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## Scleroderma Renal Crisis

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### 1. Introduction

Scleroderma renal crisis (SRC) is an infrequent complication of a rare disease. To date, many aspects of the pathophysiology of SRC are still mysterious. Since SRC biopsies are not frequently encountered in practice, our understanding of the spectrum of histologic changes is derived from a combination of a limited personal experience and data obtained from several relatively small pathologic studies.

This book chapter will be devoted to discuss the pathophysiology and the histologic manifestations of SRC and will cover the most important aspects of clinical and laboratory findings as well as treatment of SRC.

Systemic sclerosis (SSc) is a chronic systemic autoimmune disease characterized by excess collagen production. According to the extent of cutaneous sclerosis, SSc can be classified as either diffuse cutaneous (dc) or limited cutaneous (lc) variant (Sakkas, 2005). Many studies have been conducted to explore the pathogenesis of SSc. Activation of T-cells, B-cells and macrophages have been described and linked to the development and progression of fibrosis (Sakkas, Chikanza, & Platsoucas, 2006). Activated T-cells, mainly T helper lymphocyte type-2 (TH-2), are associated with increased IL-4 and IL-13 production and collagen accumulation. Activated B-cells produce autoantibodies that can facilitate transformation of fibroblasts into more fibrotic phenotypes while activated macrophages can accumulate in the perivascular spaces to produce transforming growth factor-B and platelet derived growth factor, which can also promote fibrosis. In addition to collagen accumulation, endothelial cell injury appears to play a central role in the pathogenesis of SSc. Increased permeability of the nail fold capillaries (Bollinger, Jager, & Siegenthaler, 1986) and increased endothelial apoptosis (Sgonc et al., 1996) have been described in SSc patients. Endothelial cell injury in SSc may be triggered by anti-endothelial antibody (Worda et al., 2003), cytokines (Kahaleh, 2004), complement abnormalities (Venneker, van den Hoogen, Boerbooms, Bos, & Asghar, 1994) and/or cellular cytotoxicity (Sgonc et al., 2000). Scleroderma renal crisis (SRC) can complicate the course of up to 10-20% of patients with SSc. SRC is most commonly encountered in patients with dcSSc; however, it can still occur in patients with lcSSc (Sugimoto, Sanada, & Kashiwagi, 2008; Sugimoto et al., 2006) and even in patients with no significant dermal sclerosis, termed systemic sclerosis sine scleroderma (ssSSc) (Gonzalez, Schmulbach, & Bastani, 1994). Compared to SSc, much less is known

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about the pathophysiology of SRC. This is largely attributed to the rarity of the disease and the absence of acceptable animal models for SRC. However, accumulating data suggest an important role of antibody-mediated injury in the pathogenesis of SRC. The histologic picture of SRC is not entirely specific for this disease. A similar histologic picture may be encountered in a number of primary vascular diseases and clinical conditions that may present as thrombotic microangiopathy. In addition to confirming the clinical diagnosis, renal biopsy can help predict the clinical outcome and optimize therapy in SRC patients. The mortality associated with SRC has decreased because of early diagnosis and angiotensin-converting enzyme inhibitor therapy (Collins, Patel, Eastwood, & Bourke, 1996; Steen, Costantino, Shapiro, & Medsger, 1990). Kidney transplantation remains as a treatment option for a subset of SRC patients who develop end-stage renal failure despite aggressive therapy. Unfortunately, the post-transplantation outcome for these patients continues to be worse than that of the general renal transplant population.

## 2. Clinical and laboratory features

SRC occurs more frequently in females than males and in Caucasians compared to African American (Sakkas, 2005). It is also much more common in patients with dcSSc than patients with lcSSc. However, only 10-20% of patients with dcSSc develop SRC (Ferri et al., 2002; Steen & Medsger, 2000b). SRC usually occurs early in the course of SSc. Up to 75% of SRC develop within the first four years from the diagnosis of SSc (Steen, 1994, 2003). SRC is classically associated with a sudden increase in blood pressure ( $>150/90$  mm Hg) (Mouthon et al.; Steen, 2003). This is usually accompanied by an acute deterioration in renal function. In addition, such patients often complain of headache, blurred vision and dyspnea as a result of hypertensive encephalopathy, congestive heart failure and pulmonary edema. Nevertheless, up to 10% of SRC patients present with blood pressures below malignant hypertension levels ("normotensive SRC") (Helfrich, Banner, Steen, & Medsger, 1989; Kagan, Nissim, Green, & Bar-Khayim, 1989). In these subjects, although blood pressure is within the normal range, it is commonly increased from its baseline value (Helfrich, et al., 1989; Steen, 2003).

Thrombotic microangiopathy, characterized by thrombocytopenia, normocytic hemolytic anemia, elevated levels of LDH and low serum haptoglobin can be encountered in approximately 50% of SRC patients at clinical presentation (Penn et al., 2007; Steen, 2003; Walker et al., 2003). In SRC patients, serum creatinine and blood urea nitrogen (BUN) are consistently elevated and are usually proportional to the severity of renal involvement (Steen, 2003). Renin blood levels are significantly elevated, especially in patients with malignant hypertension (Traub et al., 1983). Urinalysis may reveal microscopic hematuria and mild to moderate proteinuria (usually 0.5 to 2.5 grams per 24 hours) (Mouthon, et al.; Steen, 2003).

With regard to autoantibodies, ANA is detected in up to 90% of SRC patients. The pattern of ANA immunofluorescence is usually speckled (Penn, et al., 2007). Anti-centromere antibody, which is typically observed in lcSSc, has been infrequently reported in SRC patients (Mouthon, et al.; Steen, 2005; Teixeira et al., 2008). Some investigators even consider the detection of anti-centromere antibody to be protective against renal crises (Penn, et al., 2007). Anti-topoisomerase antibody, formerly known as Scl-70 antibody, is typically described in dSSc patients. This antibody has been shown to have some association with renal involvement as well as pulmonary fibrosis and cardiac disease (Steen, Powell, & Medsger, 1988). Anti-RNA polymerase III antibody is seen at a high frequency in patients

with SSc who develop SRC (B. Nguyen, Assassi, Arnett, & Mayes; Okano, Steen, & Medsger, 1993). Anti Th/To antibodies have been reported in some cases of SRC without pulmonary involvement (Gunduz, Fertig, Lucas, & Medsger, 2001) while anti-RNP3 or fibrillarin antibodies have a stronger association with pulmonary hypertension and skeletal muscle involvement than SRC (Aggarwal, Lucas, Fertig, Oddis, & Medsger, 2009). Compared to other autoimmune connective tissue diseases, SRC has the worst prognosis (Ferri, et al., 2002; LeRoy et al., 1988). Predictors of poor outcome in SRC include male gender, age above fifty years, cardiac disease and dcSSc with extensive skin sclerosis (higher skin score) (Denton, Lapadula, Mouthon, & Muller-Ladner, 2009; Teixeira, et al., 2008). Normal blood pressure at presentation has also been associated with a poor prognosis (Medsger, Masi, Rodnan, Benedek, & Robinson, 1971; Penn, et al., 2007; Teixeira, et al., 2008). Patients with normotensive SRC could possibly have lower activation of their renin-angiotensin system and therefore a lower blood pressure at presentation (Penn, et al., 2007). The poor prognosis observed in the latter group might be attributed to a possible delay in diagnosis and treatment (Haviv & Safadi, 1998; Helfrich, et al., 1989).

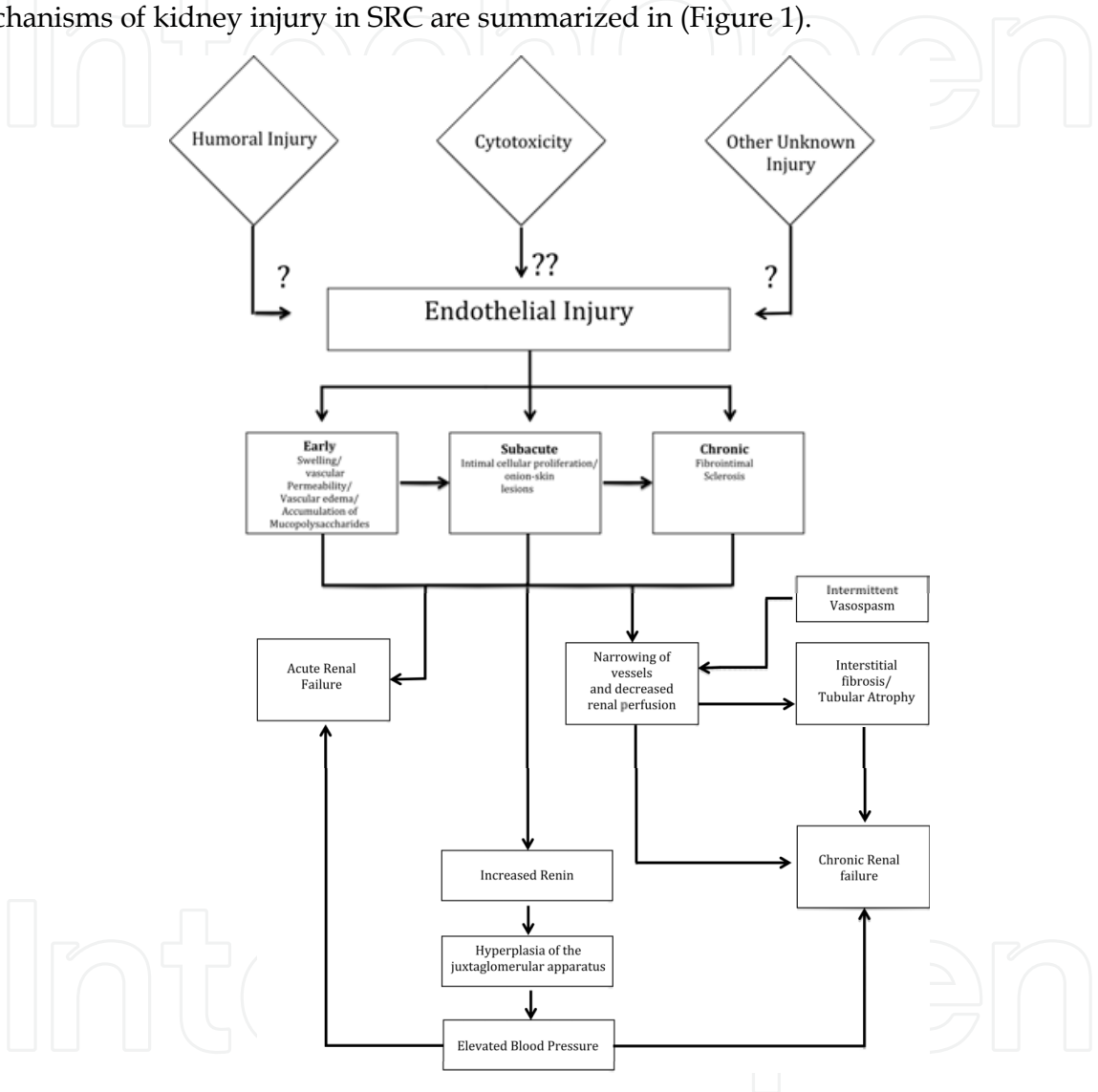
### 3. Pathophysiology

Despite efforts to investigate the underlying immune mechanisms, the pathophysiology of SRC remains incompletely understood. Injury to the vascular endothelium appears to play a key role in activating the pathological cascade of SRC. Endothelial injury leads to increased endothelial permeability, vascular edema, accumulation of mucopolysaccharide material, and proliferation of intimal cells. If the injury is sufficiently severe, endothelial damage can initiate arteriolar and arterial fibrinoid necrosis and vascular thrombosis through platelet activation and adhesion to the sub-endothelium (Batal, Domsic, Medsger, & Bastacky, 2010; Fisher & Rodnan, 1958; Steen, 2003). With time, these changes can organize leading to fibrointimal thickening and narrowing of the small arteries (Cannon et al., 1974; Fisher & Rodnan, 1958). Intimal arteritis, manifested as lymphocytic and mononuclear cell infiltration, is typically absent in SRC (Steen, 2003). Even though collagen overproduction and accumulation is well established in the skin and lung lesions of SSc patients, collagen's role in early kidney lesions appears less important. Increased collagen appears later in the form of vascular fibrointimal and adventitial thickening or as interstitial fibrosis. The latter is often attributed to decreased perfusion due to chronic ischemic vasculopathy.

Intermittent vasospasm of renal arteries, also known as renal Raynaud's phenomenon, has also been proposed as a potential contributor to SRC-induced kidney injury (Cannon, et al., 1974); Traub et al. reported an increase in the frequency of SRC in the winter suggesting cold-induced vasoconstriction of renal arteries (Traub, et al., 1983). Vasospasm can also participate in renal injury in SSc patients even in the absence of SRC. Following cold pressor testing, Cannon et al. demonstrated a significant reduction in renal cortical blood flow in SSc patients when compared to control subjects (Cannon, et al., 1974). In addition, Doppler studies showed increased vascular resistance in SSc patients without concurrent renal damage (Rivolta et al., 1996). Nevertheless, Raynaud's phenomenon does not appear to be the only explanation of renal injury in SSc patients without SRC. In an autopsy-based study, Trostle et al. were able to show well established anatomic vascular changes in the form of fibrointimal thickening in SSc patients without SRC (Trostle, Helfrich, & Medsger, 1986).

Regardless of the cause, reduction in kidney perfusion causes subsequent hyperplasia of the juxtaglomerular apparatus (JGA) and increased renin secretion (Stone, Tisher, Hawkins, &

Robinson, 1974). Kovalchik et al. (Kovalchik, Guggenheim, Silverman, Robertson, & Steigerwald, 1978) proposed that renin production in SSc patients may be proportional to the severity of vascular lesions. These authors also suggested that a substantial increment in plasma renin activity in response to cold pressor testing could identify SSc subjects with a preclinical renal involvement. However, more recent studies revealed that plasma renin levels are neither sensitive nor predictive for SRC. Hyperreninemia has been described in asymptomatic SSc patients who did not develop SRC (Mouthon, et al.). The potential mechanisms of kidney injury in SRC are summarized in (Figure 1).



Abbreviation: ?, Potential strong association; ??, potential weaker association; MPS, mucopolysaccharide

Fig. 1. Potential mechanisms of injury in scleroderma renal crisis.

Endothelin-1 is a peptide produced mainly by endothelial cells. It has three isoforms ET-1, ET-2 and ET-3. ET-1 binds to ET type A and ET type B receptors on muscular and endothelial cells (Tirapelli et al., 2005). It modulates vascular constriction and smooth muscle cell proliferation (Hirata, 1989; Takuwa, Takuwa, Yanagisawa, Yamashita, & Masaki, 1989). Accumulating data suggest that the latter might play an important role in the pathogenesis of scleroderma. Higher serum ET-1 levels were detected in SSc compared to healthy controls (Vancheeswaran et al., 1994). In kidney specimens, overexpression of ET-1



and ET type B receptors were described in two patients who died following SRC (Kobayashi et al., 1999). Mouthon et al. extended the aforementioned observations by studying the pattern of ET-1 expression in kidney biopsies utilizing the immunoperoxidase technique (Mouthon et al.). These investigators found glomerular and vascular overexpression of ET-1 in SRC specimens. In comparison, normal kidney biopsies revealed negative ET-1 glomerular staining and only weak vascular staining. In contrast, biopsies from patients with hemolytic uremic syndrome (HUS) showed increased ET-1 expression on the glomerular but not the vascular endothelium. ET-1 expression was largely detected in areas of glomerular capillary wall thickening, glomerular and vascular thrombosis, and vessels with either mucoid changes, onion-skin lesions, or fibrointimal thickening. Of note, ET-1 was recently identified as one of the most up regulated endothelial transcripts in allografts following antibody-mediated rejection<sup>48, 49</sup>.

C4d is an early complement split product of the classical pathway of activation. When detected in the peritubular capillary of an allograft biopsy, it is very suggestive of the diagnosis of antibody-mediated rejection (Racusen et al., 2003). Using immunoperoxidase techniques, we could detect similar pattern of C4d staining in a subset of SRC patients who had poor renal outcome (Batal et al., 2009). Nevertheless, the presence and/or significance of C4d deposits in SRC should be confirmed in larger studies using the more specific immunofluorescence techniques.

In summary, accumulating data suggest the contribution of antibody-mediated injury in the pathogenesis of SRC; First, specific autoantibodies have been associated with the development of SRC. Second, the detection of peritubular capillary C4d staining has been demonstrated in occasional patients with SRC. Third, ET-1 is overly expressed in SRC biopsies.

In contrast, while the role of cytotoxicity is well accepted in SSc, cytotoxicity was not systematically studied in SRC. The presence of peritubular capillary and tubulointerstitial inflammation in some SRC biopsies suggests a possible contribution of cytotoxicity to kidney injury. An immunohistochemical study to look at granzyme-B<sup>+</sup> cells in such biopsy in association with apoptosis of endothelial cells might be an initial step to investigate such possibility.

Several factors such as pericardial effusion, arrhythmia (McWhorter & LeRoy, 1974; Satoh et al., 1995; Steen et al., 1984), pregnancy (Karlen & Cook, 1974), sepsis (Steen, 2003), non steroidal anti-inflammatory drugs (NSAID) and cocaine (Lam & Ballou, 1992) can decrease renal perfusion and precipitate or aggravate SRC in SSc patients. Corticosteroids are also believed to trigger SRC; high dose prednisone might inhibit prostacyclin levels, increase in angiotensin converting enzyme (ACE) activity and subsequent vasoconstriction (Sharnoff, Carideo, & Stein, 1951).

Animal models are important tools to expand our knowledge of a particular disease process. They offer the advantage of developing targeted therapies to diseases without placing patients at risk of a direct intervention. Several experimental animal models of scleroderma have been developed (Yamamoto). One of the better-known models is bleomycin-induced scleroderma. A repeated intradermal or subcutaneous injection of bleomycin into rats and mice leads to the development of dermal sclerosis (Mountz et al., 1983; Yamamoto; Yamamoto & Nishioka, 2001, 2002, 2004; Yamamoto et al., 1999; Yamamoto, Takahashi, Takagawa, Katayama, & Nishioka, 1999). The latter is microscopically characterized by the deposition of thick collagen bundles, homogeneous acellular material, and cellular infiltrates of T-cells, macrophages, and mast cells. Ishikawa et al. has recently shown that the adoptive transfer of CD4<sup>+</sup> T-cells from bleomycin-treated mice into untreated BALB/c nude mice

induced a similar pathological picture with autoantibody production (Ishikawa, Takeda, Okamoto, Matsuo, & Isobe, 2009). Dermal sclerosis in this animal model is generally limited to the areas of bleomycin-injection and sclerotic changes are not observed in fingers or abdominal skin. In addition to rodent animal models, UCD-200 chicken is another extensively studied SSc animal model. In addition to clinical manifestations, UCD-200 is one of the very few SSc models that display renal abnormalities. Endothelial cell apoptosis has been described in the kidneys of such animals. However, the histologic picture is different from what is typically observed in humans with SRC. In contrast to the typical thrombotic microangiopathic pattern of injury, the kidneys of UCD-200 chicken are characterized by the presence of glomerulonephritis associated with IgG deposition and thickening of the muscular vascular layer (Gershwin et al., 1981; V. A. Nguyen, Sgonc, Dietrich, & Wick, 2000). From this model, one can conclude that SRC falls behind cutaneous sclerosis with regard to *in vivo* models. To date, SRC still lack a well-accepted animal model.

Finally, one should remember that despite its importance in facilitating our understanding of the pathophysiology and treatment options, differences do exist between human and murine immune systems. The use of "humanized mouse model" (Pearson, Greiner, & Shultz, 2008; Zhang, Meissner, Chen, & Su, 2010), a small immune compromised murine model possessing a functional reconstituted human immune system, might offer a potential way to overcome some existing frustrations in improving scleroderma treatment.

#### 4. Gross pathology

Macroscopic changes observed in SRC are relatively nonspecific, since similar changes can be encountered in other thrombotic microangiopathic disorders. Petechial hemorrhages are frequently observed on the surface of the affected kidneys while cut sections commonly reveal small wedge shaped infarcts or, less often, larger foci of cortical necrosis (Fisher & Rodnan, 1958).

#### 5. Microscopic pathology

##### 5.1 Light microscopy

In the absence of acceptable animal models, our current knowledge of the renal pathologic changes in SRC is largely derived from histologic assessment of kidney biopsy specimens performed during such crises. Autopsy materials provide another source to study the morphologic alterations of this disease, although the histologic changes in autopsy specimens often reflect a clinically severe and prolonged form of the disease typically associated with end stage renal failure. A complete understanding of the spectrum of pathologic changes in SRC is also limited by the low incidence of the disease and the fact that renal biopsies are not routinely performed during the crisis. Such biopsies are basically recommended when doubt exists about the etiology of renal dysfunction or, alternatively, to exclude the coexistence of other diseases.

The histologic manifestations may vary during the course of the disease and the pathologic changes predominate in small vessels and arterioles rather than larger arteries. Early vascular changes can manifest as intimal edema and accumulation of acid mucopolysaccharide material (Figure 2), which is positively stained with Alcian blue or toluidine blue. Other early vascular changes include thrombosis (Figure 3) and/or fibrinoid necrosis. Onion-skin lesions develop later as a result of cellular proliferation (Figure 4).



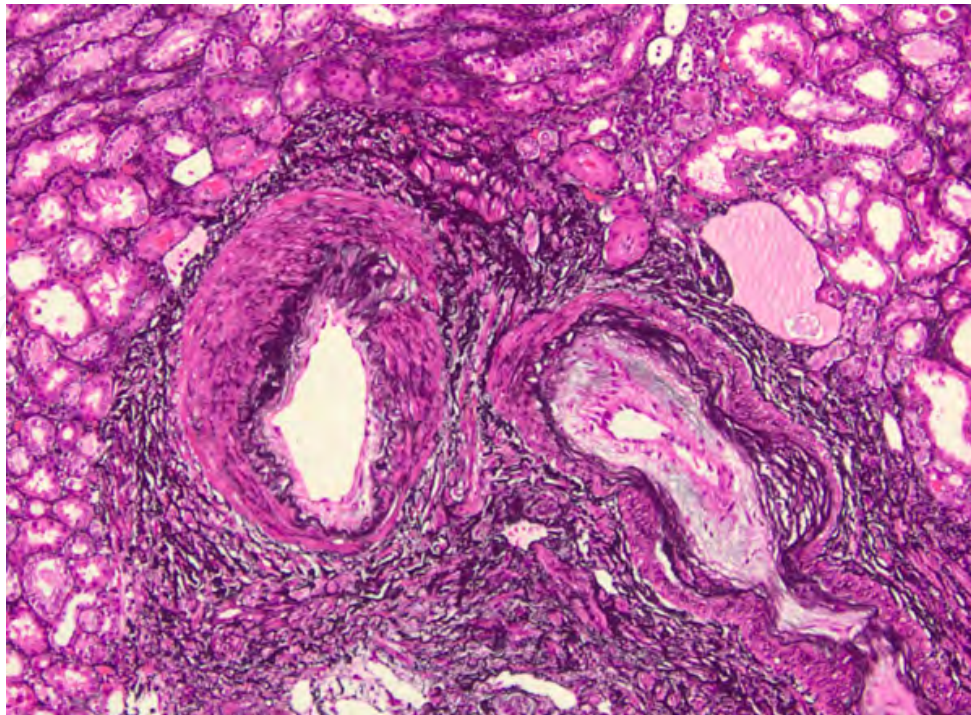


Fig. 2. Intimal accumulation of mucoid material (artery on the right) with associated adventitial fibrosis (artery of the left) in a patient with scleroderma renal crisis. (Methenamine silver stain; original magnification x100) (Batal, et al., 2010).

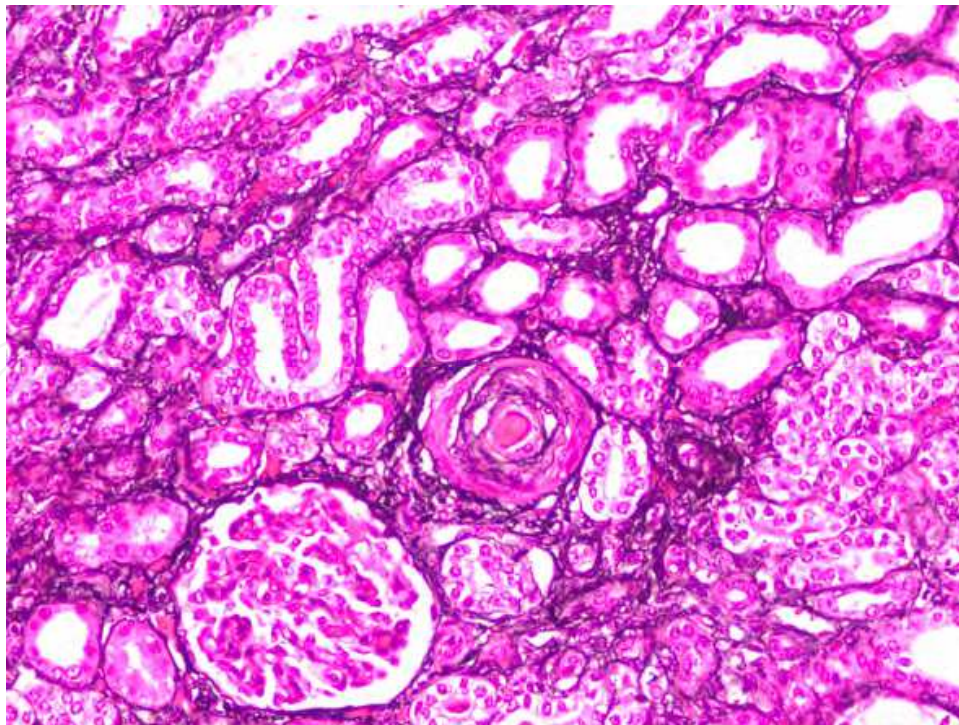


Fig. 3. Arterial thrombosis (middle) and glomerular ischemic collapse (lower left) in a patient with scleroderma renal crisis (Methenamine silver stain; original magnification x100) (Batal, et al., 2010)



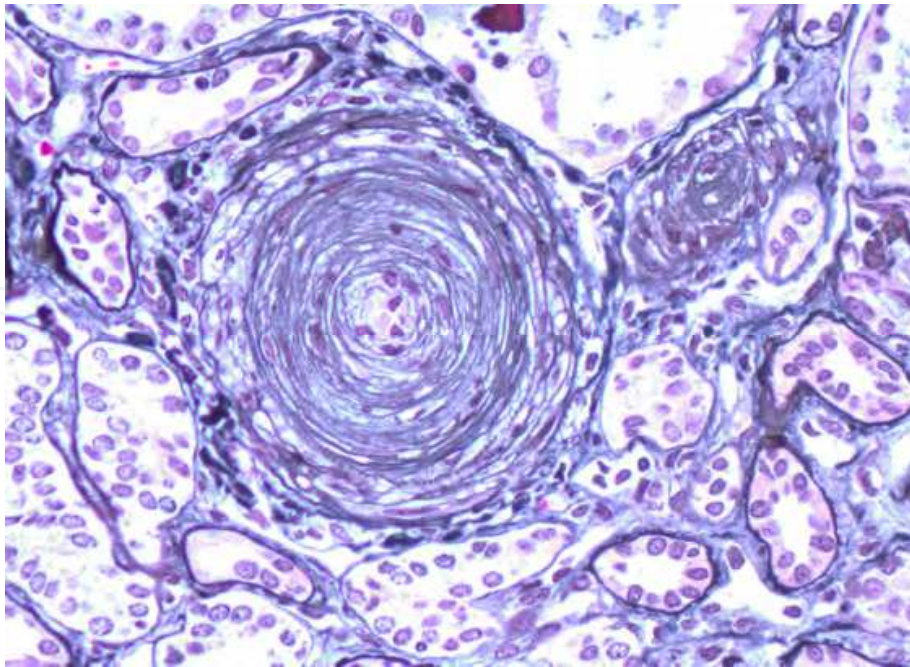


Fig. 4. Onion skin lesion causing severe vascular narrowing in a patient with scleroderma renal crisis (Methenamine silver stain; original magnification x400) (Batal, et al., 2010).

Fibrointimal sclerosis with or without adventitial fibrosis may be the result of chronic ongoing damage or, alternatively, can represent a manifestation of burned-out injury from a previous attack. Glomerular changes can be classified as acute or chronic. Acute glomerular changes manifests usually as endothelial swelling and glomerular capillary thrombosis (Figure 5).



Fig. 5. Glomerular thrombosis in a patient with scleroderma renal crisis. Note the associated mild podocytic proliferation (Methenamine silver stain; original magnification x600) (Batal, et al., 2010).

Severe glomerular injury can lead to segmental glomerular fibrinoid necrosis or mesangiolysis. Fragmentation of red blood cells and fibrin deposits can be observed within the glomerular capillaries. These findings might sometime reflect a concurrent peripheral micro-hemolytic anemia (Salzer, Salzer, & Heptinstall, 1973). A common form of secondary glomerular injury is glomerular ischemic collapse due to decreased arterial perfusion. Glomerular ischemic collapse is characterized by wrinkling and thickening of the capillary walls and shrinkage of the glomerular tuft. Repetitive glomerular endothelial cell damage results in significant remodeling of the glomerular capillary walls, with glomerular basement membrane double contours (tram tracking) and a membranoproliferative pattern of injury. In more subtle cases, these changes can be focal and segmental, but over time and with more extensive injury, the remodeling becomes more complex and involves the majority of the glomerular capillary loops. The membranoproliferative pattern in thrombotic microangiopathies is usually associated with less mesangial proliferation, when compared to immune complex-mediated diseases with a similar pattern of injury by light microscopy. Endothelial cell injury, however, may result in mesangiolysis and resultant mesangial expansion that leads to nodular glomerulosclerosis as the process heals.

Tubulointerstitial changes, usually occurring secondary to vasculopathy, are frequently manifested acutely as ischemic acute tubular injury/necrosis or, chronically, as tubular atrophy and interstitial fibrosis. A lymphohistiocytic interstitial inflammatory infiltrate can infrequently be observed. Mild leukocytic margination in the peritubular capillaries can occasionally be encountered. Small renal infarcts might be observed secondary to vascular injury. Early in the course of infarction, neutrophils accumulate at the junction between affected and non-affected areas while mononuclear cells predominate later.

The overall histologic picture is that of a thrombotic microangiopathic process (Fisher & Rodnan, 1958; Mouthon et al., 2011). No histologic feature is absolutely pathognomonic for SRC. However, in contrast to hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, small vessel changes predominate over glomerular changes in SRC. In hemolytic uremic syndrome, Tostivint et al. showed that thrombotic microangiopathic alterations were more frequently encountered in the glomeruli compared to small vessels [11/12 (92%) versus 4/12 (33%),  $p = .009$ ] (Tostivint et al., 2002). In SRC, thrombi were more commonly detected in small vessels [11/17 (65%) small vessels thrombi versus 3/17 (18%) glomerular thrombi,  $P = .01$ ] (Batal, et al., 2009).

Small vessels in SRC may display thinning of the media and/or adventitial expansion.

A few investigators suggest that the latter (Figure 2) is specific for SRC, but more data are needed to support this concept (Cannon, et al., 1974). Juxtaglomerular (JGA) hyperplasia can be observed in SRC and is believed to be associated with increased renin production (Stone, et al., 1974)(Figure 6). However, this feature is not entirely specific for SRC (Okada, Lertprasertsuke, & Tsutsumi, 2000), and is not a consistent finding. We detected a prominent JGA hyperplasia only in 12% of our SRC cases (Batal, et al., 2009).

Finally, it should be noted that vascular pathologic changes in scleroderma patients are not restricted to SRC. Trostle et al. used morphometric techniques to study vascular changes in autopsy specimens (Trostle, et al., 1986). In the absence of SRC, Trostle et al. were able to demonstrate a significant increase in arterial fibrointimal thickness in dcSSc patients, and to a lesser extent in lcSSc patients, compared to age and sex matched controls. These observations might be explained by a possible existence of mild ongoing renal vascular injury below the threshold needed to trigger SRC.



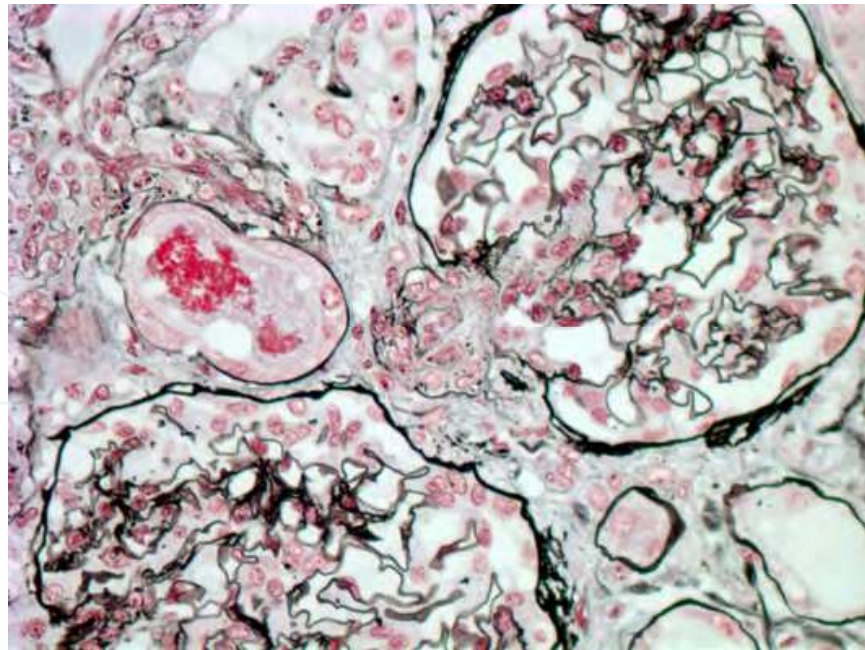


Fig. 6. Prominent juxtaglomerular apparatus (middle) in a patient with scleroderma renal crisis (Methenamine silver stain; original magnification  $\times 400$ ) (Batal, et al., 2010).

## 5.2 Immunofluorescence microscopy studies

Immunofluorescence microscopy studies typically reveal no evidence of an immune complex-mediated renal disease, unless the patient suffers from overlap syndrome. IgM deposition, which is frequently attributed to nonspecific entrapment, is the most frequently detected immunoglobulin in the glomeruli and/or blood vessels (Lapenas, Rodnan, & Cavallo, 1978; McCoy, Tisher, Pepe, & Cleveland, 1976; McGiven, De Boer, & Barnett, 1971). Similarly, complement deposits are frequently detected. Fibrin or fibrinogen deposition might also be observed in severely affected vessels or along the glomerular capillaries, usually with dull continuous reactivity. Identical findings are seen also in thrombotic angiopathies within other clinical settings.

## 5.3 Electron microscopy

Ultrastructural evaluation typically reveals severe endothelial cell injury. Well-formed electron dense deposits are not detected in SRC. However, hyaline material, which can sometime be difficult to distinguish from definite immune deposits, might accumulate in the sub-endothelium of the glomeruli and/or blood vessels (Silva & Pirani, 1988). Endothelial cell swelling and accumulation of sub-endothelial flocculent material and cell debris is a common finding in SRC (Figure 7). Injured endothelial cells detach from the underlying basement membrane and in most severe cases, the endothelial cells may be completely sloughed off and missing. As the endothelium recovers from the injury, it will re-grow the remodeled endocapillary surface and form a new basement membrane layer, resulting in double contour formation. The repair is usually irregular, resulting in complex asymmetrical glomerular basement membrane with projections and deposits of cellular debris in the expanded subendothelial space. The resultant pattern of glomerular wall injury is membranoproliferative in the absence of electron dense deposits. Within the expanded fibrointima of the small vessels, myointimal cells can also be demonstrated (Salomon, Lamovec, & Tchertkoff, 1978).

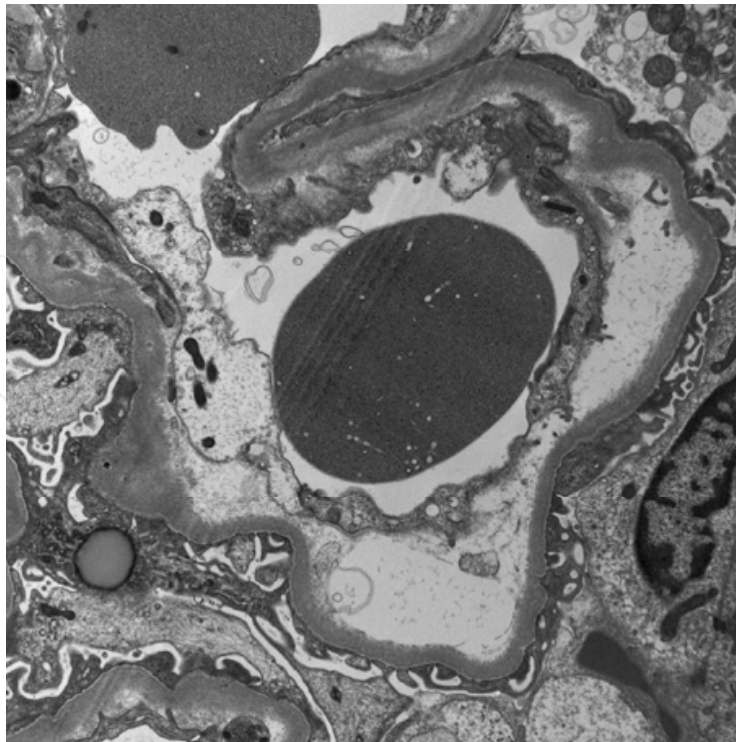


Fig. 7. Electron microscopic picture from a patient with scleroderma renal crisis. Note the prominent sub-endothelial electron lucent fluffy material (Electron microscopy; original magnification x5600)(Batal, et al., 2010).

## 6. Differential diagnosis (native kidneys)

As alluded to in paragraph four (Microscopic Pathology), acute SRC is very difficult if not impossible to be differentiated from other thrombotic microangiopathies based on histologic examination alone. Thrombotic microangiopathy is a pathologic term that encompasses a number of clinical conditions that appear to be triggered by endothelial injury. In addition to the rare SRC, this pattern of injury includes, although it is not limited to, thrombotic thrombocytopenic purpura (TTP), typical and atypical HUS, preeclampsia, antiphospholipid antibody syndrome, drug-induced thrombotic angiopathy (chemotherapy, cocaine, calcineurin inhibitors), and what is known as "idiopathic malignant hypertension". Disseminated intravascular coagulation (DIC) also enters the differential diagnosis. The latter is usually characterized by diffuse cortical necrosis and widespread glomerular, vascular and intratubular microthrombi (Kawasaki, Hayashi, & Awai, 1987). However, arterial mucoid changes and fibrinoid necrosis are usually absent. DIC is very rarely encountered in surgical pathology samples compared to autopsy specimens.

The differential diagnosis of chronic/burned-out SRC is broad. These cases often show signs of organization such as glomerular capillary double contours and glomerular scarring, and vascular sclerosis and fibrointimal thickening. In some cases, the aforementioned glomerular double contour can be associated with mesangial sclerosis and mild hypercellularity reminiscent to membranoproliferative glomerulonephritis pattern of glomerular injury. Membranoproliferative pattern of glomerular injury is typically seen in three types of disorders, including immune complex-mediated disorders (such as



autoimmune diseases and chronic infections), paraprotein and other deposition diseases (such as monoclonal immunoglobulin deposition disease, fibrillary glomerulonephritis, and immunotactoid glomerulopathy), and thrombotic microangiopathies. Immunofluorescence and ultrastructural studies are essential in distinguishing these three groups of disorders. The presence of polyclonal or monoclonal immunoglobulin deposition that show dense deposits with or without organized substructures, favors immune complex and other deposition diseases. In contrast, the absence of immunoglobulin deposition and the dull continuous reactivity for fibrin along the glomerular capillary loops by immunofluorescence studies, together with the absence of dense deposits by electron microscopy, characterize various forms of thrombotic microangiopathies.

From a clinical perspective, one should remember that not all acute renal failure in SSc patients is due to SRC. Distinguishing SRC from crescentic GN is important since immunosuppressive therapy can exacerbate the former, but is used to treat the latter. The hallmark of crescentic GN is the presence of glomerular extracapillary proliferative lesions (crescents). As in non SSc patients, the most common form of crescentic GN in SSc patients is pauci-immune ANCA-associated GN, followed by immune complex GN (Ramaswami et al., 2008) and anti-glomerular basement membrane GN (Namba et al., 2008). In these cases, immunofluorescence studies are necessary for a correct sub classification. They are negative in the first; reveal granular immune complex deposits in the second, and linear glomerular basement membrane IgG staining in the third group of diseases. In contrast, crescents are typically absent in typical SRC, and if present, they are rare and very small (Kamen, Wigley, & Brown, 2006; Ramaswami, et al., 2008). Ischemic glomerulopathy lesions in SRC can sometime be accompanied by extracapillary epithelial cell proliferation, which can occasionally mimic a crescentic proliferative process. However, these ischemic “pseudocrescents” are characterized by the absence of necrotizing lesions, extracapillary fibrin, or glomerular basement membrane destruction. Furthermore, although each of crescentic glomerulonephritis and thrombotic microangiopathies can show vascular thrombosis and/or fibrinoid necrosis, one should remember that small vessel vasculitis/inflammatory changes are frequently observed in the former but are typically absent in the latter.

Lastly, in addition to confirming the diagnosis, renal biopsy may help in predicting the clinical outcome in SRC patients. A few studies have investigated the prognostic values of different histologic parameters in SRC. When expressed as binary variables (presence/absence), Penn et al. found that the presence of mucoid edema or vascular thrombosis was associated with a suboptimal renal outcome (Penn, et al., 2007). We extended Penn et al. observations by demonstrating that the severity and extent of acute vascular damage and its consequences, namely arterial thrombosis/fibrinoid changes and glomerular ischemic collapse, were indeed predictors of poor prognosis (Batal, et al., 2009). In contrast to the study by Penn et al., we could not associate mucoid changes with poor renal outcome.

## 7. Treatment

Before the advent of angiotensin converting enzymes (ACE) inhibitors, nephrectomy or dialysis were the only available treatment options for SRC (Mitnick & Feig, 1978; Traub, et

al., 1983). At that time, less than 10% of patients with SRC survived more than five months (Steen, 2003). ACE inhibitors were first introduced as a potential treatment of SRC in the late 1970s (Lopez-Ovejero et al., 1979). Since then, they have altered the management and outcome of this disease (Thurm & Alexander, 1984; Zawada et al., 1981), considerably increased patients' five year survival (up to 65%) (Steen, 2003) and rapidly became the first line of treatment of both hypertensive and normotensive SRC (Steen, 2003). Bosentan is an endothelin receptor blocker which is also considered a first line therapy (Dhaun, MacIntyre, Bellamy, & Kluth, 2009). However, Bosentan did not show any significant advantage over ACE inhibitors in regards to mortality and outcome (Patel et al., 2009). While angiotensin receptor blockers (ARBs) had promising results in animals with hypertension, clinical experience with these agents has not been very convincing (Siragy, de Gasparo, El-Kersh, & Carey, 2001). Currently, these medications are only considered in patients who cannot tolerate ACE inhibitors (Caskey, Thacker, Johnston, & Barnes, 1997; Mouthon, et al.; Steen, 2003).

In patients with SRC started on ACE inhibitors, one should aim for a blood pressure of 120/70 mm Hg (Steen, 2003). If this is not achieved within 12 hours of initiation of therapy, then intravenous calcium channel blocker therapy should be considered. Conservative medical treatment alone can successfully control blood pressure in approximately 30-40% of SRC patients. These patients usually have a good prognosis. However, despite this aggressive therapy, a proportion of patients (~20%) die within three months of the onset of SRC due to multiorgan failure. Subjects in this group are often older males, presenting with highly elevated serum creatinine and have pre-existing cardiac conditions (Steen & Medsger, 2000a). In the remaining patients, the aforementioned medications fail to normalize blood pressure and dialysis should be initiated. Of note, patients requiring temporary dialysis (up to 18 months) had a five-year survival comparable to SSc patients who never had SRC (90%). In contrast, patients who required permanent dialysis had a considerably lower five-year survival (40%). A large subset of these patients fails to recover renal function and require renal transplantation (Penn, et al., 2007; Steen & Medsger, 2000a).

## 8. Transplantation

Transplantation should be considered when renal failure persists beyond 18 months from initiation of dialysis (Steen, 2003). In SRC, graft and patient survival post-transplantation is inferior to general renal transplant patient (Pham et al., 2005). Recurrence of scleroderma may participate in this poor outcome (Cheung, Gibson, Rush, Jeffery, & Karpinski, 2005). Post-transplant recurrence of SRC has been reported even after transplantation from a twin sister (Caplin, Dikman, Winston, Spiera, & Uribarri, 1999; Woodhall, McCoy, Gunnells, & Seigler, 1976). Pham et al. (Pham, et al., 2005) suggested that SRC recurrence occurs early in the post-transplantation course. However, Cheung et al. (Cheung, et al., 2005) challenged this view when describing a late SRC recurrence observed seven years post-transplantation. From a histologic perspective, establishing a diagnosis of recurrent SRC in a renal allograft is more difficult than in a native kidney biopsy. The differential diagnosis in this case is broader and includes acute antibody-mediated rejection, acute calcineurin inhibitor toxicity, and occasionally infections such as CMV. Any other thrombotic microangiopathic disease described in native kidneys can also manifest in the allograft as *de novo* thrombotic

microangiopathic process (Liptak & Ivanyi, 2006). Chronic SRC changes are even more challenging. Glomerular double contour resulting from SRC can be indistinguishable from chronic transplant glomerulopathy, which has been recognized as a histologic manifestation of chronic antibody-mediated rejection. Therefore, a careful clinicopathological and immunological correlation with serum creatinine changes, blood pressure, circulating donor-specific antibody, calcineurin inhibitor levels, and opportunistic infections are highly important to achieve a correct diagnosis. A careful assessment of C4d in allograft biopsies could also suggest the diagnosis of antibody-mediated rejection (Racusen, et al., 2003). However, one should keep in mind that a few patients with SRC might show some levels of peritubular capillary C4d staining while in contrast, C4d staining may be absent in some cases of antibody-mediated rejection. C4d negative antibody-mediated rejection cases have also been recently described (Haas, 2011; Sis & Halloran, 2010).

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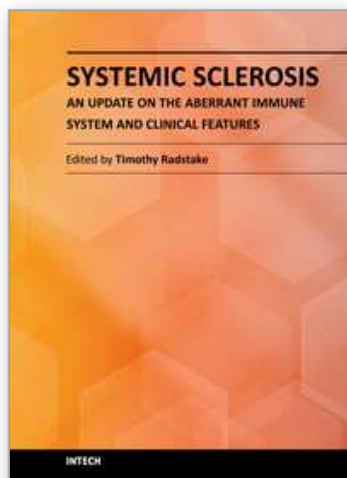
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## **Systemic Sclerosis - An Update on the Aberrant Immune System and Clinical Features**

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Systemic sclerosis (SSc), or often referred to as Scleroderma (tight skin), is characterized by an exaggerated formation of collagen fibers in the skin, which leads to fibrosis. Accumulating evidence now points toward three pathological hallmarks that are implicated in Ssc, the order of which has yet to be determined: endothelial dysfunction, autoantibody formation, and activation of fibroblasts. This current book provides up-to-date information on the pathogenesis and clinical features of this severe syndrome. It is our hope that this book will aid both clinicians and researchers in dealing with patients with this clinical syndrome. In addition, we hope to shed more light on this rare and severely disabling syndrome, ultimately leading to better research and successful therapeutic targeting.

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