

# Scleroderma Renal Crisis in a Normotensive Patient



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## INTRODUCTION

Systemic sclerosis (scleroderma) is an autoimmune disorder of unclear etiology that leads to fibrosis and vascular injury of the skin and multiple organs, including the lungs, heart, gastrointestinal tract, kidneys, and the musculoskeletal system. It is classified as either diffuse or limited cutaneous based on the extent of skin thickening. In the diffuse form of systemic sclerosis, skin thickening is extensive and usually occurs within 1 year, compared with the limited cutaneous form, in which skin thickening is often confined to the face, fingers, and hands. Diffuse systemic sclerosis is also characterized by Raynaud’s phenomenon and significant visceral involvement.

Renal complications are common in patients with systemic sclerosis. The most serious renal manifestation is scleroderma renal crisis, which occurs in up to 10% of patients with diffuse cutaneous systemic sclerosis, and only rarely (1%–2%) in limited cutaneous systemic sclerosis.<sup>1,2</sup> It is a relatively early complication of systemic sclerosis, typically occurring within 5 years of diagnosis, and may be the initial presentation of systemic sclerosis.<sup>3</sup> Scleroderma renal crisis is usually characterized by abrupt onset of marked hypertension, rapidly progressive renal failure due to thrombotic microangiopathy (TMA), vasospasm, and tissue ischemia. However, up to 10% of patients with scleroderma renal crisis are normotensive, although their blood pressure may be increased from baseline values.<sup>4</sup>

## CASE PRESENTATION

A 34-year-old man presented with a 2-week history of progressively worsening shortness of breath and hemoptysis. His past medical history dated back to 6 months prior when he presented to the hospital with several weeks’ history of maculopapular rash on his forearms and legs that was associated with arthralgia.

Because he had positive rapid plasma reagin, antinuclear antibody, and Lyme titer, he was treated for presumed secondary syphilis, and then subsequently for Lyme disease. His symptoms progressed, so he was referred to rheumatology. His workup at that time revealed elevated creatinine phosphokinase and transaminases levels, positive anticyclic citrullinated peptide antibody, antithreonyl-tRNA synthetase, and antitopoisomerase I. Other tests, such as antidouble-stranded DNA, anti-Smith, ribonucleoprotein, anti-Sjögren’s-syndrome-related antigen A, anti-Sjögren’s-syndrome-related antigen B, anti Jo-1, antimitochondrial antibody, antismooth muscle antibody, HIV, hepatitis B and C, Lyme titer, parvovirus, chlamydia, and gonorrhea, were all negative.

Shortly after testing, he was hospitalized for progressive myalgia, arthralgia, and dysphagia associated with severe right shoulder pain, a 50-lb unintentional weight loss, and skin thickening in the hands. He was treated with a short course of low-dose glucocorticoids. Magnetic resonance imaging without contrast was suggestive of myositis.

He had an outpatient muscle biopsy that showed myositis; his creatinine phosphokinase level at the time was about 3000 U/l. He was diagnosed with systemic sclerosis based on his clinical symptoms, and positive anti topoisomerase 1 and cyclic citrullinated peptide antibody (>250.0 U). He was subsequently prescribed prednisone 60 mg daily and methotrexate 12 mg weekly. Routine lab tests performed at this time showed hemoglobin of 14.0 g/dl, platelet count of 197/nl, and a serum creatinine level of 0.7 mg/dl. Spot urine protein-creatinine ratio was 0.74 g/g. One week after initiation of prednisone, his serum creatinine level increased from 0.7 to 2.2 mg/dl.

He presented to the hospital 2 weeks later with progressively worsening shortness of breath, dysphagia, and hemoptysis. At the time, he was taking 40 mg prednisone daily, gabapentin 300 mg 3 times daily, folic acid 1 mg daily, and acetaminophen-oxycodone as needed for pain.

On presentation to the emergency room, his blood pressure was 129/84 mm Hg and his pulse was 99 bpm. Baseline blood pressure was about 100/60 mm Hg. His physical exam was normal with the exception of mild skin tightening of his hands and forearms, and diffuse decreased breath sounds. He did not have any synovitis, joint swelling, tendon rubs, or proximal weakness on exam. See [Table 1](#) for relevant laboratory test results on admission. Peripheral smear revealed anisocytosis, poikilocytosis, and many schistocytes.

Urine microscopy revealed dysmorphic red blood cells and numerous granular casts. Urine drug screen was negative. Echocardiography showed an ejection fraction of 35%, with left ventricular moderate global hypokinesis, mild mitral regurgitation, and aortic valvular sclerosis. Chest radiograph showed equivocal left lower lobe opacity.

He was started on broad-spectrum antibiotics with vancomycin, cefepime, and azithromycin for suspected pneumonia. Shortly after admission, he developed worsening dyspnea and tachycardia, with an acute drop in hemoglobin to 7 mg/dl. His serum creatinine level continued to worsen, with associated anuria. He was diagnosed with TMA; the differential diagnoses at this time included scleroderma renal crisis, thrombotic thrombocytopenia purpura, antiphospholipid antibody syndrome, or atypical hemolytic uremic syndrome. He was started on captopril 6.25 mg 3 times daily on Hospital Day 1. The dose could not be titrated up because his systolic blood pressure was in the range of 80 to 99 mm Hg. Plasma exchange was started on Hospital Day 1. Hemoglobin level, platelet count, lactate dehydrogenase and reticulocyte counts rapidly improved after 5 sessions of plasma exchange. Hemodialysis was initiated on Hospital Day 2 due to deteriorating kidney function, anuria, and hyperkalemia. On Hospital Day 3, antineutrophil cytoplasmic autoantibodies, antitymeloxygenase and

antiproteinase-3, antiglomerular basement membrane antibodies, anticardiolipin assay (cardiolipin antibodies IgG and IgM and  $\beta$ -2 glycoprotein-1), and ADAMTS-13 were reported to be normal.

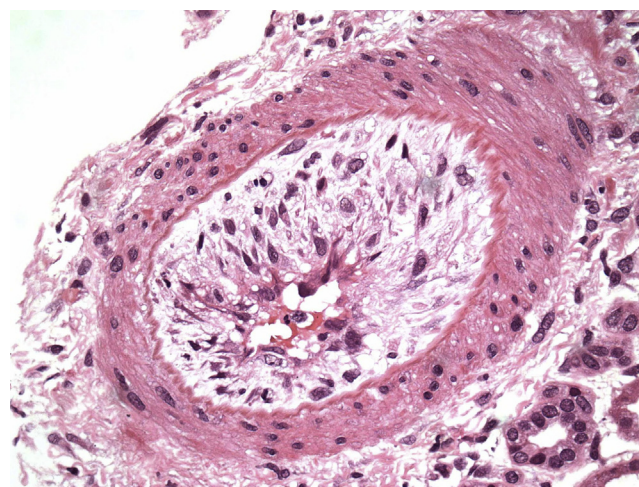
A kidney biopsy was done on Hospital Day 7. It showed TMA with predominant involvement of blood vessels and secondary acute and severe ischemic glomerular changes involving 17 out of 17 glomeruli ([Figures 1–6](#)). Diffuse and severe tubular degenerative changes and arteriosclerosis were noted. Immunofluorescence microscopy revealed no deposition of IgG, IgA, IgM, C3, and C1q, providing evidence against immune complex glomerular diseases. Light microscopy revealed findings consistent with severe TMA with predominant involvement of blood vessels and secondary ischemic glomerular changes. The predominance of TMA vascular changes on the biopsy in contrast to glomerular involvement, and the clinical presentation pointed to a diagnosis of scleroderma renal crisis.

The patient was discharged on enalapril 10 mg daily, mycophenolate mofetil 1000 mg twice a day, and instructions for hemodialysis 3 times a week. He did well until 4 weeks later, when he reported atrial fibrillation with rapid ventricular response. At this time, his serum creatinine level was 3.25 mg/dl with a 24-hour creatinine clearance of 26 ml/min. Hemodialysis was discontinued. He was discharged home on Hospital Day 4 with furosemide and enalapril. He was rehospitalized 16 days later with shortness of breath and hypotension (systolic blood pressure 70–89 mm Hg). His chest radiograph was normal with no signs of pulmonary edema. Clinically, he was euvolemic. His repeat echocardiogram revealed a worsening ejection fraction of 10% from 35% 10 weeks prior. A cardiac catheterization revealed low right-sided filling pressures with a pulmonary wedge pressure of 9 mm Hg. Cardiac index was 1.59. There was no evidence of significant

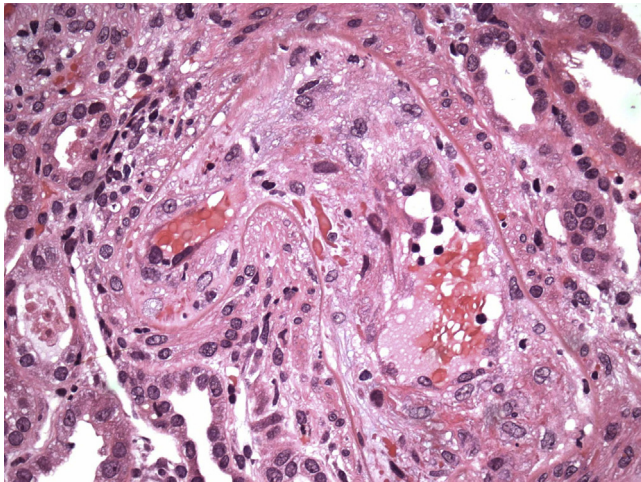
**Table 1.** Relevant laboratory results

Test	Result	Reference range
Hemoglobin (g/dl)	8.9	13.3–17.7
Platelets (/nl)	29	150–400
Haptoglobin (mg/dl)	< 8	30–200
Creatinine (mg/dl)	6.2	0.7–1.3
Blood urea nitrogen (mg/dl)	116	8–22
Total bilirubin (mg/dl)	5.5	0.2–1.0
Indirect bilirubin (mg/dl)	1.8	0.0–0.3
Alanine transaminase (IU/l)	166	0–54 U/l
Alkaline phosphatase (IU/l)	70	50–135
Lactate dehydrogenase (IU/l)	10,461	310–620
Creatinine phosphokinase (IU/l)	2376	40–250
Complements <sup>a</sup>	Normal	
Disseminated intravascular coagulation panel	Negative	

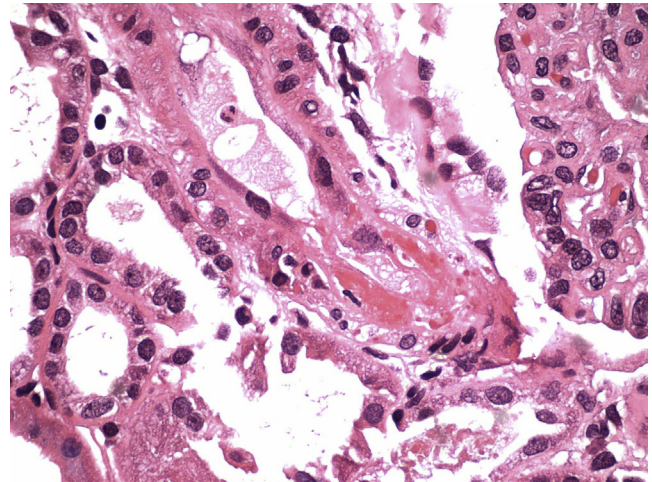
<sup>a</sup>C3, C4, and CH50.



**Figure 1.** Mucoïd intimal edema.



**Figure 2.** Intimal edema and fibrin.



**Figure 4.** Fibrinoid necrosis in an arteriole.

obstructive coronary artery disease. A milrinone drip was initiated. However, the patient went into cardiac arrest and died on Hospital Day 6.

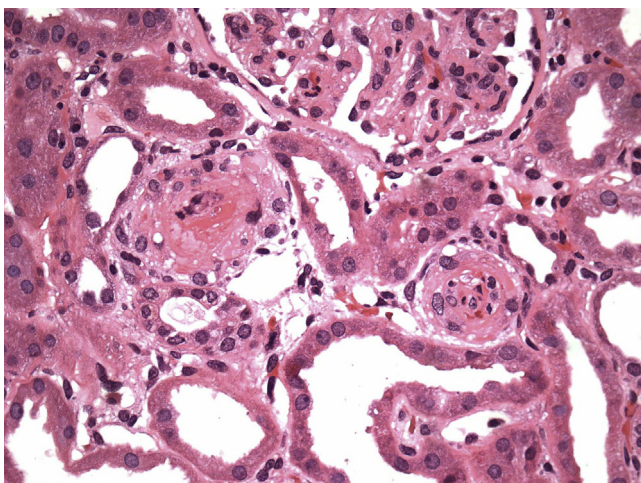
## DISCUSSION

A diagnosis of scleroderma renal crisis was strongly favored in this patient based on the finding of thrombotic microangiopathy, the presence of preexisting high suspicion of systemic sclerosis, and recent glucocorticoid use.

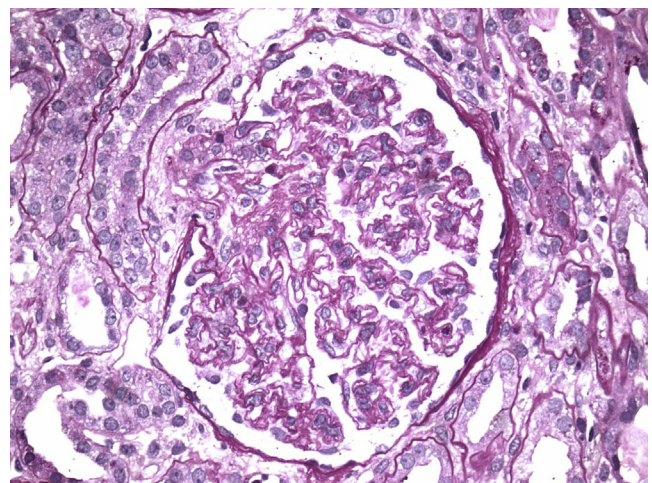
Scleroderma renal crisis is associated strongly with a positive speckled antinuclear antibody pattern as well as with positive anti-RNA polymerase III. Because renal crisis is more common in diffuse systemic sclerosis, it is associated more with positive antitopoisomerase in contrast to anticentromere, which is seen more with limited cutaneous systemic sclerosis. The findings of positive antithreonyl-tRNA synthetase and anticyclic citrullinated peptide antibody in this patient suggest an overlap syndrome with other systemic rheumatic diseases.

Scleroderma renal crisis in the absence of hypertension is associated with worse renal outcome and higher mortality compared with scleroderma renal crisis with hypertension.<sup>4</sup> The poor prognosis has been attributed to subclinical renal injury leading to TMA in the setting of delayed diagnosis. This presentation is more common in patients with cardiac involvement and previous treatment with glucocorticoids, as in this patient. Although this patient was normotensive, his blood pressure of 125/84 mm Hg upon admission was higher than his baseline blood pressure of 100/60 mm Hg.

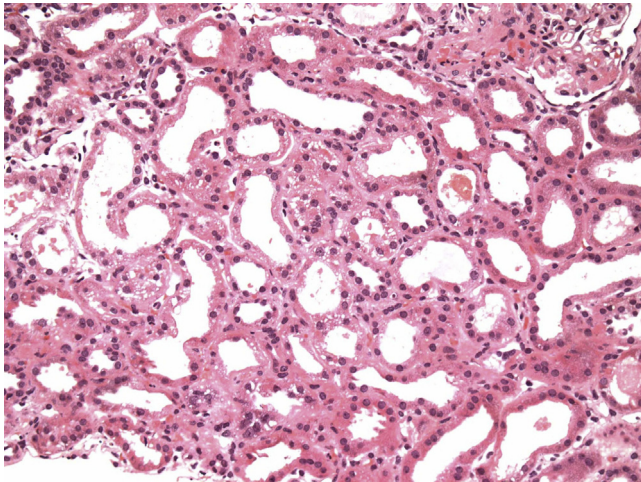
The risk factors for developing scleroderma renal crisis include the presence of diffuse disease; positive antitopoisomerase III antibody test; onset of scleroderma within the previous 1 year; fatigue, weight loss, and polyarthritis; drugs such as prednisone at doses >15 mg/day, cyclosporine within the preceding 3 months, and cocaine use. Other risk factors reported include contractures at the large joints, new-onset anemia, new heart failure, or pericardial effusion.<sup>2</sup>



**Figure 3.** Fibrin thrombus in an arteriole.



**Figure 5.** Ischemic glomerulus.



**Figure 6.** Diffuse tubular injury.

The diagnosis of scleroderma renal crisis is based on clinical suspicion and presence of autoantibodies. The presence of TMA on a renal biopsy does not provide a definite diagnosis, but is useful for excluding other diagnoses and predicting clinical outcome. TMA is characterized by microangiopathic hemolytic anemia, thrombocytopenia, elevated lactate dehydrogenase levels, and low serum haptoglobin level. Microangiopathic hemolytic anemia and thrombocytopenia may be present in up to 60% and 50%, respectively, of patients with scleroderma renal crisis.<sup>5</sup> The urine sediment is usually normal, but may be associated with microscopic hematuria and proteinuria. Urinary granular casts may be present on urine microscopy.

The differential diagnoses for TMA are broad and include malignant hypertension, thrombotic thrombocytopenia purpura, atypical hemolytic uremic syndrome, radiation nephritis, antiphospholipid antibody syndrome, chronic transplantation rejection, drug toxicity due to antimicrobial agents, quinine, calcineurin inhibitors, and chemotherapy drugs such as antivascular endothelial growth factor agents and gemcitabine, to name a few. Procoagulant states such as malignancy and oral contraceptive use have also been shown to cause TMA. The etiology of TMA in a large percentage of cases remains unknown.<sup>5</sup> In this patient, thrombotic thrombocytopenia purpura and antiphospholipid syndrome were excluded because ADAMTS-13 and anticardiolipin assay were normal. The other diagnoses were excluded based on his history.

TMA is characterized histologically by vessel wall thickening with endothelial swelling and detachment of endothelial cells from the basement membrane and formation of platelet-fibrin hyaline microthrombi that occlude arterioles and capillaries.<sup>5</sup> These changes are typically localized to the small arcuate and interlobular arteries and the glomeruli. In contrast to atypical

hemolytic uremic syndrome and thrombotic thrombocytopenia purpura, the renal biopsy findings in scleroderma renal crisis, like malignant hypertension, have a predominance of primary small vessel changes compared with glomeruli alterations.<sup>6</sup> The characteristic finding in scleroderma renal crisis is intimal proliferation and thickening that leads to narrowing and obliteration of the vascular lumen, with concentric onion-skin hypertrophy.

Acute vascular changes usually manifest as intimal accumulation of mucoid material, thrombosis, and fibrinoid necrosis, as seen in [Figures 1, 3, and 4](#). The severity and extent of the acute vascular injury is associated with poor prognosis.<sup>7</sup> Chronic findings usually manifest as onion-skin lesions and subsequently fibrointimal sclerosis with adventitial fibrosis. Glomerular changes may occur as a result of the vascular injury or decreased renal perfusion, and may manifest as endothelial swelling, glomerular capillary thrombosis, and ischemic glomerulus, which is characterized by wrinkling and thickening of the capillary walls and shrinkage of the glomerular tuft ([Figure 5](#)). Tubulointerstitial changes may occur as a result of the vascular injury, and typically manifest as ischemic acute tubular necrosis ([Figure 6](#)), and subsequently as tubular atrophy and interstitial fibrosis. Immunofluorescence and electron microscopy are of limited utility in the diagnosis of scleroderma renal crisis. However, the presence of peritubular capillary C4d deposits in scleroderma renal crisis, as well as vascular thrombosis and severe glomerular ischemic collapse, have been shown to correlate with poor renal recovery.<sup>7</sup>

Angiotensin-converting enzyme inhibitors are the first-line treatment for both hypertensive and normotensive scleroderma renal crisis. Since their introduction the late 1970s, patients' 5-year survival has increased from <10% to up to 65%.<sup>2</sup> Although use of angiotensin-converting enzyme inhibitors has been associated with spontaneous regression of systemic sclerosis skin manifestations in patients with positive RNA polymerase III, they have not been shown to cause skin regression.<sup>8,9</sup>

It is important to avoid sudden and excessive decreases in blood pressure because excessive reduction in renal perfusion may lead to acute tubular necrosis. Once the diagnosis of scleroderma renal crisis is made, a low-dose angiotensin-converting enzyme inhibitor should be continued indefinitely. As in all other forms of renal dysfunction, nephrotoxic drugs must be avoided. Plasma exchange is considered only in cases of severe TMA. Administration of eculizimab was considered briefly for this patient. However, because the patient had rapid hematologic recovery after

plasma exchange therapy and initiation of captopril, this was not pursued. Also, from our literature review, we found no data to support the use of eculizimab in scleroderma renal crisis.

As many as 25% of patients with scleroderma renal crisis require dialysis at presentation. Long-term survival is poor, especially if there is no renal recovery. The improvement in renal function with discontinuation of hemodialysis within 6 weeks supports the diagnosis of scleroderma renal crisis, and is consistent with previously published benefits of captopril use in scleroderma renal crisis.

## CONCLUSION

Scleroderma renal crisis in the absence of hypertension is associated with worse renal outcomes and increased mortality. It should be suspected in any patient with systemic sclerosis, especially in patients who have diffuse cutaneous systemic sclerosis and have recently been treated with glucocorticoids. Prompt initiation of an angiotensin-converting enzyme inhibitor is of utmost importance despite the presence of acute kidney injury and normal blood pressures. Prompt treatment may be associated with improved renal outcomes. However, scleroderma renal crisis in the absence of hypertension is associated with high mortality due to associated cardiac disease.

## DISCLOSURES

The author declared no competing interests.

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