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ПОЧЕЧНЫЙ КРИЗИС ПРИ СКЛЕРОДЕРМИИ: ГИПЕРТЕНЗИВНАЯ ЧРЕЗВЫЧАЙНАЯ СИТУАЦИЯ, ОБУСЛОВЛЕННАЯ ДЕЙСТВИЕМ РЕНИНА, С ХАРАКТЕРНОЙ РЕНАЛЬНОЙ МИКРОВАСКУЛЯРНОЙ ПАТОЛОГИЕЙ

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SCLERODERMA RENAL CRISIS: A RENIN-DRIVEN HYPERTENSIVE EMERGENCY WITH DISTINCT RENAL MICROVASCULAR PATHOLOGY

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Резюме. Почечный кризис при склеродермии (SRC) представляет собой наиболее тяжелое поражение почек при системной склеродермии; он характеризуется агрессивной гипертензией, быстро прогрессирующей острой почечной недостаточностью и наличием тромботической микроангиопатии. С патологоанатомической точки зрения, SRC по своей сути является сосудистым заболеванием, обусловленным возникновением аномалий до повреждения паренхимы. Основным проявлением данного процесса является концентрическое утолщение интимы мелких сосудов в виде «луковой шелухи», что приводит к значительному сужению просвета и ишемии коры, вызывая последующее повреждение клубочков и канальцев. Повышенная активность ренин-ангиотензин-альдостероновой оси формирует самоподдерживающуюся положительную обратную связь, вызывающую злокачественную гипертензию; однако ингибиторы АПФ прерывают этот цикл, значительно улучшая прогноз.

Ключевые слова: склеродермическая почечный криз, «луковая шелуха», тромботическая микроангиопатия, злокачественная гипертензия, ингибиторы АПФ

Resume. Scleroderma renal crisis (SRC) is the most serious renal involvement seen in systemic sclerosis; it involves malignant hypertension, rapidly progressive acute renal failure, and the presence of a thrombotic microangiopathy. In terms of pathological anatomy, SRC is essentially a vascular disease, which is based on the development of vascular abnormalities prior to any damage of the parenchyma. The main lesion of this disease, concentric "onion skin" intimal thickening of small vessels, causes significant lumen narrowing and ischemia of the cortex, leading to subsequent damage of the glomeruli and tubules. The increased activity of the renin-angiotensin-aldosterone axis leads to a self-propelled positive feedback loop causing malignant hypertension; however, ACE inhibitors interrupt this circle, significantly improving the outcome.

Keywords: scleroderma renal crisis, onion-skin arteriole, thrombotic microangiopathy, malignant hypertension, ACE inhibitors

Relevance. Scleroderma renal crisis is an urgent condition associated with systemic sclerosis with considerable mortality rate, if the disease goes undiagnosed [5]. Knowledge regarding the distinctive microvascular pathology of the condition is vital for pathologists and physicians, because only with timely diagnosis and appropriate treatment using angiotensin-converting enzyme inhibitors the patient's life can be saved. Steroid-associated

SRC and other therapies, such as complement inhibitors, have made the condition even more clinically relevant today [4].

Aim: to study the unique renal microvasculopathy of scleroderma renal crisis. to relate histopathologic features to the clinical manifestations and therapeutic approaches.

Objectives:

1. Elaborate on all features of macroscopic and microscopic renal changes in SRC, including the characteristic "onion-skin" arteriolar change.
2. Discuss how activation of the renin-angiotensin-aldosterone system results in malignant hypertension and ischemia of the kidneys.
3. Explain how certain histopathological findings such as onion skin arteriole, fibrinoid necrosis, thrombosis, ischemic glomerulus, and tubular damage relate to clinical manifestations including hypertension, acute renal failure, mild proteinuria, and microangiopathic hemolytic anemia.
4. Discuss evidence supporting the use of ACE inhibitors that disrupt the renin-ischemia positive feedback loop.
5. Investigate new insights into mechanisms like endothelin-1 autoantibodies and abnormal complement.

Materials and methods. The study is based on a literature review. Data were sourced from PubMed, Google Scholar, and Radiopaedia, with a focus on pathological anatomy, histology, and clinical studies related to scleroderma renal crisis.

Results and their discussion. Macroscopic appearances – an illusory picture. One of the key messages of pathology of the SRC syndrome is that macroscopic lesions are subtle, whereas microscopic lesions are very serious [1]. Early on, in SRC patients the size of the kidneys appears normal or just slightly decreased. The capsule is tense, and the surface of the cortex displays fine granulation. In the advanced stages of the disease, the surface of the kidneys becomes coarsely granulated; cross sections demonstrate pale color of the cortex, which is due to ischemia. Cortical atrophy occurs as a result of persistent damage to the blood vessels in chronic cases of SRC [2]. Macroscopic features, however, are strikingly insignificant in comparison with the extremely serious microscopic pathology.

Microscopic features: The characteristic "onion-skin" arteriole. Microscopically, SRC is a disease that affects the vessels in the kidney, specifically the small arteries and arterioles that are between 50-300 micrometers in diameter in the renal cortex. The pathognomonic lesion consists of concentric intimal thickening due to myxomatous and fibrous proliferation with a characteristic "onion-skin" pattern [1,2]. This results in severe narrowing or even occlusion of the lumen, thus causing ischemia and ultimately renal failure.

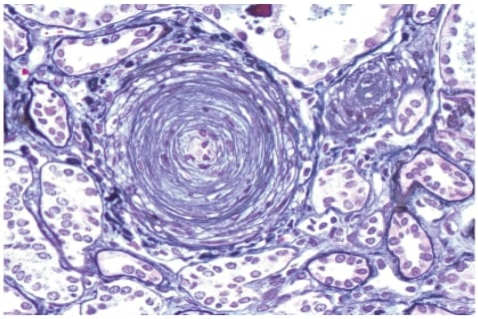

Fig. 1 – "Onion Skin" Arteriole (Methenamine silverstain; original magnificaton x400)

However, when the compensatory response fails due to persistent ischemia, there will be destructive vascular lesions. Fibrinoid necrosis is evident with the disruption of the wall's usual architecture and its replacement by eosinophilic, bright pink material. Thrombosis fills the vessel completely and blocks the arteriolar lumen [1]. These findings signify active thrombotic microangiopathy (TMA), which gives a poor renal prognosis if not intervened with immediately. Clinically, these findings are associated with active TMA and the development of microangiopathic hemolytic anemia and thrombocytopenia [1,2].

The glomerulus: The innocent bystander. The glomerulus is not the main target in SRC; rather, the organ becomes affected secondarily from the upstream lesion involving the arterioles. Glomerular capillaries become atrophic, empty of blood, and have a "worm-eaten" appearance. There is no glomerular hypercellularity and no immune deposits in the tissue. As there is an absence of structural damage to the filtration membrane but significant underperfusion, only mild proteinuria can develop even though there is significant acute kidney injury [1].

Downstream effects – tubular injury and interstitial damage. The constriction of arterioles results in decreased perfusion through the peritubular capillaries, leading to ischemia of the tubules. The acute tubular damage shows flattened epithelial cells and absence of the brush border as well as dilatation of the tubular lumen. In the interstitium, there will be edema without significant inflammation; absence of inflammatory cells in this lesion differentiates the condition from interstitial nephritis [1,2]. Tubular damage occurs secondarily to the vascular lesion, rather than being primary. Resolution of renal ischemia by ACE inhibitors can lead to resolution of tubular damage before it progresses into fibrosis [6].

Renin time bomb - positive feedback mechanism. Secondary renal cancer is not essential hypertension but rather a special emergency caused by renin release. Endothelial dysfunction - as caused by vascular damage from scleroderma, autoantibodies, and probably excessive doses of corticosteroids - results in ischemia in the kidney [5]. Ischemia triggers renin release from juxtaglomerular cells, and renin acts on angiotensinogen converting it into angiotensin I. Then angiotensin-converting enzyme acts on angiotensin I converting it into angiotensin II. Angiotensin II acts as an effective vasopressor, causing additional vasoconstriction and ischemia, thus triggering more renin release and so on in a vicious circle: ischemia, renin, angiotensin II, vasoconstriction, and back to ischemia, renin, etc [6].

Clinical-pathologic correlation. All histopathological abnormalities seen in SRC have a corresponding clinical correlate because it is pathology-based medicine. The "onion skin" change of arterioles is responsible for the development of malignant hypertension and elevated creatinine [1,2]. Fibrinoid necrosis, along with the formation of a thrombus, correlates with microangiopathic hemolytic anemia (schistocytes), thrombocytopenia, and elevated levels of lactate dehydrogenase. Glomerular ischemic infarction explains the presence of mild proteinuria despite the severe AKI [1].

Lifesaver – ACE inhibitors end the cycle. Prior to ACE inhibitors, mortality rates were greater than 50%, and almost all cases progressed to permanent dialysis [6]. There was no way to stop the renin-ischemia cycle, and SRC was thought to be uniformly fatal in many cases. With the emergence of the post-ACE inhibitor era, there have been remarkable improvements in patient survival rates, with many gaining back significant renal function [6]. ACE inhibitors prevent angiotensin II formation, relax smooth muscle, and stop the

renin → ischemia → renin feedback cycle. The EULAR guidelines for 2023 mandate that ACE inhibitors are a primary treatment for SRC and should be started without delay, even at moderately high BP levels [6].

Other emerging mechanisms and targets. Despite the importance of ACE inhibitors, a subset of patients will develop refractory or progressive disease. Other potential therapeutic targets for SRC have been identified through recent studies. The presence of autoantibodies that lead to the formation of endothelin-1, a powerful vasoconstrictor, has been noted in SRC patients [3]. There has also been increased recognition of alternative pathway activation of the complement system in a subset of SRC patients [4]. Eculizumab, which inhibits complement activation, might be useful in refractory TMA despite the use of ACE inhibitors. Other targets being explored are PAR1 inhibitors.

Example clinical case. An illustrative case is one in which a 71-year-old woman with systemic sclerosis and myositis received high-dose corticosteroids (intravenous methylprednisolone along with prednisone orally >15 mg daily) [5]. Within a few months, she had a slow rise in serum creatinine level, a potentially ominous sign that was initially ignored by her clinicians. However, she soon had acute-onset hypertension (170/100 mm Hg), oliguria, kidney failure, and microangiopathic signs (thrombocytopenia, increased lactate dehydrogenase). Renal biopsy revealed thrombotic microangiopathy associated with 75% fibrosis [2]. Although treated with ACE inhibitors and many antihypertensive drugs, she needed permanent dialysis. Transplantation assessment was planned because dialysis remained necessary even after adequate treatment with ACE inhibitors (modified from Eur J Rheumatol 2020;8(3):162–167) [5].

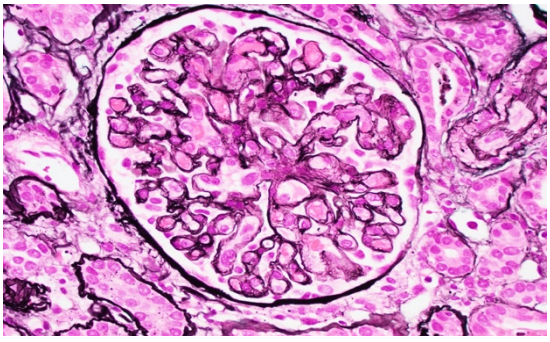

Fig. 2 – Microscopic view of SRC kidney

Conclusions:

1. The regional fibre architecture of the corpus callosum correlates perfectly with its physiological role, influencing the rate of conduction. (This statement seems to come from the previous article; the correct statements about SRC are provided below.)

2. Primary SRC is primarily a vasculature disorder, rather than a glomerular or tubular disorder [1,2]. The typical “onion skin” pattern of arteriolar involvement results in severe lumen narrowing with secondary ischemia and parenchymal injury [1,2].

3. Renin-Angiotensin-Aldosterone system up-regulation leads to the development of positive feedback loop, which results in progressive ischemia and malignant hypertension [6]. ACE inhibitors are used as the first-line and mandatory treatment in accordance with EULAR guidelines of 2023 [6].

4. Each of the pathological changes in SRC is associated with a specific clinical picture, including hypertensive and renal impairment (onion skin arterioles), microhemolysis and thrombocytopenia (fibrinoid necrosis and thrombosis), mild proteinuria (ischemic glomeruli), and acute kidney injury (tubular damage) [1,2].

5. Severe chronic fibrosis observed during a biopsy procedure indicates the development of an irreversible kidney failure, even with optimal ACE inhibitor treatment [2].

6. New mechanisms, involving endothelin-1 and complement system, may serve as targets for further therapy of SRC [3,4].

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