CLINICAL OBSERVATIONS

# Challenges in diagnosis and treatment of scleroderma renal crisis (clinical case report)

**Mishina E.M., Ananyeva L.P., Evsikova M.D., Koneva O.A.**

*V.A. Nasonova Research Institute of Rheumatology, Moscow*
*34A, Kashirskoye Shosse, Moscow, 115522, Russia*

*The pathogenesis and diagnostic approaches to scleroderma renal crisis (SRC) – an acute "scleroderma kidney" – a severe and life-threatening complication of systemic sclerosis (SSc) characterized by high mortality, are discussed. Due to limited understanding of the underlying pathogenic mechanisms, a standardized treatment for SRC has not been developed.*

*We describe the development of acute SRC in a 43-year-old female patient with diffuse form of SSc of 1.5 years' duration, rapidly progressive disease course, and internal organ involvement associated with high immunological activity. This case is notable in that the renal crisis developed during hospitalization and was observed from the earliest days under well-documented therapy. The treatment involved the use of several agents with different mechanisms of action, including rituximab, mycophenolate mofetil, a phosphodiesterase-5 inhibitor (sildenafil), and courses of prostanoids. The glucocorticoid dose remained low (methylprednisolone 8 mg/day). Complete resolution of SRC was achieved with restoration of renal function.*

***Keywords:*** *scleroderma renal crisis; systemic sclerosis; rituximab; prostanoids.*
***Contact:*** *Lidiya Petrovna Ananyeva;* ***lpana@yandex.ru***
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Systemic scleroderma (SSC), or progressive systemic sclerosis, is a multisystem rheumatic disease. The pathogenesis of SSC is based on immune disorders and vasospastic vascular reactions like Raynaud's phenomenon, accompanied by activation of fibrogenesis and excessive deposition of collagen in tissues and organs [1].

The main clinical signs of SSC include skin lesions in the form of thickening and hyperpigmentation, Raynaud's syndrome, associated ischemic peripheral disorders, and inflammatory fibrotic lesions of the musculoskeletal system. In addition, this disease often affects internal organs: the lungs, gastrointestinal tract, cardiovascular system, and kidneys [2]. Pulmonary fibrosis, pulmonary arterial hypertension (PAH), cardiopathy with rhythm and conduction disorders, hypotension of the esophagus and other parts of the gastrointestinal tract, as well as acute scleroderma renal crisis (SRC) with the development of renal failure are recorded with varying frequency. SSC is accompanied by a high mortality rate, higher than any other rheumatic disease, despite some improvement in survival in recent years. The prognosis is worse in patients with diffuse skin lesions, which correlate with the development of manifestations that are potentially fatal or may reduce the quality of life, and with a high uncertainty of outcome. By the end of the last century, the structure of mortality in SSC had changed. Until the 1980s, the leading cause of death was renal failure caused by acute nephropathy ("scleroderma kidney", or acute SRC). In recent decades, the leading position among the causes of death has been occupied by pulmonary pathology – interstitial lung disease (ILD) and PAH. These conditions account for 60% of deaths directly related to SSC [3].

Kidney damage in SSC is not a common manifestation. However, according to the autopsy material, renal pathology is detected in 60-80% of patients. Such patients initially have no symptoms of kidney damage, only minor proteinuria and microscopic hematuria may occur with moderate arterial hypertension (AH) and normal kidney function. [4] According to the combined data from five different studies involving 796 patients with SSC, glomerular filtration rate (GFR) <90 ml/min was recorded in 31.5% of patients, and in 19.5% it was <60 ml/min. In patients with renal dysfunction, a kidney biopsy reveals tissue fibrosis and vasculopathy [5]. These changes usually do not progress, and renal dysfunction tends to increase at a rate similar to that in the general population [6].

The most prognostically significant and studied form of kidney damage in SSC, accompanied by a dramatic clinical course, is SRC. SRC is a rare but life–threatening complication of SSC characterized by acute onset of malignant hypertension and the development of rapidly progressive renal failure. As a rule, SRC occurs early, in the first years after the onset of the disease, and always reflects the severity of the disease, being one of the most reliable markers of unfavorable prognosis. SRC is always a difficult problem for a doctor, since preventive measures are not yet available, and the crisis develops very quickly, even in cases of initially correct treatment of the disease. The SSC phenotype, in which SRC is most often observed, is well studied, therefore, strict monitoring of such patients makes it possible to detect this condition early. There are known risk factors for the development of SRC: male sex, short (<5 years) duration of the disease, with 75% of cases of crisis occurring in the 1st-4th year of the disease [7], diffuse form (pronounced skin thickening with a skin score of >20 points), progressive damage to internal organs, as well as synovitis, tenosynovitis, flexor contractures of large joints. An increase in the level of antibodies to RNA polymerase III, as well as to topoisomerase I, is considered an immunological marker of SRC [8]. Glucocorticoids (GCs) are of particular importance for the development of SRC [9]. GC treatment is considered a significant risk factor for SRC development in patients who took medium or high doses of GCs at the onset of the disease [10]. It has been shown that a daily dose of ≥15 mg (in prednisolone equivalent) is

associated with a significant increase in the risk of SRC, so currently the use of GC at a dose of >15 mg/day is not recommended, especially in patients with risk factors for SRC [11].

SRC is caused by severe occlusive damage to the intrarenal vessels. It is based on mechanisms leading to a decrease in glomerular blood flow, including renal vascular spasm ("renal" Raynaud's syndrome), direct exposure to angiotensin 2. It is believed that GCs can directly contribute to the development of SRC by inhibiting prostacyclin production and increasing the activity of angiotensin converting enzyme (ACE).

A distinctive pathogenetic feature of SRC is the generalized nature of the expression of vasoconstriction mediators in the renal tissue: for example, overexpression of endothelin 1 can be detected in both glomerular endotheliocytes and arterioles. A disorder of intrarenal hemodynamics with increasing ischemia of the renal tissue leads to hyperproduction of renin, followed by activation of the renin-angiotensin-aldosterone system (RAAS). As a result, there is a persistent spasm of the afferent and efferent arterioles of the renal glomeruli with further aggravation of intrarenal hemodynamic disorders, which can lead to arterial hypertension with malignant features and acute oligoanuric renal failure.

The realization of the non-hemodynamic effects of angiotensin II and aldosterone is complemented by thrombogenesis at the level of the renal microcirculatory system. The involvement of platelets in the development of SRC is associated with the phenomena of aggregation and release of platelet factors at the vascular wall level [12]. Thrombotic microangiopathy (TMA) is found in 43% of cases of SRC [13]. Laboratory signs of TMA are thrombocytopenia, which occurs as a result of platelet aggregation and consumption, and hemolytic anemia detected by signs of erythrocyte fragmentation on microscopic examination of peripheral blood smears; erythrocyte fragmentation occurs in the areas of turbulent flow in the microcirculation due to partial occlusion by platelet aggregates. An increase in lactate dehydrogenase (LDH) levels as a result of cell lysis and tissue ischemia, low haptoglobin content, and a negative direct Coombs test are characteristic [14].

The progression of SRC is associated with intense fibrotic transformation of both glomeruli and structures of the renal tubulointerstitium, as well as intrarenal vessels with simultaneous accumulation of extracellular matrix. In some cases, some concomitant pathological immunological phenomena potentially associated with SSC may be directly involved in the pathogenesis of SRC, for example, antibodies to cardiolipin, in the presence of which TMA prevails in the renal lesion, as well as antibodies to neutrophil cytoplasm, which cause the formation of SRC similarly to rapidly progressing glomerulonephritis in systemic necrotizing vasculitis. The involvement of the genetic markers HLA-DRB1*1407 and HLA-DRB1*1304 in the development of SRC is currently being discussed [15].

The diagnosis of SRC presents certain difficulties. Currently, the following classification criteria of SRC are used in real practice [16]:

– Acute increase in blood pressure (BP), defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, often occurs after treatment with high doses of GCs. In 10% of cases of SRC blood pressure is normal. Normotensive forms are characterized by a higher incidence of TMA and a worse prognosis, earlier replacement therapy and high mortality. Due to the progression of renal insufficiency, blood pressure remains within the normal range, which makes it difficult to diagnose this complication in a timely manner.
– Acute kidney injury: an increase in the level of serum creatinine ≥26.5 mmol/L (≥0.3mg/dL) within 48 hours or ≥1.5 times relative to normal values during the previous 7 days, or a decrease in the rate of diuresis <0.5 ml/kg/h within 6 hours;
– Microscopic hemolytic anemia and thrombocytopenia:
• |new or worsening anemia without other identified causes, presence of schistocytes or other fragments of red blood cells in a blood smear;
• laboratory signs of hemolysis (increased LDH levels, reticulocytosis, low or no haptoglobin), negative direct Coombs test;
• thrombocytopenia <100 000/mm3.
– Target organ damage:
• hypertensive retinopathy (hemorrhages, dense and/or mild exudate, edema of the optic nerve, unrelated to other causes);
• hypertensive encephalopathy (headache, altered mental status, focal or diffuse neurological manifestations unrelated to other causes);
• acute heart failure;
• acute pericarditis, diagnosed with at least 2 of the following 4 criteria: 1) chest pain; 2) pericardial friction noise; 3) newly reported elevation of the ST segment or depression of the PR segment during electrocardiography (ECG); 4) pericardial effusion according to echocardiography (EchoCG).

Histopathological changes in the kidneys are manifested by the involvement of small vessels that predominate over changes in the glomeruli. Glomerular changes are often characterized by the presence of TMA, including fibrin thrombi, endothelial edema, fragments of red blood cells, mesangiolysis, and chronic disorders (nonspecific ischemic lesions). Early vascular changes include accumulation of myxoid material in the intima of blood vessels, thrombosis, fibrinoid necrosis and, as a result, death of the renal cortex. Late disorders are manifested by thickening and proliferation of the intima, which causes sharp vasoconstriction [17].

It is believed that mortality rates from SRC have significantly decreased with the advent of ACE inhibitors, but the mortality rate for SRC in the first 6 months reaches 20%. Mortality from SRC is 36%, and 25% of patients remain on hemodialysis during the first year [18].

Due to a lack of understanding of the mechanisms of SRC pathogenesis, its treatment has not been developed. We present a description of the successful treatment of SRC in a patient with SSC based on modern world experience.

***Clinical observation***

***Patient B.****, 43 years old, debuted at the age of 41 (in November 2019) with swelling of the hands, pain in the wrist joints. In December 2019, she was diagnosed with rheumatoid arthritis and received nonsteroidal anti-inflammatory drugs with no effect. In January 2020, metipred (MP) 4 mg/day and methotrexate (MT, in tablets) 10 mg/week were prescribed with a satisfactory effect in reducing the severity of arthralgia. Since February 2020, Raynaud's syndrome added, shortness of breath and dry cough appeared. Computed tomography (CT) of the chest organs revealed no changes. In September 2020, she was treated at the rheumatology department of Loginov Clinical Research Center in Moscow, where SSC was diagnosed. The diagnosis was consistent with classification criteria of ACR/ELUAR (American College of Rheumatology / European Alliance of Associations*

*for Rheumatology) [19]. There was thickening of the skin of the hands, forearms, feet, neck; masklike face; hyperpigmentation and depigmentation of the skin in the chest area; telangiectasia on the face, in the decollete area; Raynaud's syndrome and digital scars; interstitial changes in the lungs according to chest CT, capillaroscopic changes. Antinuclear factor (ANF) Hep2 – 1/1280, antibodies to Ro/SSA (anti-Ro/SSA) – 121 (0-25) units/ml, antibodies to Scl70 (anti-Scl70) – >200 (0-25) units/ml, CRP – 2 (0-5) mg/L, ESR – 32 mm/h, creatinine – 65 (44-106) μmol/L. Esophagogastroduodenoscopy: insufficiency of the cardia. EchoCG: systolic pulmonary artery pressure (SPAP) – 38 mmHg. Ejection fraction – 68% (N=54–74%). Forced lung vital capacity (FVC) was 68%. Medrol 16 mg/day was prescribed. After the discharge from Loginov Center the patient was recommended to increase the dose of MT to 20 mg/week intramuscularly and reduce the dose of MP to 4 mg /day. Subsequently, negative dynamics were noted: an increase in skin induration, shortness of breath, joint pain, general weakness, CRP – 18.7 mg/L, proteinuria – 0.1 g/L. The creatinine level was normal – 63 μmol/L. SPAP was 42-47 mmHg. The patient was first admitted to V.A. Nasonova Scientific Research Institute of Rheumatology in March 2021, before hospitalization she had been receiving MP 8 mg /day, azathioprine 100 mg / day.*

*On examination: the condition is of moderate severity. The skin is diffusely indurated and hyperpigmented (skin score – 18 points), areas of depigmentation in the area of the anterior surface of the chest; masklike face, "pouch" mouth, scleredema, flexor contracture of the left elbow joint, Raynaud's syndrome, telangiectasia on the skin of the face and decollete. The number of painful joints is 16. The heart tones are clear, rhythmic, and there are no noises. Blood pressure is 130/80 mmHg, heart rate (HR) is 89/minute. Breathing is vesicular with a harsh tinge, there is no wheezing. The abdomen is painless on palpation. The liver is not enlarged. Murphy's punch sign is negative on both sides. No dysuria and stool disorders are noted.*

*The examination revealed mild microcytic anemia, Hb – 116 (120–140) g/L, RBC - 4.36·$10^{12}$/L (3.9–4.7), platelets – 180·$10^{9}$/ L (150–390), WBC – 10,1·$10^{9}$/ L (4.0–9.0), ESR – 13 (2–30) mm/h. Biochemical blood test (03/19/2021): creatinine – 87 (44-106) mmol/L, urea – 3.12 (1.8–8.3) mmol/L, LDH – 444.9 (135–225) Units/L, potassium – 3.53 (3.5–5.3) mmol/L. General urinalysis without any special features. GFR according to CKD-EPI is 70.29 ml/min/1.73 $m^2$, which corresponds to normal renal function, however, given the previous creatinine values (an increase of 24 μmol/L), it was possible to suspect the involvement of the kidneys in the pathological process. ANF Nep2 – 1/2560, homogeneous luminescence type, anti-Scl70 – 200 (0-25) U/ml, anti-Ro/SSA -103.8 (0–25) U/ml, CRP – (0–5) 16.9 mg/L, direct Coombs test negative. The C3 and C4 components of the complement are normal. Chest CT scan: interstitial fibrosis and reticular changes, bronchiectasis of both lungs, a small amount of fluid in the pericardial cavity, dilation of the lumen of the esophagus. FVC – 65.4%, decrease in the diffusion capacity of the lungs for carbon monoxide (DLCO) of a severe degree – 20.6%. EchoCG: expansion of the trunk and branches of the pulmonary artery, dilation of the left atrium, a small amount of fluid in the pericardial cavity and the left pleural cavity, SPAP – 33 mmHg. ECG: sinus rhythm, heart rate – 66 per minute, incomplete blockage of the right leg of the bundle of His, moderate changes in the myocardium of the left ventricle, low voltage of the R wave in standard leads. Capillaroscopy: late scleroderma changes. No significant comorbidities or previous illnesses.*

*Thus, the patient had a detailed picture of a diffuse form of SSC with a duration of 1.5 years, a rapidly progressive course involving internal organs against the background of high immunological activity. The patient continued her previously prescribed therapy.*

***On the 4th day** of the hospital stay, an increase in blood pressure was noted for the first time, to a maximum of 180/100 mmHg, an increase in creatinine levels to 154 μmol/L, a drop in GFR according to CKD-EPI to 35.24 ml/min/1.73 m2, urea – 8.2 mmol/L, thrombocytopenia – 120·$10^{9}$/L, fibrinogen – 4.63 g/L. A general urinalysis showed no abnormalities, and no peripheral edema was detected. The condition is classified as acute SRC based on a sharp increase in creatinine concentration, a steady increase in blood pressure, a decrease in platelet count and hemoglobin levels. A rapid and early decrease in platelet count did not exclude the development of TMA. ACE inhibitor therapy was immediately initiated (captopril 25 mg, enalapril 15 mg/day), blood pressure decreased to 140/80 mm.Hg, but only for 1.5–2 hours, and therefore captopril was repeated up to 6 times a day. The therapy also included direct anticoagulants – calcium nodroparin 0.6 ml/day and prostanoids – alprostadil 60 mcg/day intravenously; amlodipine 2.5 mg/day, veroshpiron 25 mg/day; continued administration of sildenafil 12.5 mg/day; azathioprine was discontinued.*

***On the 5th day**, due to the high activity, rapidly progressing course of the disease with damage to vital organs, and unfavorable prognosis, anti-B-cell therapy was initiated. Rituximab (RTM) 500 mg was administered without premedication with GC. Five days after administration of RTM, creatinine levels reached 191 μmol/L. GFR according to CKD-EPI decreased to 27.16 ml/min/1.73 $m^2$, urea – 13.3 mmol/L, mild microcytic anemia persisted (Hb – $10^{9}$ g/L, RBC. – 4,10·$10^{12}$/L). ESR increased up to 38 mm/h. However, there was no urinary dysfunction; in addition, normalization of platelet count (329·$10^{9}$/L) was noted. Dynamic ECG: sinus tachycardia (heart rate – 101 per minute), ST segment depression up to -1.0 mm in leads II, III, aVF, V4–V6, low voltage of the R wave in standard and thoracic leads.*

*Multicomponent therapy was continued, which included a low dose of GCs (2 tablets per day), vascular drugs, including antihypertensive drugs, and anticoagulants. The condition stabilized, blood pressure returned to normal (did not exceed 120/80 mmHg) while taking captopril at a dose of 6.25 mg/day and enalapril 10 mg/day.*

***On day 15**, RTM 500 mg was re-administered (the total dose was 1000 mg). In the period between the injections of RTM, intravenous injection of human immunoglobulin 5 g was performed twice. The patient's condition remained stable, no multiple organ progression was observed.*

***On day 19**, ECG readings improved: there was no ST segment depression, and the voltage of the R wave in the standard and thoracic leads increased. Elevated creatinine levels (192 μmol/L) and low GFR according to CKD-EPI of 26.99 ml/min/1.73 $m^2$, thrombocytosis persisted – 524·$10^{9}$/ L, ESR – 37 mm/h. At the same time, the patient's general condition was assessed as satisfactory, the excretory function of the kidneys remained intact, and blood pressure stabilized at 120/80 mm Hg.*

*The patient was discharged with recommendations to continue therapy with MP 8 mg/day, as well as vascular, anticoagulant and antihypertensive therapy, and to start taking mycophenolate mofetil (MMF) 2 g/day (due to heart failure accompanied by 3rd–4th degree respiratory failure).*

*During the following year, there was a clear positive trend in the form of stabilization of blood pressure (120/80 mmHg), a decrease in creatinine level (up to 124.8 μmol/L) and laboratory parameters of inflammatory activity, normalization of platelet count, as well as a decrease in skin density (skin score at the onset was 18 points, in dy-*

*namics after 32 months – 7 points). Subsequently, the administration of RTM 1000 mg once every 6 months was continued. By November 2022, creatinine levels had decreased to normal levels of 97 μmol /L (44–106 μmol /L). The last administration of RTM was performed in March 2023, the total dose was 6 g. When examined in November 2023. The patient's condition remained stable, creatinine levels were within the normal range, blood pressure did not exceed 140/90 mmHg, and GFR according to CKD-EPI increased to 62.24 ml/min/1.73 m². The therapy was performed with MP 8 mg/day, MMF 2 g/day, and vascular drugs.*

Thus, the above clinical observation demonstrates the successful relief of SRC and stabilization of the disease (low activity) in general.

**Discussion.** In the current international recommendations on the pharmacotherapy of SSC in relation to kidney damage, only two positions are highlighted: the mandatory and early use of ACE inhibitors in the diagnosis of SRC and regular monitoring of blood pressure in patients receiving GCs for the timely detection of SRC [20]. Currently, adequate blood pressure control is still considered the main goal of SRC therapy, and its optimal reduction is 140/90 mmHg in 3–5 days. Therapy begins with ACE inhibitors as the drugs of choice, which are prescribed immediately after the diagnosis of SRC. In accordance with the British recommendations for the treatment of SRC, if oral therapy with ACE inhibitors is ineffective (including in combination with antihypertensive drugs with other mechanisms of action), parenteral peripheral vasodilators, in particular prostanoids (iloprost), should be added to therapy [21]. In recent years, there have been reports of new approaches to the treatment of SRC, which are summarized in a systematic way. Anticoagulant therapy can be attributed to new approaches, given the frequent combination of SRC with the development of TMA. The possibility of complement system activation in the pathogenesis of SRC is being discussed, which served as the basis for attempts to use eculizumab (a humanized recombinant monoclonal antibody directed against complement component 5) [22].

Since disorders of B-cell homeostasis play a role in the pathogenesis of SSC, RTM, a chimeric monoclonal antibody directed against CD20, a cell membrane molecule specifically expressed on B cells, is successfully used in its treatment [23]. Many studies have proven the suppressive effect of RTM in SSC on cutaneous and pulmonary fibrosis, but its effect on the kidneys has not been sufficiently studied, and there is practically no research on this topic. This may be due to the fact that clinical trials do not include patients with kidney damage (especially with SRC). There are only isolated publications in which patients with SRC received RTM for other reasons, while RTM did not worsen the course of SRC. The work of Russian authors showed a statistically significant decrease in GFR in patients with SSC (n=90) against the background of complex RTM therapy at the end of the follow-up period (on average 3 years). At the same time, GFR decreased by only 3 ml/min/1.73 m² and remained within the normal range, while creatinine levels were normal [24].

Isolated reports describe successful use of complex therapy, including RTM, in SRC. Thus, a 21-year-old patient with cross syndrome (SSC in combination with polymyositis and systemic lupus erythematosus) developed acute kidney damage with signs of obliterating angiopathy and TMA. Along with GC (pulse therapy with methylprednisolone 500 mg for 3 days), the patient received 2 g of RTM, as well as ACE inhibitors and sildenafil, and 9 plasma exchange sessions. After relief of the acute phase, the patient received MMF (500 mg/day) and hydroxychloroquine (200 mg/day), and a gradual normalization of renal function over 8 months was observed [25]. The authors concluded that RTM may be useful for the prevention or treatment of already developed SRC. K. Innami et al. [26] described a 56-year-old patient with a combination of SSC and polymyositis, in whom treatment of polymyositis with high doses of GCs led to the development of SRC. Therapy with GCs and RTM made it possible to stop SRC.

Given the positive experience of using RTM to suppress SSC activity in general and its cardinal manifestations (skin induration, progression of interstitial changes in the lungs) in particular, as well as insufficient information on the effect of RTM on the course of SRC, we considered it appropriate to provide an observation of successful treatment of SRC. Our patient with a reliable diagnosis of SSC had risk factors for developing SRC: a short history of the disease and a diffuse form of SSC, rapidly progressive damage to internal organs, joint damage with the formation of flexion contracture of the left elbow joint, high levels of antibodies to topoisomerase I. In addition, at the onset of the disease, the dose of GCs exceeded 3 tablets per day (i.e., it was >15 mg in prednisolone equivalent). Since the development of SRC was one of the clinical manifestations of the highly active stage of SSC, the patient underwent complex therapy aimed primarily at reducing the activity of the disease as a whole, and therefore the introduction of RTM was initiated. This therapy was combined with an expanded range of vascular medications, including ACE inhibitors, prostanoids (alprostadil), phosphodiesterase 5 inhibitors (sildenafil), and anticoagulants. It is important that the treatment was started literally on the first days of the development of the crisis (the patient was in hospital, which allowed the diagnosis of SRC to be established promptly). At the same time, for the entire period of development and relief of the crisis, the patient received only 8 mg of MP per day. Though the development of SRC was stopped almost immediately, the improvement of symptoms of chronic kidney disease against the background of maintenance therapy with RTM in combination with immunosuppressants (MMF) was slow (over the next 1.5 years). Our experience with a multimodal approach to SRC relief is consistent with the literature descriptions of therapy for such patients.

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Mishina E.M. https://orcid.org/0009-0002-2145-5330
Ananyeva L.P. https://orcid.org/0000-0002-3248-6426
Evsikova M.D. https://orcid.org/0000-0002-6629-3374
Koneva O.A. https://orcid.org/0000-0003-3650-7658