REVIEW

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SCLERODERMA RENAL CRISIS

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Abstract

Systemic sclerosis (SSc), also known as scleroderma, is a disease that can affect many tissue and organ systems. Contrary to expectations, SSc can also frequently affect the kidneys. Most renal involvements are in the form of asymptomatic proteinuria and elevated creatinine levels. Scleroderma renal crisis (SRC), which is one of the mortal clinical findings of SSc, is rarely seen. The diffuse skin involvement subtype of SSc, early stage of the disease (first 4 years), anti-RNA-polymerase III antibody positivity, and corticosteroid use are risk factors for SRC. Angiotensin-converting enzyme inhibitor (ACEi) is used for treating SRC. For this reason, a close follow-up of patients with high risk of SRC is recommended because early initiation of treatment increases the chance of success. In the prophylactic use of ACEi, the prognosis may be worse since the clinical manifestations of SRC are suppressed, and the diagnosis of SRC is delayed, and thus SRC treatment is delayed (ACEi are used in higher doses in treatment). Angiotensin receptor blockers and iloprost are alternatives to ACEi in SRC treatment. The decision for renal transplantation should not be rushed in patients treated for SRC, as renal function may return late.

Keywords: Systemic sclerosis, renal involvements, scleroderma renal crisis

INTRODUCTION

Systemic sclerosis (scleroderma, SSc) is a chronic autoimmune/inflammatory disease characterized by fibrosis the skin and internal organs. Although the prevalence of SSc may show significant differences in relation to ethnic and regional factors, it varies between 30 and 240 per million. The disease is most commonly seen between the ages of 30 and 50 and the female/male ratio is 8-9/1 (1-3). In a study conducted in the Edirne region, the prevalence of SSc was determined to be 110 per million in our country (4). Immune activation, vasculopathy, oxidative stress, and subsequent increased fibroblastic activation are considered to be the basic steps in the pathogenesis of SSc. Activated fibroblasts (myofibroblasts) produce many pro-fibrotic cytokines and growth factors, along with the production of extracellular matrix main structures. Episodic vasospasm in the vascular bed and fibrointimal proliferation that occur in the later stages contributes to tissuing damage by causing ischemia/hypoxia in the tissues. Because of these events, structural and functional problems occur in the skin and visceral organs (lung, kidney, gastrointestinal system, and heart) with diffuse fibrosis (5,6). Although the clinic of the patients is shaped according to the severity of the skin and internal organ involvement, the first complaints and findings often nonspecific. Weakness, fatigue, joint pain, and morning stiffness is common nonspecific complaints. The Raynaud phenomenon (RF) is the earliest manifestation of SSc and may occur years before the disease develops. RF is characterized by triphasic color changes consisting of pallor, cyanosis, and erythema triggered by cold and emotional stress in the extremities of the body, especially in the hands and feet. The first specific finding in SSc is swelling and hardening

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of the skin of the hands and fingers. The clinical course after this stage is highly variable. Patients may present with dyspnea, cough, arthralgia/arthritis, dental problems, gastroesophageal reflux, dysphagia, or sexual problems depending on the organ involved and the severity of involvement, as well as skin findings such as RF, digital ulcer/gangrene, itching, and dryness (5,6).

According to the clinical findings of scleroderma, it is divided into two subgroups: localized and systemic. In localized forms, unlike SSc, there is no RF, autoimmune markers, or visceral involvement. SSc with diffuse cutaneous involvement (dcSSc) and SSc with limited cutaneous involvement (lcSSc), which are the most common systemic forms encountered in the clinic, are mainly differentiated according to the localization and extent of skin involvement and differ from each other in many aspects (3,7). In lcSSc, skin involvement is present on the face and distal parts of the knees and elbows, whereas the proximal trunk and extremities are not involved. In lcSSc, internal organ involvement is less common than dcSSc or occurs latter. Common clinical findings of lcSSc are calcinosis, RF, esophageal dysmotility, sclerodactyly, and telangiectasia, and these findings are also called calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia syndrome. In addition, pulmonary arterial hypertension (PAH) without interstitial lung disease (ILD) is an important complication of lcSSc. Anti-centromere antibody positivity is frequently found in lcSSc and its prognosis is better than dcSSc (5,6). In dcSSc, skin involvement progresses to the proximal extremities and trunk. Unlike lcSSc, the time between the RF and the onset of the skin involvement is shorter. In these patients, anti-centromere antibody was negative and anti-topoisomerase-I (anti-Scl-70) antibody was positive. In dcSSc, internal organ involvement is more common and the prognosis is worse. It may lead to ILD and/or PAH in the lung. In addition to these, scleroderma renal crisis (SRC), gastrointestinal findings, and digital vasculopathies constitute serious problems (5,6). Skin findings play a key role in the diagnosis of SSc. The patient has a typical facial appearance. Facial mimic lines disappear, radial lines appear around the mouth, mouth opening decreases (tapir mouth appearance), the nose becomes sharper, and teeth due to atrophy in the gums become visible. In addition, hypo- and hyperpigmented areas of the skin, telangiectasias, calcinoses, and ulcerated areas on bone protrusions may occur in the later stages. The diagnosis of SSc can be made easily in patients with typical skin and visceral organ involvement. American College of Rheumatology diagnosis/classification criteria are used in diagnosis. However, these criteria are insufficient in diagnosing patients presenting with early RF, edematous skin involvement, and mild skin hardness. In such cases, autoantibodies (anti-nuclear antibody, anti-centromere, and anti-Scl-70 antibodies) and typical nail bed capillaroscopy findings (giant capillaries, microhemorrhages, avascular areas, “droup out” sign and neovascularization) guide us and enable us to make an early diagnosis (2).

RENAL INVOLVEMENT IN SCLERODERMA

It is stated that more than half of SSc patients have asymptomatic renal involvement (such as proteinuria, elevated creatinine level and hypertension). In the autopsy series, 60-80% of SSc patients have renal pathologies. On the other hand, the presence of renal involvement is one of the indicators of poor prognosis in SSc patients (8-10). SRC is a well-known and rare form of renal involvement of SSc. Mild proteinuria and renal failure are more common examples of renal involvement in SSc. In addition, membranous glomerulonephritis and renal failure associated with anti-neutrophil cytoplasmic antibody (ANCA) positivity (crescentic glomerulonephritis) are other rare examples of renal involvement that can be seen in SSc. Proteinuria is one of the mortality risk factors in SSc patients. In patients with overt proteinuria, lupus serology should be studied. Systemic lupus erythematosus (SLE) may anti-dsDNA positive without clinical signs and may be associated with proteinuria in SSc. In SSc, we rarely encounter patients with proteinuria more than 1 g/day. However, it should be known that 17.5% of the patients have proteinuria and 25% have albuminuria (10). Albuminuria is associated with long disease duration and high blood pressure in SSc. Angiotensin-converting enzyme inhibitor (ACEi) therapy in proteinuria seen in SSc can reduce the amount of proteinuria, as in other proteinuria-causing diseases. ANCA positivity can be rarely seen (9%) in SSc patients. Slow-progressing renal failure and glomerulonephritis symptoms can be seen in ANCA-positive SSc patients, and unlike SRC, blood pressure does not elevate. ANCA positivity is seen more frequently in the lcSSc subtype, and clinical findings that may be associated with ANCA positivity occur in the late stages of the disease. On the other hand, SRC occurs in the dcSSc subtype and in the early years of the disease (8,11,12).

SCLERODERMA RENAL CRISIS

SRC is a mortal complication of SSc. Although its frequency has decreased recently, it is seen at a rate of 4% in dcSSc and 1% in sSSc (7). SRC usually occurs within the first 4 years of the onset of the disease. SRC manifests itself with sudden elevation of blood pressure and deterioration in kidney function (Table 1). In these patients, findings such as hyperreninemia, microangiopathic hemolytic anemia, thrombocytopenia, heart failure, pulmonary edema, hypertensive encephalopathy, and retinopathy can be

Table 1. Diagnostic criteria and supporting evidence were determined in the set of classification criteria for scleroderma renal crisis UKSSG 2016 (13)

Diagnostic criteria (essential)	Supportive evidence (desirable)
1. High blood pressure a. New onset BP >150/85 mmHg b. Increase ≥20 mmHg from usual systolic BP **2. Acute kidney failure** a. >50% increase in serum creatinine from stable baseline b. Increase of 0.3 mg/dL in serum creatinine level	- Microangiopathic hemolytic anemia, thrombocytopenia, and biochemical findings of hemolysis. - Accelerated hypertension on retinal examination microscopic hematuria. - Oliguria or anuria pulmonary oedema. - Renal biopsy: onion skin proliferation within the walls of intrarenal arteries and arterioles, fibrinoid necrosis, glomerular shrinkage.

BP: Blood pressure, UKSSG: UK Scleroderma Study Group

seen (8,13). Blood pressure usually high in SRC. However, at a rate of 10%, blood pressure can be found to be normal due to previous antihypertensive drug use or myocardial involvement. This situation is called normotensive renal crisis (14). It is thought that excessively elevated renin in patients with SRC changes perfusion in the juxtaglomerular apparatus, leading to renin-mediated hypertension, which may be a factor in the development of SRC. In renal histopathology, ischemic changes in glomeruli and proliferative occlusive vessel pathologies in arterioles (nested "onion membrane" appearance) can be observed in renal histopathology in SRC (10).

DIAGNOSIS

For the diagnosis of SRC, new-onset blood pressure (arterial blood pressure >160/100 mmHg), presence of fragmented erythrocytes in peripheral blood, elevated creatinine, and presence of proteinuria are sought. The major risk factors for developing SRC are the early stage of the disease, dcSSc subtype, and the history of corticosteroid use. Roughly 80% of SRC is observed within the first 4 years of the disease (8,15). Similarly, using ≥15 mg/day prednisone in the last 6 months increases the risk of SRC from 12% to 36% (13). Therefore, the blood pressure and renal functions of SSc patients who need to use corticosteroids should be closely monitored (16). In addition, anti-RNA polymerase III antibody positivity (8,17), high serum CD147 (18), high skin score, joint contracture, tendon friction sound, *HLA-DRB1*0407*, and **1304* presence are other risk factors for SRC in SSc patients (19) (Table 2).

Table 2. Risk factors for scleroderma renal crisis

1. Subtype with diffuse skin involvement
2. Rapid progression of skin involvement
3. Disease duration <4 years
4. New cardiac event: pericarditis and left ventricular failure
5. New-onset anemia
6. Anti-RNA-polymerase III antibody positivity
7. Using corticosteroids (>15 mg/day) in the last 3 months
8. Using cyclosporine in the last 3 months

DIFFERENTIAL DIAGNOSIS

SRC causes rapidly progressive renal failure and high blood pressure. Diseases such as thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, renal artery stenosis, and toxic nephropathy should be kept in mind in the differential diagnosis of SRC (Table 3). SSc patients may have anti-dsDNA antibody positivity without SLE and ANCA test positivity without vasculitis findings. However, the possibility of renal involvement is high in patients with SSc positive for these antibodies. It is necessary to pay attention to the distinction between renal involvement and SRC in an ANCA positive SSc patient (Table 4). ANCA positivity occurs in the lcSSc subtype after many years of SSc diagnosis. However, SRC is common in the dcSSc subtype and in the first years of SSc diagnosis. While corticosteroids are used for treating renal involvement associated with ANCA positivity, ACEi is ineffective. In contrast, ACEi is used in the treatment of SRC and corticosteroid is one of the risk factors of SRC (10,20).

Table 3. Diseases to be considered in the differential diagnosis of scleroderma renal crisis

1. Renal artery stenosis
2. Thrombotic thrombocytopenic purpura (TTP)
3. Atypical hemolytic uremic syndrome (aHUS)
4. Rapidly progressive (crescentic) glomerulonephritis (RPGN)
5. ANCA-associated vasculitis
6. Toxic nephropathy
7. Transplant rejection

ANCA: Anti-neutrophil cytoplasmic antibody

TREATMENT

SRC is an emergency that requires hospitalization and close monitoring and treatment (Figure 1). Treatment of SRC should be carried out in specific centers because mortality due to SRC is still quite high in centers that do not specialize in this disease (8). ACEi

Table 4. Comparison of scleroderma renal crisis and ANCA-associated vasculitis

Scleroderma renal crisis	ANCA-associated vasculitis
Occurs mainly in dcSSc and only rarely (1-2%) in lcSSc	Occurs mainly in lcSSc
Patients develop SRC within 7.5 months to 4 years of SSc onset	Typically occurs several years after SSc onset
Malignant hypertension (seen in less than 10% of normotensive SRC)	Mild hypertension
Anti-RNA polymerase III positive	ANCA positive
Acute renal failure and severe hypertension	The subacute presentation with progressive renal failure (crescentic glomerulonephritis)
Steroids (≥15 mg/day) are one of the major risk factors	Responsive to steroids
ACEi as the first-line treatment in SRC	Does not respond to ACEi. Cyclophosphamide (or rituximab) and corticosteroids are used in the treatment

ANCA: Anti-neutrophil cytoplasmic antibody, dcSSc: Diffuse cutaneous systemic sclerosis, SSc: Systemic sclerosis, lcSSc: limited cutaneous systemic sclerosis, SRC: Scleroderma renal crisis, RNA: Ribonucleic acid, ACEi: Angiotensin-converting enzyme inhibitors

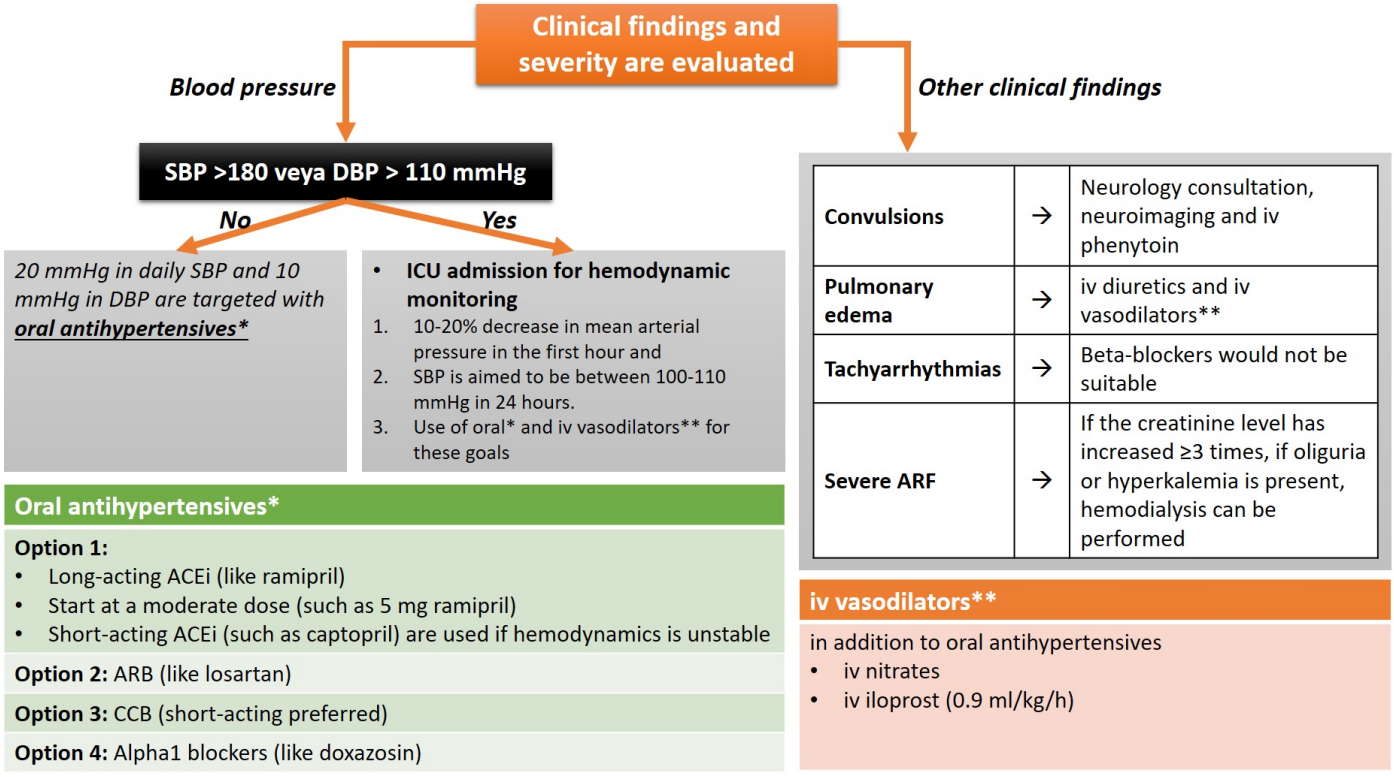

Figure 1. Scleroderma renal crisis treatment recommendations created by the UK Scleroderma Study Group (UKSSG) (13)
ACEi: Angiotensin-converting enzyme inhibitor, ARB: Angiotensin 2 receptor blocker, CCB: Calcium channel blocker, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

are the first choice for treating SRC. With the use of ACEi, there was a significant decrease in the mortality of SRC, and the 5-year survival increased from 10% to 68-90%. Also, ACEi have severely reduced the need for continuous dialysis (10). Even in patients on dialysis, 30% improvement in renal function has been reported with ACEi treatment. The efficacy of ACEi is related to the baseline renal injury. If ACEi is started while the serum creatinine value is below 4 mg/dL, renal functions can be improved to a great extent (8). If blood pressure remains high despite treatment with the maximum dose of ACEi, angiotensin 2 receptor blockers (ARBs) can be added to the treatment. However, ARB therapy alone is insufficient without ACEi (8,21). If these treatments fail, calcium channel blockers (CCBs) or alpha blockers may be added to the treatment (15,16). If a drug belonging to the ACEi group needs to be discontinued due to its side effects, another ACEi should be tried first (switched). The systolic

blood pressure should be reduced by 20 mmHg daily and the diastolic blood pressure by around 10 mmHg daily until the blood pressure returns to normal limits. Hypotension should be avoided; for this purpose, blood pressure should be titrated with close monitoring (8). Pregnancy is not recommended in SRC. If 5 years after SRC, the skin score is low and the patient feels well, ACEi can be discontinued, and pregnancy may be permitted in selected cases. During pregnancy, blood pressure and renal functions should be closely monitored by starting a drug that is not contraindicated in pregnancy, such as CCB, or before any medication is started (13). Despite the positive developments, SRC is still an important cause of mortality and morbidity. Knowing the risky patients in advance and the precautions to be taken are more effective than the treatment given after SRC development. The use of ground-breaking ACEi for treating SRC for prophylaxis is discussed. The reason for this confusion is that in a previously published case series, it was suggested that the clinical course was more severe in patients who developed SRC while using ACEi for any reason, and more patients needed dialysis (22). ACEi are used at high doses for treating SRC; ACEi that are not effective when used in low doses may delay the diagnosis by masking the initial findings of SRC. In SRC patients who need dialysis, at least 2 years should be waited for kidney transplantation because kidney functions may improve in the future. Re-occurrence of SRC in the same patient is extremely rare (23,24).

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.R.A., S.S.K., Concept: F.A., A.K., Design: M.R.A., S.S.K., Data Collection or Processing: F.A., A.K., Literature Search: M.R.A., S.S.K., Writing: M.R.A.

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REFERENCES

1. Özgen M, Koca SS. Etiopathogenesis and Current Treatment of Scleroderma. Fırat University Medical Journal of Health Sciences 2010;24:69-76.
2. Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. Autoimmun Rev 2010;9:A311-8.
3. Walker UA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007;66:754-63.
4. Cakır N, Pamuk ÖN, Derviş E, Imeryüz N, Uslu H, Benian Ö, et al. Theprevalences of somerheumaticdiseases in western Turkey: Havsa study. Rheumatol Int 2012;32:895-908.
5. Denton CP, Black CM. Scleroderma--clinical and pathological advances. Best Pract Res Clin Rheumatol 2004;18:271-90.
6. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-5.
7. Meier FM, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2012;71:1355-60.
8. Shanmugam VK, Steen VD. Renal disease in scleroderma: an update on evaluation, risk stratification, pathogenesis and management. Curr Opin Rheumatol 2012;24:669-76.
9. Steen VD, Medsger TA Jr. Long-term outcomes of scleroderma renal crisis. Ann Intern Med 2000;133:600-3.
10. Chrabaszcz M, Małyszko J, Sikora M, Alda-Malicka R, Stochmal A, Matuszkiewicz-Rowinska J, et al. Renal Involvement in Systemic Sclerosis: An Update. Kidney Blood Press Res 2020;45:532-48.
11. Jennette JC, Falk RJ, Gasim AH. Pathogenesis of antineutrophil cytoplasmic autoantibody vasculitis. Curr Opin Nephrol Hypertens 2011;20:263-70.
12. Derrett-Smith EC, Nihtyanova SI, Harvey J, Salama AD, Denton CP. Revisiting ANCA-associated vasculitis in systemic sclerosis: clinical, serological and immunogenetic factors. Rheumatology (Oxford) 2013;52:1824-31.
13. Lynch BM, Stern EP, Ong V, Harber M, Burns A, Denton CP. UK Scleroderma Study Group (UKSSG) guidelines on the diagnosis and management of scleroderma renal crisis. Clin Exp Rheumatol 2016;34 Suppl 100:106-9.
14. Helfrich DJ, Banner B, Steen VD, Medsger TA Jr. Normotensive renal failure in systemic sclerosis. Arthritis Rheum 1989;32:1128-34.
15. Walker KM, Pope J. Treatment of systemic sclerosis complications: what to use when first-line treatment fails--a consensus of systemic sclerosis experts. Semin Arthritis Rheum 2012;42:42-55.
16. Kowal-Bielecka O, Landewé R, Avouac J, Chwiesko S, Miniati I, Czirjak L, et al. EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis 2009;68:620-8.
17. Nikpour M, Hissaria P, Byron J, Sahhar J, Micallef M, Paspaliaris W, 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 Res Ther 2011;13:R211.
18. Yanaba K, Asano Y, Tada Y, Sugaya M, Kadono T, Hamaguchi Y, et al. Increased serum soluble CD147 levels in patients with systemic sclerosis: association with scleroderma renal crisis. Clin Rheumatol 2012;31:835-9.
19. Nguyen B, Mayes MD, Arnett FC, del Junco D, Reveille JD, Gonzalez EB, et al. HLA-DRB1*0407 and *1304 are risk factors for scleroderma renal crisis. Arthritis Rheum 2011;63:530-4.

20. Woodworth TG, Suliman YA, Li W, Furst DE, Clements P. Scleroderma renal crisis and renal involvement in systemic sclerosis. Nat Rev Nephrol 2016;12:678-91.

21. Cheung WY, Gibson IW, Rush D, Jeffery J, Karpinski M. Late recurrence of scleroderma renal crisis in a renal transplant recipient despite angiotensin II blockade. Am J Kidney Dis 2005;45:930-4.

22. Xiong A, Cao Y, Xiang Q, Song Z, Zhang Y, Zhou S, et al. Angiotensin-converting enzyme inhibitors prior to scleroderma renal crisis in systemic sclerosis: A systematic review and meta-analysis. J Clin Pharm Ther 2022;47:722-31.

23. Pham PT, Pham PC, Danovitch GM, Gritsch HA, Singer J, Wallace WD, et al. Predictors and risk factors for recurrent scleroderma renal crisis in the kidney allograft: case report and review of the literature. Am J Transplant 2005;5:2565-9.

24. Siva B, McDonald SP, Hawley CM, Rosman JB, Brown FG, Wiggins KJ, et al. End-stage kidney disease due to scleroderma--outcomes in 127 consecutive ANZDATA registry cases. Nephrol Dial Transplant 2011;26:3165-71.