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Acute renal failure – revealing manifestation of an autoimmune condition

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ABSTRACT

Scleroderma renal crisis is an important cause of morbidity and mortality in systemic sclerosis patients, occurring in about 5-10% of the cases. It is seen mostly early in the progression of the disease, about 75% of the scleroderma renal crises affecting the patients in their first 4 years since the onset of the disease.
We present the case of a 62 year old woman who was admitted in our clinic for oliguria, edema, an important elevation of the kidney function tests, arterial hypertension and severe anemia. Immunological tests showed intensely positive antinuclear antibodies with positive anti RNA polymerase III antibodies. She was diagnosed with systemic sclerosis according to ACR/EULAR 2013 criteria and scleroderma renal crisis. Specific therapy was started along with hemodialysis imposed by the progression of the kidney failure.

Keywords: systemic sclerosis, scleroderma renal crisis, acute renal failure

BACKGROUND

Scleroderma renal crisis (SRC) is a rare manifestation of scleroderma presenting as new-onset hypertension or rapidly deteriorating renal function, frequently accompanied by signs of microangiopathic hemolytic anemia. Certain signs and symptoms of scleroderma, such as diffuse cutaneous involvement, proximal and/or truncal skin thickening, rapid progression of skin thickening and the presence of large joint contractures could point towards the early recognition and treatment of scleroderma renal crisis (1).

The prompt and correct treatment with angiotensin-converting-enzyme inhibitor (ACEi) has a great impact regarding the prognosis of these patients. However, despite ACE inhibitors treatment and the advances in nephrology and intensive care, the morbidity and mortality remain high (1). Given the fact that scleroderma renal crisis remains one of the most rapidly progressive complications of systemic sclerosis and that the management of its sequellae is complex (involving not only problems related to end-stage renal failure, dialysis, and transplantation, but also the general management of systemic sclerosis) one must focus on early diagnosis. Therefore, training not only rheumatologists, but also physicians from other specialties (such as nephrology, emergency medicine, internal medicine and intensive care) in recognizing this condition becomes an imperative.

CASE PRESENTATION

We present the case of a 62 year old female admitted in our clinic in January 2016 for oliguria, edema, a severe anemic syndrome and a marked increase in the kidney function tests. The onset of the patient's condition seems to be in late 2014 when she presents in a Rheumatology private practice for symmetrical distal polyarthritis and Raynaud phenomenon, when further tests were recommended along with a low dose of Prednisone, but she did not present for her check-up, whilst continuing to take Prednisone. Prior to the admission in our department she was given diuretic therapy (Furosemide).

The clinical examination upon admission showed a dyspneic patient (respiratory rate 22/min), oxygen saturation spO2 93% a blood pressure of 200/100 mm Hg, heart rate of 88 bpm., subcrepitant rales in the inferior third of the chest, oliguria, important edema, Raynaud's phenomenon, which progressed

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to digital gangrene (fingers III, IV on the right hand), skin thickening of the fingers of both hands extending proximal to the MCP joints, rare telangiectasia on the anterior thorax.

Initial investigations showed the following: haemoglobin (Hb) levels to be 6.5 g/dL with schistocytes and reticulocytosis on the peripheral blood smear; white blood count (WBC) 9,000/mm³ with normal formula, thrombocyte count 65,000 mm³; serum creatinine 14.31 mg/dl, eGFR = 5.04 ml/min; blood urea 273 mg/dL; serum bicarbonate HCO3 17.0 meq/L; serum sodium 130mmol/L; and serum potassium 6.8 meq/L ESR 37 mm/h, CRP 1 mg/dl, total bilirubin 2 mg/dl, indirect bilirubin 1.9 mg/dl. Urine examination showed the presence of proteins and no active sediment. The antinuclear antibody titer was 1/320, with positive anti RNA polymerase III antibodies. The protein electrophoresis, liver function tests, and other immunological tests (anti dsDNA, anti Sm, anti CCP, cANCA, pANCA, anti centromere antibodies, anti SCL-70, anti HCV antibodies, HBs antigen and cryoglobulins). were negative. Nailfold capilaroscopy and kidney biopsy have not been performed. The imaging studies (native chest CT and abdomen ultrasound) were unremarkable.

We established the diagnosis of scleroderma based on ACR/EULAR 2013 criteria for systemic sclerosis (18 points) (2). We also calculated the Rodnan score summing up 7 points.

TABLE 1. *ACR/EULAR 2013 criteria for systemic sclerosis*

Criteria domain	Sub-criteria	Weight
Skin thickening (count the higher of the three)	Skin thickening of the fingers of both hands extending proximal to the MCP joints	9
	Puffy fingers	2
	Whole finger, distal to MCP joint	4
Fingertip lesions (count the higher of the two)	Digital tip ulcers	2
	Pitting scars	3
Telangiectasia		2
Abnormal nailfold capillaries		2
Lung involvement	PAH and/or ILD	2
Raynaud's phenomenon		3
SSc-related antibodies	Any of ACA, ATA (anti-Scl 70), RNA polimerase	3

Hoogen, F., Khanna, D 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis & Rheumatism, 65(11), pp.2737-2747 (2).

Due to the renal status of our patient, hemodialysis was initiated. We also initiated therapy with ACE inhibitor, Captopril 12.5 mg, with progressive dose escalation until the goal blood pressure was reached (75 mg/day).

While the patient's kidney function showed slight improvement, at the moment this paper was written, she continued to receive hemodialysis on an outpatient basis.

DISCUSSIONS

Scleroderma renal crisis (SRC) develops in approximately 10 to 20 percent of patients with the diffuse cutaneous systemic sclerosis and much less frequently in limited cutaneous systemic sclerosis. It is characterized by: abrupt onset of moderate to severe hypertension, urine sediment that is normal or reveals only mild proteinuria with few cells or casts, progressive renal failure (3).

The nomenclature of scleroderma renal crisis was proposed in 1952 by Moore and Seehan when they first described the typical histopathological lesion. Even after all this time, the pathogenic mechanisms are poorly understood. Recent studies suggest several factors that can be helpful to stratify and identify patients at high risk for SRC (3,4,5).

Throughout the literature, the factors associated with SRC include a disease duration of <4 years, corticotherapy, diffuse and rapidly progressive skin thickening, new cardiac events, and the presence of anti–RNA polimerase III antibodies (4-8). Steen (also demonstrated that reduction of renal blood flow caused by sepsis, dehydration, and cardiac dysfunction could be a potential trigger for SRC (5). There are also case reports that Cyclosporin A precipitated renal crisis when used in diffuse skin involvement systemic sclerosis (9).

There is consistent evidence throughout the literature suggesting steroids may trigger scleroderma renal crisis. Staring of 1952 multiple case reports and studies have supported this association. It has been estimated that 60 % of the patients with SRC had corticotherapy in their medication history. There is also a temporal relation regarding corticotherapy. Steen and Medsger observed that the recent use of large doses CS preceded the diagnosis, with the new onset corticotherapy groups being at a higher risk (5). In a systematic review Gerald Trang et al (6) found that 2% of all the patients with SSC and 4% of the patients with early diffuse disease developed

SRC, most of these cases (75-86%) occurring in the first 4 years of the disease (7). The current EUSTAR recommendations for the treatment of systemic sclerosis suggested that steroids were associated with a higher risk of SRC (8).

The presence of certain immunological patterns is also a predictive factor for SRC. RNA polymerase III is a scleroderma-specific antibody that is seen almost exclusively in diffuse scleroderma, and 24-33% of patients with this antibody develop SRC. However, this antibody is not a specific marker for renal crisis but rather for diffuse cutaneous involvement. The anticentromere antibody seems to be a protective factor for renal crisis (1). These antibodies do not coexist in the majority of patients and autoantibody profiles usually do not change during the disease course (10-12).

Other reported associations of anti-RNA polymerase III antibodies include tendon friction rubs, myositis, synovitis, joint contractures gastric antral vascular ectasia and a close temporal association between the onset of SSc and diagnosis of neoplasia (11).

Another risk factor identified as being linked with SRC is rapid progressive skin involvement. More than three quarters of cases of SRC (75-80%) occur in the patients with diffuse skin changes Penn et al observed on a group of 706 scleroderma patients that up to 22% of the patients with diffuse disease had developed SRC as compared to 12% of the patients with limited cutaneous disease. The rapid progression of the skin thickening (and therefore an increase in Rodnan score seems to have a good predictive value regarding SRC (13).

Additional factors that may identify patients at risk for SRC include cyclosporine therapy, contractures of the large joints, recent anemia, new cardiac events and pericarditis. Preexisting hypertension, elevated serum creatinine, abnormal urinalysis, or antibodies against topoisomerase-1 are not predictive (1,13)

In order to establish the diagnosis of SRC in high-risk patients with systemic sclerosis. one may find helpful the criteria developed by Varga et al (Table 2) (3).

There are however some diagnosis pitfalls (3): SRC as the presenting manifestation of scleroderma, scleroderma renal crisis patients with limited cutaneous disease, normotensive scleroderma renal crisis (10%) (13), SRC in patients with systemic sclerosis sine scleroderma.

TABLE 2. *Clinical Criteria for Definition of Scleroderma Renal Crisis (SRC)*

Clinical Criteria for Definition of Scleroderma Renal Crisis (SRC)
Scleroderma renal crisis is defined as follows, requiring both of:
1. A new onset of blood pressure >150/85 obtained at least twice over a consecutive 24-h period. This blood pressure is chosen because it is that defined by the New York Heart Association as significant hypertension
2. Decrease in the renal function as defined by a decrement of at least 10% in the calculated glomerular filtration rate (eGFR) or measured GFR of below 90. When possible, a repeat serum creatinine and recalculation of the GFR should be obtained to corroborate the initial results.
In order to corroborate further the occurrence of acute renal crisis, it would be desirable to have any of the following, if available:
Microangiopathic hemolytic anemia on blood smear
Retinopathy typical of acute hypertensive crisis
New onset of urinary RBCs (excluding other causes)
Flash pulmonary edema
Oliguria or anuria
Renal biopsy with typical features including onion skin proliferation

J. Varga et al. (eds.), Scleroderma: From Pathogenesis to Comprehensive Management (3)

SRC must be distinguished from other forms of thrombotic microangiopathy, such as thrombotic thrombocytopenic purpura-hemolytic uremic syndrome in adults, other causes of acute kidney failure in scleroderma patients (acute renal failure due to anti-neutrophil cytoplasmic antibodies (ANCA)-related crescentic glomerulonephritis or due to D-penicillamine therapy) or other conditions such as amyloidosis, myeloma and gammapathies. (14).

The biopsy in SRC is not mandatory but it may be necessary when in doubt regarding the positive diagnosis or to rule out other concurrent pathological process. In our patient, due to her refusal, we did not attempt such investigation. This issue did not impact our therapeutic option especially since the chronic damage index, which has prognostic value in many other renal disorders seems to have little to no use in assessing SRC (1,13).

Once the diagnosis has been established, aggressive therapy using ACE inhibitors is vital. The survival of the patients with SRC has been dramatically improved by the routine use of angiotensin-converting enzyme inhibitors (ACEi) and the novel approaches in kidney replacement therapy. Prior to the use of these agents, 1 year survival rate was around 10%, whereas nowadays 5-year survival rate is 60% (15).

The primary goal in SRC is to lower the systolic blood pressure down by 20 mmHg per 24 h and the diastolic blood pressure down by 10 mmHg per 24 h until the blood pressure is within normal limits, while avoiding hypotension (16).

Captopril is the first-line therapy due to its short half-life that allows it to be readily titrated (10). Even though the ACE inhibitors improve the survival of these patients, when given in SRC, there is no evidence regarding their role in preventing the SRC, and it seems that the patients on ACE inhibitors have a poorer outcome if previously treated with these drugs. The hypothesis is that using low doses of ACEi in normotensive patients (for "prevention" reasons) masks the acute manifestations of SRC delaying the patient's presentation to the physician, leading to irreversible kidney damage (3,16).

It is important to increase the ACEi dose until the blood pressure reaches normal values. It may take several days for blood pressure reach this target, and renal function may continue to deteriorate even after the initiation of ACEi. Therefore the inappropriate reduction or the abrupt discontinuation of ACEi must be avoided (9,16).

Between 35 and 45% with SRC do not require kidney replacement therapy at all, these patients recovering their kidney function in short time after the blood pressure is normalized. Out of the group that require hemodialysis about half recovers their kidney function to the extent that they discontinue it 3–18 months later, with the GFR improving slowly in time without further deterioration if the blood pressure is controlled (3,17).

However, the long term prognosis of the rest of patients is influenced by the complications of long term dialysis or from other manifestations of the disease in which case the therapeutic options are diminished by the impaired kidney function and the restrictions imposed by the dialysis regimens (17,18). Renal transplant may be considered but the decision should be delayed for up to18–24 months in order to allow renal recovery (14,17-20).

CONCLUSIONS

We have presented the case of a patient with RNA polymerase- associated limited cutaneous systemic sclerosis who developed scleroderma renal crisis. This case demonstrates the importance of increased awareness of the ways that SRC may present, especially in patients with minimal skin changes.

Another problem raised by this case is the unreasonable use of corticotherapy in a patient with Raynaud phenomenon that was not investigated properly. This issue may be due to the poor addressability of the population to the rheumatology specialists in our country and the fact that some investigations, such as immunological tests and capillaroscopy, are limited to certain facilities. There is also the problem of patient education regarding the importance of compliance to the investigation plan.

Despite ACE inhibitors, dialysis, renal transplantation and modern intensive care, SRC is still one of the most rapidly progressive systemic sclerosis complications both in the short and in the long term. Therefore, the identification of high-risk groups and early detection of SRC is critical for improving outcome. Our patient had several risk factors: recent onset disease, the use of corticosteroids and positive anti RNA polymerase III antibodies, placing her in the high-risk group. The inclusion of SRC in the differential diagnosis of hypertensive emergencies and acute kidney failure could improve the outcome of these patients.

In conclusion, this case demonstrates that a rigorous history is vital in these patients, treatment with ACE inhibitors improving the prognosis. It also emphasizes the importance of rheumatologists' and nephrologists' involvement, but also the need of supplementary training of physicians from other specialties in recognizing this rare type of hypertensive crisis for a prompt and correct management.

REFERENCES

1. **Stern E.P., Steen V.D. et al.** Management of Renal Involvement in Scleroderma Current Treatment Options in Rheumatology March 2015, Volume 1, Issue 1, pp 106-118
2. **van den Hoogen F., Khanna D. et al.** Classification Criteria for Systemic Sclerosis: An American College of Rheumatology/ European League Against Rheumatism Collaborative Initiative† Arthritis & Rheumatism Volume 65, Issue 11, pag 2737–2747, November 2013
3. **Varga J., Denton C.P. et al.** Scleroderma From Pathogenesis to Comprehensive Management, *Springer,* 2012 pag 361-369, DOI10.1007/978-1-4419-5774-0_29.
4. **O'Callaghan C.A.** Renal manifestations of systemic autoimmune disease: diagnosis and therapy. Best Practice & Research Clinical Rheumatology. 2004 Jun 30;18(3):411-27.
5. **Moore H.C., Sheehan H.L.** The kidney of scleroderma. *Lancet*. 1952; 1:68.

6. **Teixeira L., Mahr A., Mouthon L. et al.** Scleroderma Renal Crisis, Still a Life, Threatening Complication. *Annals of the New York Academy of Sciences*, 20071108(1), pp.249-258.
7. **Steen V.D.** Scleroderma renal crisis. *Rheum Dis Clin North Am* 2003; 29:315–33.
8. **Kowal-Bielecka O., Landewé R., Avouac, et al.** EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). *Annals of the Rheumatic Diseases*, 68(5), pp.620-628, 2009.
9. **Denton C.P., Sweny P., Abdulla et al.** Acute renal failure occurring in scleroderma treated with cyclosporin A: a report of three cases. *Rheumatology*, 33(1), pp.90-92, 1994.
10. **Trang G., Steele R., Baron M. et al.** Corticosteroids and the risk of scleroderma renal crisis: a systematic review. *Rheumatology international*. 2012 Mar 1; 32(3):645-53.
11. **Nikpour M., Hissaria P., Byron J., et al.** Prevalence, correlates and clinical usefulness of antibodies to RNA polymerase III in systemic sclerosis: a cross-sectional analysis of data from an Australian cohort. *Arthritis research & therapy*, 13(6), p.1, 2011.
12. **Hamaguchi Y., Hasegawa M., Fujimoto et al.** The clinical relevance of serum antinuclear antibodies in Japanese patients with systemic sclerosis. *British Journal of dermatology*, 158(3), pp.487-495, 2008.
13. **Teixeira L., Mouthon L., Mahr A., et al.** Mortality and risk factors of scleroderma renal crisis: a French retrospective study of 50 patients. *Annals of the rheumatic diseases*. 2008 Jan 1; 67(1):110-6.
14. **Hamaguchi Y., Kodera M., Matsushita T., et al.** Clinical and Immunologic Predictors of Scleroderma Renal Crisis in Japanese Systemic Sclerosis Patients With Anti–RNA Polymerase III Autoantibodies. *Arthritis & Rheumatology*, 67(4), pp.1045-1052, 2015.
15. **Penn H., Howie A.J., Kingdon E.J., et al.** Scleroderma renal crisis: patient characteristics and long-term outcomes. *Qjm*. 2007 Aug 1; 100(8):485-94.
16. www.uptodate.com
17. **Steen V.D., Medsger T.A.** Long-term outcomes of scleroderma renal crisis. *Annals of internal medicine*. 2000 Oct 17; 133(8):600-3.
18. **Shanmugam V.K., Steen V.D.** Renal disease in scleroderma: an update on evaluation, risk stratification, pathogenesis and management. *Current opinion in rheumatology. 2012 Nov; 24(6):669.*
19. **Lee C.M., Girnita D., Sharma A. et al.** A Unique Presentation of Anti-RNA Polymerase III Positive Systemic Sclerosis Sine Scleroderma. *Case Reports in Rheumatology*, 2016.
20. **Hesselstrand R., Scheja A. Wuttge D.M. et al.** Scleroderma renal crisis in a Swedish systemic sclerosis cohort: survival, renal outcome, and RNA polymerase III antibodies as a risk factor. *Scandinavian journal of rheumatology*, 2012 41(1), pp.39-43.