore, despite being a key element in its pathogenesis, hyperreninemia does not predict the onset of SRC, as well as vascular renal abnormalities. Thus, to date, it is not definitively clear what is the trigger factor or the relations between more, already known, potential trigger factors of acute hyperreninemia during the course of SRC.

Clinical pictures and histopathological elements

A moderate proteinuria (a non-nephrotic range proteinuria is more frequent) with few cylinders and cells, a mild-to-severe arterial hypertension, an increase in azotemia and creatininemia, a microscopic hematuria are the main clinical expressions of kidney involvement during the course of SRC. Each of these clinical patterns is present in at least 50% of patients.

The typical (and the most formidable) type of SRC, secondary to the acute activation of the renin-angiotensin system, shows up with a rapid manifestation of renal failure and/or a severe arterial hypertension and it is frequently associated with a grade III hypertensive retinopathy (hemorrhage and exudates). At urinary level the clinical picture, which may not always be revealing, is characterized by an initially slight proteinuria that tends to increase during the crisis, and by a microhematuria if the hypertensive clinical picture is malignant. Other manifestations and clinical symptoms that are secondary to the important hypertensive clinical picture and to vascular renal disease are possible, such as a microangioptic hemolytic anemia, a pulmonary edema caused by an increase in post load and oliguria induced by water and salt retention, and a hypertensive encephalopathy with cephalalgia. The occurrence of arthralgias with worsening of prognosis is also possible. SRC is a medical emergency often preceded or accompanied by a rapid worsening of cutaneous involvement. Diffuse cutaneous forms should be frequently checked-up (3 times per year) with regard to the renal function and proteinuria, for at least the first 5 years after the onset of the disease. All patients have high levels of renin, a circulating mediator of SRC. The onset is more frequent during the cold months, thus suggesting a trigger role of low temperatures concerning the vasospasm.

In the more subtle or normotensive (less symptomatic) forms of SRC, which are much less frequent (10% of the typical hypertensive SRC), arterial pressure is normal while microangiopathic hemolytic anemia is much more severe, and sometimes it assumes the characteristics of a hemolytic uremic syndrome which is also often accompanied by plasctocytopenia (possible activation of a disseminated intravascular coagulation). It is important to underline that the microangiopathic hemolytic anemia found in the typical hypertensive form of SRC is, on the contrary, more related to malignant hypertension than primary artery/arteriole injury. In cases with severe microangiopathic hemolytic anemia it is important to intervene urgently. Plasmapheresis is a measure that would allow the infusion of fresh plasm (so as to contrast the consumption of coagulation factors during the course of DIC). In addition to the two forms of acute injury there is a chronic syndrome, not pathogenetically assimilable to a clinical subset of SRC, and generally characterized by a mild degree of renal insufficiency (creatinine >1.4-1.5) and by modest urinary signs (microhematuria and proteinuria). Arterial hypertension is variable, as well as the percentage of patients showing this clinical form in relation to the case study. According to some authors it is frequent (even over 40% of patients); for others it is rare and possible only in course of an evolving SRC. In fact, it is possible that patients with scleroderma develop a chronic renal injury in course of a scleroderma-related arterial hypertension and without any acute SRC event. The diagnosis of this chronic form does not benefit from biopsy, but rather from the simultaneous multi-organ anamnestic involvement that usually affects this type of patients (scleroderma renal crisis without simultaneous involvement of other organs, cutis in particular, is rare). It is also worth mentioning the renal failure induced by D-Penicillamine (5-30% of treated patients), a drug fallen into disuse, which is characterized by membranous and proliferative glomerulonephritis and proteinuria often within the range of nephrotic syndrome. The damage can manifest itself at any moment, but more often during the first year of treatment. The interruption of the therapy could slowly adjust the clinical picture. Under the magnification of light microscopy, in case of a slowly-evolving chronic kidney disease, the alterations tend to be limited to the arcuate arteries and interlobular arterioles and they are similar to a benign nephrosclerosis. The pathological changes of SRC related to kidney are similar to those noticeable in the malignant arterial hypertension, in thrombotic microangiopathy and in the hemolytic uremic syndrome. From a macroscopic perspective, the renal capsule shows areas of infarcts, hemorrhages, and cortical necrosis. Vascular changes affect arcuate arteries, interlobular arterioles and glomeruli. In the acute phase, the edema of the intima is documented on the arched arteries and the interlobular arterioles; while fibrin thrombi and areas of fibrinoid necrosis are variously represented at this early stage. Afterwards, it is possible to observe the proliferation of the intimal cells and the deposition of amorphous mucinous material (glycoproteins and mucopolysaccharides) up to the final onion bulb aspect of the interlobular arterioles. Larger arteries are little affected, except by a mild atherosclerosis. Glomeruli suffer indirectly from the ischemic picture characterized by the arteriolar/arterial damage. The picture that can be observed is characterized by the thickening and collapse of the glomerular loop. Also, renal tubules suffer from ischemia with cases of flattening/degeneration of the tubular cells. It is clear that in SRC the damages that are observed in the vascular areas are primary and not secondary as in the malignant arterial hypertension. Concerning the observation in electron microscopy, it is possible to observe a thickening of the mesangial walls and a focal thickening of the capillary walls due to subendothelial accumulation of electron-shining material. In arterioles, parietal areas of fibrinoid necrosis alternat-
ing with deposit areas of electron-dense material can be noted. The glomerular and arteriolar areas visible under electron microscopy show the typical fibrinoid necrosis and, under immunofluorescence, deposits of fibrin, fibrinogen, immunoglobulins (IgM in particular, and, to a lesser extent, IgA and IgG), and complement (C3, C1q). Arterial obliterative lesions mainly affect the arcuate arteries, the interlobular arterioles and the glomeruli. Fibrin thrombi and areas of fibrinoid necrosis are the manifestations of the acute phase. As mentioned above, during the cicatrization in the chronic phase, a mucoid intimal thickening and concentric onion-bulb type alterations of the vessel wall occur, as it can also be observed in the malignant nephroangiosclerosis and in the hemolytic uremic syndrome. Fibrinoid necrosis and the mucoid-type intimal thickening of interlobar arterioles, occurring respectively in the acute and in the chronic phase, are the histopathological aspects of SRC that are associated with a poorer renal outcome.1

### Therapy

In SRC, if the pharmacological control of blood pressure occurs before the vascular injury becomes irreversible, the renal function could be stabilized or even improved in approximately 70% of cases. The pathogenic vicious circle of SRC with decreased blood flow, ischemia, hyperreninemia, hypertension and, eventually, vasoconstriction, invariably resulted in a fatal outcome prior to the introduction of ACE inhibitors. At that time, only less than 10% survived the three-month life expectancy of the prognosis. ACE inhibitors, competitive inhibitors of the conversion of angiotensin I to angiotensin II, have become, since the early 1970s (the era of captopril), the drugs of choice with a good response in approximately 90% of patients. These inhibitors are able to reduce the percentage of evolution towards a progressive renal insufficiency together with an increase in the survival rate to one year from the onset of SRC. Although angiotensin I and renin continue to accumulate, they are biologically inactive on blood pressure. ACE inhibitors also proteolyze bradykinins, potent vasodilatory substances that could have a role in the hypotensive action mechanism of these drugs.21 Since ACE inhibitors have been used for treatment, pulmonary involvement has become the main cause of death among scleroderma patients in recent years.22 Should the therapy begin late, a state of advanced renal insufficiency could occur within two or three months. Nevertheless, over 20% of patients with SRC, despite therapies with ACE inhibitors, head for terminal renal failure.30 The value of creatininemia at the onset of SRC seems to correlate with the outcome of these patients. Pre-treatment values of creatininemia >3 mg% or values of the arterial pressure that cannot be improved within the first three days of therapy are associated with a bad outcome.3 The treatment with ACE inhibitors is always to be maintained, even at minimal doses and on dialysis by reason of its potential of improvement in the renal function of these patients even for long periods after the onset of SRC. There is also the possibility, during the pharmacological therapy, of a return to adequate renal function even after one year and with subsequent interruption of dialysis. This specific aspect must be considered regarding the insertion, or otherwise, of the patient in transplant lists.23 Rarely SRC have a relapse due to persistent hyperreninemia of the native kidney, and only in post-transplantation cases.31 A renal biopsy should be strongly considered in cases with acute renal involvement suggesting SRC but with incomplete clinical picture (for instance in the non-hypertensive forms of SRC) because, in these cases, the therapy with ACE inhibitors, even at small doses, is effective if started in the early (reversible) phases of the process. The use of second line ACE inhibitors does not lose efficacy compared to captopril, whose shorter half-life makes it flexible and practical in the early treatment of SRC. In cases with inadequate blood pressure control other drugs can be added, in particular calcium antagonists such as felodipine and amlodipine.32 If renal function continues to worsen, although with arterial pressure within the physiological limits, the therapy with ACE inhibitors should not be interrupted because it is not related to the loss of their function or a deteriorating action. Their interruption would definitely compromise the attempt to restrain SRC. Although not much has been written in the scientific literature, the use of angiotensin receptor blockers and direct renin inhibitors, in combination or not with ACE inhibitors is not to be proscribed.31,33,34 Also other anti-hypertensives, such as beta-blockers, can be used, although they can sometimes aggravate Raynaud’s phenomenon. The dialysis of these patients can be chronic in the most severe cases22 even though for some of these patients the peripheral arterial access may not be easy due to the presence of a peripheral vasculopathy. An important option to facilitate the functional recovery of the kidney is peritoneal dialysis. In case of microangiopathic hemolytic anemia it is necessary to employ fresh plasma, which is especially useful when combined with plasmapheresis. It should be emphasized that renal transplantation is not always possible due to the severe multi-organ conditions that can sometimes be found in these patients. However, the survival rate of a sclerodermat patient with kidney transplant is superior to that of the scleroderma patient awaiting a renal transplant, shifting from 62% to 47% respectively after one and five years from the transplantation (the survival percentages are however lower than non-scleroderma kidney transplants). Despite that, the therapy with ACE inhibitors reduces post-transplant SRC recurrences from 20% of the pre-ACE inhibitor era to approximately 2% of the following one.35 The treatment of Raynaud’s phenomenon should also be considered as a therapy aimed at protecting the kidney (hence the usefulness of calcium antagonists in combination with ACE inhibitors). The anti-hypertensive therapy, even aggressive if required, is the early basic treatment in patients with scleroderma and, in particular, with SRC. However, the therapy should be gradually reinforced so as to avoid a systemic and renal hypo-afflux and DBP should not exceed 85-90 mmHg.32,36-38 The increase in creatinine and proteinuria over 0.5 grams are elements that suggest the development of SRC. Checks of those parameters should be made every 3-4 months in course of scleroderma. As mentioned above, ACE inhibitors are the first-choice drugs for both their anti-hypertensive efficacy and their role in the pathogenetic mechanism of SRC and, therefore, for their capacity to protect the kidney.21 Moreover, it should not be forgotten that kidney disease is similar to a bilateral stenosis of the renal arteries. Therefore, the use of ACE inhibitors should be monitored for the risk of incurring into a severe and persistent hypotension that can, paradoxically, worsen the renal injury. Platelet and fibrinogen counts are also important, in addition to the search for schistocytes in the peripheral smear, for the early detection of the microangiopathic hemolytic anemia onset, which is an active manifestation of the normotensive form of SRC.24 Due to the presence, since the earliest phases of SSc, of TXA2 and Endothelin-1, which are the main responsible for scleroderma macroangiopathy, it is conceivable that scleroderma patients treated since the onset of the disease with acetylsalicylic acid, iloprost, receptor antagonists of Endothelin-1, and ACE inhibitors may be less at risk of developing renal vasculopathy (macroangiopathy) prior to the development of
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