Kidney Medicine

Eculizumab Use in Scleroderma Renal Crisis With Thrombotic Microangiopathy: A Case Report

Claire Trivin-Avillach, Aala Jaberi, Joel M. Henderson, Laurence H. Beck Jr, and Jean Francis

A Black woman in her 40s with past medical history significant for obesity treated with Roux-en-Y bypass surgery and a history of Raynaud's phenomenon, presented with acute pulmonary edema secondary to severe malignant hypertension and critically accelerated acute kidney injury, with evidence of systemic microangiopathic hemolytic anemia in the setting of clinical suspicion of systemic sclerosis sine scleroderma. Renin-angiotensin system blockade (angiotensin-converting enzyme inhibitor) was immediately started at the maximum possible dose in the setting of scleroderma renal crisis. Despite better control of blood pressure and volume status, kidney function continued to rapidly decline, thus a decision was made to go ahead with a kidney biopsy on day 3 of admission, which revealed severe features of scleroderma renal crisis with active thrombotic microangiopathy. The multidisciplinary team elected to treat the patient with terminal complement blockade using eculizumab in addition to high dose lisinopril and blood pressure control. Her serum creatinine peaked at 9.3 mg/dL shortly after eculizumab initiation, but improved soon after, dropping to 2.8 mg/dL after completion of the final eculizumab dose and 1.8 mg/dL 3 years later.

Complete author and article information provided before references.

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INTRODUCTION

Scleroderma renal crisis is a rare, but life-threatening condition and carries increased risk of mortality and morbidity. Up to 25% of affected patients develop kidney failure requiring kidney replacement therapy.[1,2] The etiology of scleroderma kidney disease is unclear, however, complement activation has been proposed and may be contributing to the pathogenesis of the disease.[3-5] Here we report a case of newly diagnosed scleroderma renal crisis with accelerated severe uncontrolled hypertension and rapidly progressive rising creatinine, with features of thrombotic microangiopathy (TMA) successfully treated with eculizumab after failure of angiotensin-converting enzyme inhibition in reversing the clinical course.

CASE REPORT

A Black woman in her 40s was admitted to our hospital with a history of 6 weeks of worsening dyspnea associated with lower extremity edema. Past medical history included Roux-en-Y bypass surgery for obesity and a history of Raynaud phenomenon with laboratory testing significant for positive antinuclear antibody 4 years before her presentation. However, no further investigations were performed at that time. She presented to the hospital with worsening shortness of breath, orthopnea, and chest tightness on exertion. In the emergency department, her physical examination was significant for severe hypertension with blood pressure measured at 180/110 mm Hg, peripheral edema, and elevated jugular venous pressure. The skin examination revealed multiple telangiectasias on the face, tongue, lips, upper chest, arms, and palms but no evidence of sclerodactyly. Laboratory results were significant for serum creatinine of 4.5 mg/dL (baseline creatinine of 0.8 mg/dL, 4 years prior), evidence of microangiopathic hemolytic anemia with hemoglobin of 9 g/dL, lactate dehydrogenase at 516 U/dL, undetectable haptoglobin, and the presence of schistocytes in the peripheral smear with negative Coombs test. Platelets were normal at 197 K/μL. Complement factors, including C3 and C4, were not consumed; an autoantibody panel revealed a positive nucleolar antinuclear antibody at 1:320, but double-stranded DNA, rheumatoid factor, Sjogren antibodies SSA/SSB, SCL 70, and anti-RNA polymerase III were all negative (Table 1). Urinalysis revealed microscopic hematuria and low range proteinuria (1+) quantified as 408 mg per gram of creatinine. The urine microscopy showed rare granular pigmented casts consistent with some degree of acute tubular necrosis. Kidney ultrasound revealed normally-sized kidneys with no increased echogenicity.

Treatment with high dose diuretics was immediately commenced with the relief of dyspnea. A right heart catheterization performed when the patient was more euvolemic revealed an elevated pulmonary artery pressure of 57/18 (35) mm Hg, with a wedge pressure of 14 mm Hg consistent with pulmonary hypertension. Given the clinical suspicion of scleroderma renal crisis with secondary TMA, the patient was rapidly started on nifedipine 30 mg once daily, carvedilol 12.5 mg twice daily, and captopril 6.25 mg 3 times daily on day 2 of admission, with remarkable blood pressure improvement to an average systolic reading of 140-150 mm Hg. However, a decision was made to pursue a kidney biopsy given the ongoing decline in glomerular filtration rate, despite control of blood pressure for over 24 hours. A kidney biopsy was performed on day 3 of admission. The biopsy showed acute TMA, with severe arteriolar narrowing due

Table 1. Laboratory Tests at Baseline

Test	Normal Range	Result	Test	Normal Range	Result
WBC (K/μL)	4.0-11.0	5	Anti-SSA/SSB	Negative	Negative
Hemoglobin (g/dL)	11.8-16.0	9.4	Anti-Scl 70	Negative	Negative
Platelets (K/μL)	150-400	197	Anti-CENP-A	Negative	Negative
Creatinine (mg/dL)	0.5-1.1	4.5	Anti-CENP-B	Negative	Negative
BUN (mg/dL)	7-25	52	Anti- RP11	Negative	Negative
Haptoglobin (mg/dL)	44-184	<8	Anti-RP155	Negative	Negative
Lactate dehydrogenase (U/L)	171-308	516	Anti-U1-snRNP RNP A	Negative	Negative
Direct and indirect Coombs test	Negative	Negative	Anti-U1-snRNP RNP C	Negative	Negative
BNP (pg/mL)	0-46.7	2527	Anti-U1-snRNP RNP-70kd	Negative	Negative
C3 (mg/dL)	79-160	101	Anti-fibrillarin	Negative	Negative
C4 (mg/dL)	17-48 pg/mL	39	Anti-Th/To	Negative	Negative
Anticardiolipin Ab	Negative	<8	Anti-PM/Scl100	Negative	Negative
β2-Glycoprotein Ab	Negative	<10	Anti-PM/Scl75	Negative	Negative
ANA (titer)	Negative	1:320	Anti-Sm	Negative	Negative
Rheumatoid factor	Negative	<10	Anti-RNP	Negative	Negative
Anti-dsDNA Ab	Negative	Negative	ANCA	Negative	Negative

Abbreviations and definitions: Ab, antibody; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; BNP, B-type natriuretic peptide; CENP, centromere proteins B; BUN, blood urea nitrogen; dsDNA, double-stranded DNA; PM, polymyositis; RNP, ribonucleoprotein; RP, ribosomal phosphoprotein; Sm, Smith; snRNP, small nuclear ribonucleoprotein; SSA, Sjogern Syndrome A; SSB, Sjogren syndrome B; WBC, white blood cell.

to "onion-skin" muco-intimal thickening and sclerosis, and focal glomerular capillary microthrombi formation associated with widespread glomerular hypoperfusion, and signs of glomerular capillary loop remodeling. One glomerulus showed a collapsing lesion. Some moderate chronic changes of the parenchyma with global glomerulosclerosis (9 of 63 glomeruli) and tubular atrophy and interstitial fibrosis involving 30%-40% of the cortex. Of note there was mild acute tubular injury (Fig 1).

Despite blood pressure control on increasing doses of captopril (up to 62.5 mg 3 times daily), kidney function continued to deteriorate with persistent hemolysis in the setting of biopsy features consistent with significant TMA. The TMA team was consulted promptly[6] and after careful assessment, eculizumab (a terminal complement pathway blocker) was considered. Subsequently, the patient was vaccinated against meningococcal and 900 mg of eculizumab was administered on day 5 of admission. Initially, creatinine continued to increase to 9.3 mg/dL; then, kidney function progressively improved on eculizumab combined with angiotensin-converting enzyme inhibitor (ACEi) treatment with lisinopril 40 mg daily, preventing the need to start dialysis (Fig 2). Eculizumab was discontinued after 3 months, at which point the hemoglobin had risen from a nadir of 8.4 g/dL to 11.2 g/dL and the lactate dehydrogenase had normalized at 212 U/L from a high of 516 U/L at clinical presentation. The patient's kidney function continued to improve, declining to 2.8 mg/dL immediately after the final eculizumab dose and to the most recent creatinine value of 1.8 mg/dL 3 years after discontinuation of eculizumab. Proteinuria was mild at presentation, with a urine protein-to-creatinine ratio of 0.41 g/g, which improved to 0.1 g/g 2 years after stopping eculizumab.

DISCUSSION

Scleroderma renal crisis is a rare albeit extreme consequence of scleroderma, occurring in 5%-15% of patients with diffuse cutaneous systemic sclerosis. Scleroderma renal crisis is characterized by an acute onset of acute kidney injury associated with an abrupt onset of hypertension and usually normal urine sediment with low-grade proteinuria. The presence of anti-RNA polymerase III antibodies, rapid progression of skin thickness, tendon friction rub, synovitis, and use of steroids have been identified as predictive factors for scleroderma renal crisis. In a cohort of 322 patients with systemic sclerosis, Gordon et al[7] identified that the presence of at least 3 of the following risk factors was predictive of scleroderma renal crisis with a sensitivity of 77% and a specificity of 97%: proteinuria, chronic kidney disease, hypertension, anemia, elevated erythrocyte sedimentation rate, thrombocytopenia, hypothyroidism, anti-Ro antibodies, and anti-RNA polymerase III antibodies. The outcome of scleroderma renal crisis has significantly improved with the introduction of ACEi therapy. Despite maximal angiotensin-converting enzyme inhibition therapy, scleroderma renal crisis remains a severe complication of systemic sclerosis with poor outcome resulting in death or kidney failure in 39% of patients.[8] Our patient had an atypical presentation. In fact, it is unusual to have scleroderma renal crisis as an inaugural presentation of systemic sclerosis without diffuse cutaneous involvement defining systemic sclerosis sine scleroderma and negative serologies. Pursuing a kidney biopsy in our case was critical for the diagnosis, and the histological features were crucial to determine the decision to treat with eculizumab. In a retrospective study of 17 scleroderma renal crisis kidney biopsies, Batal et al[9] showed a correlation between kidney failure or death

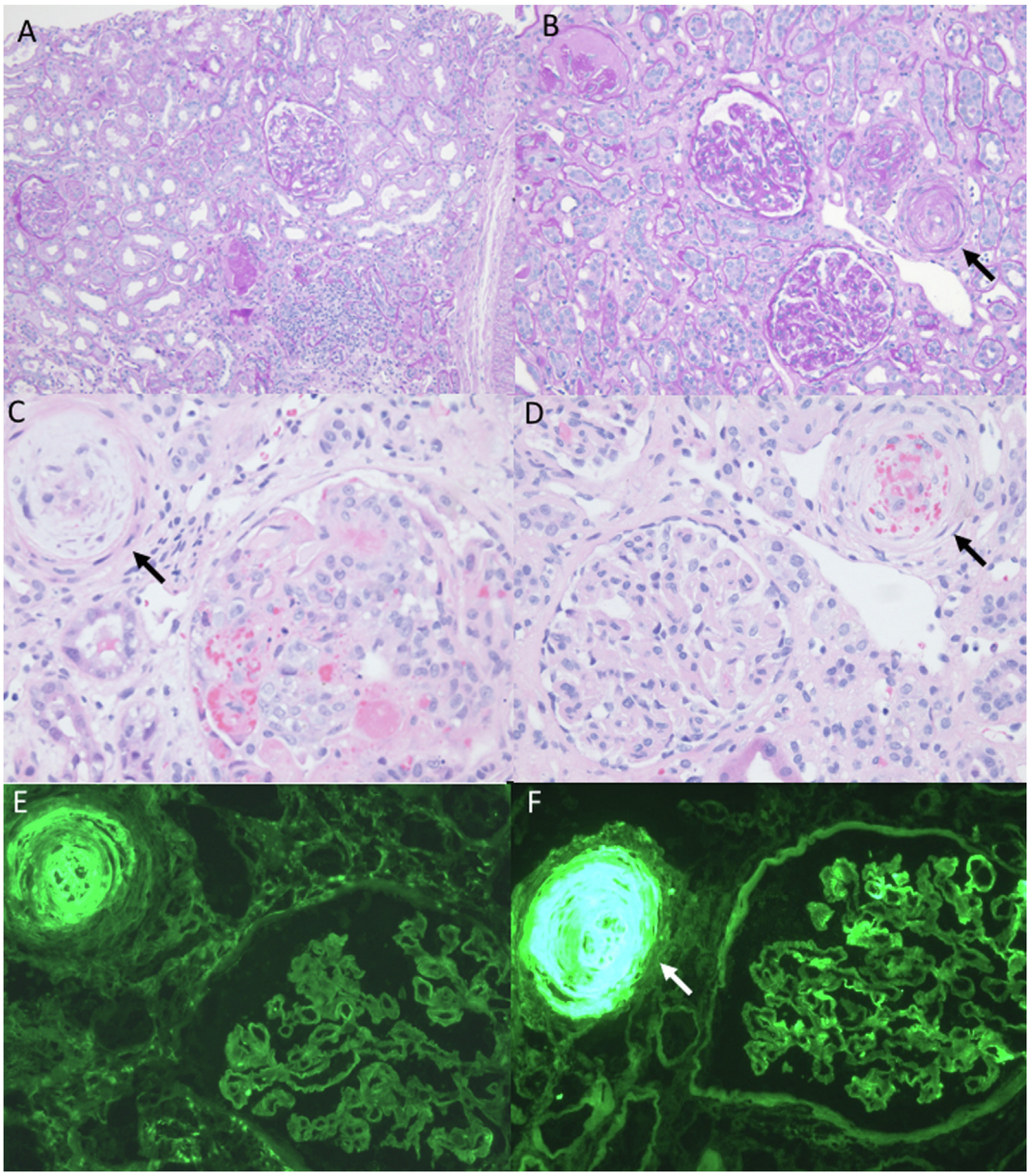

Figure 1. Kidney biopsy showing acute thrombotic microangiopathy associated with severe arteriolar narrowing. (A) Low magnification, periodic acid–Schiff stain showing moderate chronic tubular atrophy and minimal acute tubular injury. (B) Arteriole (black arrow) with typical onion-skin muco-intimal thickening and sclerosis with widespread glomerular hypoperfusion. (C, D) Higher magnification showing acute thrombotic microangiopathy involving glomerular capillaries and arteriole (black arrow). (E) Fibrinogen immunostaining. (F) C4d immunostaining in arteriole (white arrow) and glomerular capillaries but not in peritubular capillaries.

and vascular thrombosis, severe glomerular collapse and positive C4d staining in peritubular capillaries but not in small vessels. In our case, the presence of both widespread microvascular thrombosis and severe glomerular collapse prompted the use of eculizumab despite the absence of peritubular capillary C4d staining.

TMA is a common feature of scleroderma renal crisis, reported in about 50% of cases. The positive C4d staining supports complement activation through the classical or mannan-binding lectin pathway. The mechanism of endothelial injury is unclear. Several studies identified the presence of autoantibodies directed against endothelial cells: anti-endothelial cell antibodies[10] against intercellular adhesion molecule-1,[11] angiotensin I receptor and endothelin 1 type A receptor have been described.[12] Antibody-mediated endothelial cell injury could lead to complement activation via the classical or lectin pathways as evidenced by C4d deposition, leading to the TMA observed in scleroderma renal crisis. However, little evidence supports this hypothesis. The ability to detect autoantibodies against endothelial cells is limited in clinical practice. Presence of autoantibodies against vascular receptors have been associated with pulmonary hypertension, pulmonary fibrosis[13] and digital ulcers,[12] but no association with scleroderma

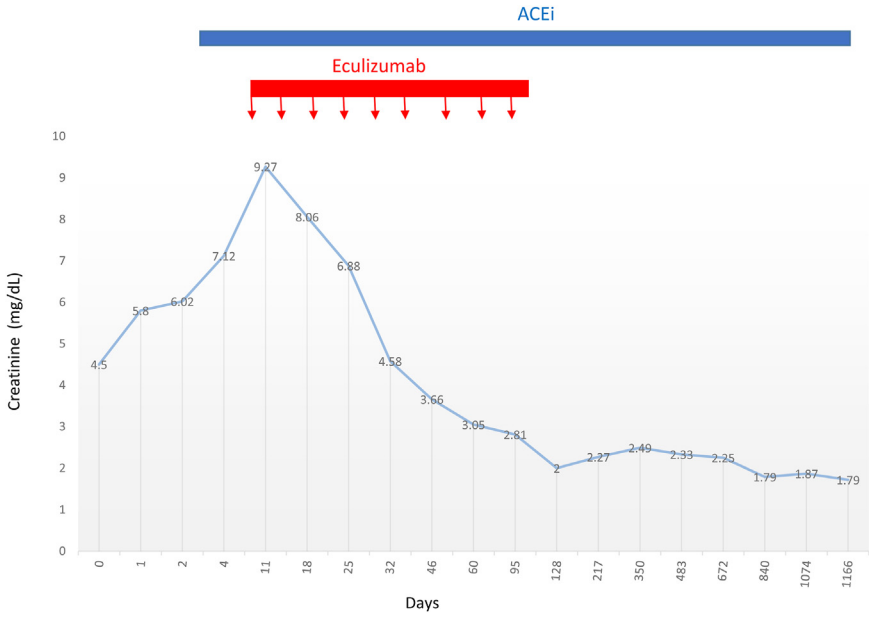

Figure 2. Creatinine over time since hospital admission. Patient presented to the emergency department with a creatinine of 4.5 mg/dL from a baseline at 0.8 mg/dL 4 years prior. Kidney function rapidly deteriorated and the patient was rapidly started on angiotensin conversion enzyme inhibitors followed by complement blockade, and subsequently showed sustained recovery with a creatinine of 1.8 mg/dL more than 3 years after eculizumab discontinuation. Angiotensin-converting enzyme inhibitor (ACEi) treatment has been maintained.

renal crisis and TMA has been reported yet. In contrast, hemodynamic shear stress itself has been shown to activate the classical pathway[14] and could lead to secondary TMA. In a case report of a dramatic scleroderma renal crisis with TMA, Devresse et al[15] showed an increased Factor Bb/Factor B ratio suggestive of subsequent recruitment of the alternative pathway through the C3b feedback cycle. This feedback circle would maintain complement activation leading to further endothelial injury, suggesting the potential role of complement blockade for treatment.

Evidence for eculizumab use in TMA scleroderma renal crisis is limited to few case reports[15,16] with variable outcomes. Despite the absence of any sign of systemic complement consumption in our patient, the rapid kidney deterioration despite normalization of the blood pressure on ACEi and the major endothelial injury on kidney biopsy prompted us to treat with complement blockade (eculizumab), which yielded a positive outcome. In this setting of presumed secondary TMA, no genetic studies were performed. Eculizumab was maintained for 3 months and then stopped with close follow-up. The patient has remained on ACEi. Prolonged follow-up for 3 years after eculizumab discontinuation demonstrated sustained remission.

A multidisciplinary approach is imperative in managing patients presenting with scleroderma renal crisis. A team including a nephrologist, rheumatologist, and a hematologist or a TMA team, as in our institution, is recommended for the management of patients with scleroderma renal crisis.[6] This approach has definitely led to prompt diagnosis, and implementation of targeted interventions in the treatment of our patient.

Kidney biopsy has been very valuable in our case to demonstrate the TMA and the complement activation, but we would recommend that severe hypertension and thrombocytopenia be corrected prior to consideration of kidney biopsy in similar cases. Those findings supported our decision to use eculizumab for the treatment of the severe scleroderma renal crisis in this patient.

Scleroderma renal crisis is a life-threatening complication of scleroderma that requires rapid treatment. Complement inhibition initiated promptly in addition to ACEis can be effective to control the disease and limit irreversible chronic kidney tissue damage and the unfortunate consequence of developing kidney failure.

ARTICLE INFORMATION

Authors' Full Names and Academic Degrees: Claire Trivin-Avillach, MD, Aala Jaberi, MD, Joel M. Henderson, MD, PhD, Laurence H. Beck Jr, MD, PhD, and Jean Francis, MD

Authors' Affiliations: Department of Pathology and Laboratory Medicine (CT-A, JMH), Boston Medical Center, Boston University Chobanian & Avedisian School of Medicine, Boston, MA; and Section of Nephrology (AJ, LHB, JF), Department of Medicine, Boston Medical Center, Boston University Chobanian & Avedisian School of Medicine, Boston, MA.

Address for Correspondence: Claire Trivin-Avillach, MD, Department of Pathology, Boston Medical Center, 670 Albany St, Boston, MA 02118. Email: cavillach@partners.org

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