Title

Scleroderma Renal Crisis in a Patient with Limited Systemic Sclerosis

Journal

Proceedings of UCLA Health, 23(1)

Authors

Alam, Usman
Celedon, Manuel A.
Basrai, Zahir

Publication Date

2019-02-06

CLINICAL VIGNETTE

Scleroderma Renal Crisis in a Patient with Limited Systemic Sclerosis

Usman Alam, Manuel A. Celedon, MD and Zahir Basrai, MD

Background

Systemic sclerosis (SSc), also known as scleroderma, is a rare autoimmune disease that can cause fibrosis in the skin and underlying connective tissue. Patients with SSc can be classified as having either limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc) based on the pattern of cutaneous sclerosis as well as the progression rate of internal organ involvement.[1] In contrast to lcSSc, dcSSc is associated with a more rapid progression of lung, kidney, and cardiac involvement.[2–4]

Scleroderma renal crisis (SRC) is a severe complication of SSc seen in about 10-15% of patients with dcSSc and is considered a medical emergency.[5,6] Patients in SRC will present with progressively declining renal function, often accompanied with malignant hypertension and signs of thrombotic microangiopathy. The use of angiotensin-converting enzyme inhibitors (ACEIs) has dramatically improved survival and functional outcomes in patients with SRC. Despite effective management through treatment with ACEIs, the 5-year survival remains poor for patients after initial diagnosis of SRC.[5,7,8] The majority of cases of SRC develop in patients with dcSSc and is rarely seen in patients with lcSSc.[9] We present a case of SRC, in a patient with lcSSc, and discuss appropriate diagnosis and subsequent management.

Case Presentation

A 70-year-old male with metastatic melanoma, recently diagnosed with limited scleroderma, was sent to the ER for evaluation of generalized weakness, dyspnea on exertion, leg swelling, and renal insufficiency. He reported months of progressively worsening symptoms and had received a partial evaluation at an outside hospital. Other symptoms included skin tightening as well as painful forearms, hand, and fingers. He also stated his fingers changed color with cold exposure as well as occasional dysphagia and acid reflux for years. He had no prior history of hypertension, cardiac, liver, or renal disease.

On chart review, he had a history of positive ANA with nucleolar pattern and carried the diagnosis of rheumatoid arthritis but was not receiving medical treatment. He had no prior corticosteroid therapy and was not taking NSAIDs or other nephrotoxic medications. He denied nausea, vomiting, diarrhea, decreased oral intake, gastrointestinal bleeding symptoms, or infectious symptoms.

His intake vitals were as follows: T97.7, BP 148/83, HR 67, RR 18, 100% saturation on room air. He was in no acute distress and speaking in full sentences. His lungs were clear bilaterally. His cardiovascular and abdominal examinations were unremarkable. He had 2+ pitting edema in his bilateral lower extremities tracking up to his sacrum. His skin exam revealed telangiectasias over legs, arms, and chest with thickening of skin over fingers, hands, forearms, toes, feet, and shins. His nail beds showed capillary dilation.

His ECG revealed a sinus rhythm with a left bundle branch block but no ST-elevations, ST-depressions, or T-wave inversions. Pertinent initial labs included: Hb 8.7 g/dL, PLT 121 k/uL, WBC 11.84 k/uL, BUN 66 mg/dL, Cr 4.27 mg/dL, INR 1.2, Tbili 2.1 mg/dL, Troponin 0.386 ng/mL, UA without blood or white cells but with proteinuria to 30 mg/dL. FENa 2.8%. His chest x-ray showed mild cardiomegaly, with mild vascular congestion and no hydronephrosis was seen on renal ultrasound.

While in the ED, the patient had intermittent episodes of severe hypertension. Rheumatology was consulted given concern for possible SRC in the setting of hypertension and acute kidney injury without a clear insult. He was started on low dose captopril and admitted to the medical ICU. Ultimately, the patient left against medical advice but was given captopril and scheduled for follow-up with rheumatology and nephrology.

Discussion

The diagnosis of scleroderma renal crisis is rare and difficult to confirm during the emergency room stay. Therefore, our discussion of this case will center around the systematic approach to acute kidney injury in the emergency room. It is important to maintain a working differential of the most common causes of AKI and to systematically evaluate them based on the mechanism of disease. AKI is characterized by a sudden decline in renal function marked by an increase in serum creatinine or urea with or without decreased urine production.[10] AKI is typically classified as either prerenal, intrarenal, or postrenal in nature.

Prerenal AKI is associated with hypoperfusion that results from generalized tissue ischemia or selective renal ischemia and if left untreated may result in intrinsic AKI. Generalized tissue ischemia leads to absolute decrease in effective circulatory blood volume (ECBV) versus true volume depletion. True

volume depletion may occur from increased output (vomiting, diarrhea, diuretic use, burns), decreased input (lack of oral intake), or shock state (acute hemorrhage, sepsis, or myocardial dysfunction). Hypervolemic states, as may occur with cirrhosis or heart failure, lead to a relative decreased ECBV that result in renal hypoperfusion despite total body volume overload. Renal artery stenosis and renal vein thrombosis are examples of selective renal ischemia. Intrinsic AKI results from direct structural damage to components of the kidney including: tubular disease, glomerular diseases, interstitial diseases, nephrotoxins, and small vessel diseases (i.e., vasculitis, scleroderma, malignant hypertension). Postrenal AKI occurs from an obstruction in the urinary collecting system distal to the kidneys. The two main mechanisms of postrenal AKI are bladder outlet obstruction (i.e., urethral stricture, BPH, neurogenic bladder) and bilateral ureteral obstruction (i.e., renal calculi, mechanical compression by mass).

Although the pathogenesis of SRC has not been fully characterized, it is understood to result from endothelial cell injury in the renal vasculature. Scleroderma renal crisis results primarily from uncontrolled formation of vascular lesions resulting in intraluminal narrowing of the renal interlobular and arcuate arteries.[11] Injury to endothelial cells also results in increased vascular permeability in addition to elevated fibrin deposition and collagen formation.[12] Episodic vasospasms, often referred to as 'renal Raynaud's," may also occur concurrently.[13] Together these features lead to further intraluminal narrowing which results in renal ischemia and hyperplasia of the juxtaglomerular apparatus. Subsequent activation of the renin-angiotensin-aldosterone system manifests as a rise in blood pressure due to vasoconstriction that further exacerbates renal injury.

Along with progressive renal failure, acute onset hypertension is a defining characteristic feature of SRC. Although SRC has been reported in normotensive patients, their blood pressures are still elevated from baseline.[11] Patients may also experience non-specific symptoms secondary to hypertension including hypertensive retinopathy and encephalopathy. Renal failure in SRC can be characterized by oliguria and azotemia in the absence of other renal pathology.[9,11]

While renal biopsies are not necessary to make the diagnosis of SRC, histology often reveals fibrinoid necrosis of arterioles and presence of mucin in the intertubular arteries.

In treating patients with SRC, the primary therapeutic goal is reduction of elevated blood pressure through the use of ACEIs. Captopril has been established as first line treatment for SRC because of rapid onset and short duration of action compared to other ACEIs.[7,14] Despite the established efficacy of ACEIs in the acute management of SRC, use of ACEIs as prophylaxis has been associated with poorer renal outcomes in scleroderma patients.[11,15] In addition to aggressive control of blood pressure, dialysis is frequently indicated in SRC.[14]

Although having dcSSc is the most significant predictor for developing SRC, other independent risk factors have also been discussed in the literature. Rapid progression of skin thickening and presence of anti-RNA polymerase III antibody are both strongly associated with increased risk of developing SRC.[16,17] Other studies have also suggested that patients who receive corticosteroid treatment have an increased likelihood of developing SRC.[5,6,9,11] This may be an important association to note considering that corticosteroids are routinely used in the management of myalgia and arthralgia in patients with SSc.

Although use of ACEIs have dramatically improved survival of patients in SRC, 5-year mortality is estimated to be 31-59%.[5–8,18] Mortality associated with SRC is largely attributable to development of end stage renal disease that is precipitated by irreversible renal injury. Patients who do not require permanent dialysis after SRC have comparable survival to SSc patients who have not had renal crisis.[14] In patients who required dialysis, higher blood pressure and serum creatinine were associated with improved long term renal recovery.[5] The basis for this phenomenon is not entirely understood but may relate to increased responsiveness to ACEIs or a lack of cardiac involvement.[19] Overall, the prognosis of patients remains poor and thus highlights the need for novel therapeutic agents in effective long term management.

REFERENCES

1. **van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA Jr, Carreira PE, Riemekasten G, Clements PJ, Denton CP, Distler O, Allanore Y, Furst DE, Gabrielli A, Mayes MD, van Laar JM, Seibold JR, Czirjak L, Steen VD, Inanc M, Kowal-Bielecka O, Müller-Ladner U, Valentini G, Veale DJ, Vonk MC, Walker UA, Chung L, Collier DH, Ellen Csuka M, Fessler BJ, Guiducci S, Herrick A, Hsu VM, Jimenez S, Kahaleh B, Merkel PA, Sierakowski S, Silver RM, Simms RW, Varga J, Pope JE**. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis*. 2013 Nov;72(11): 1747-55. doi: 10.1136/annrheumdis-2013-204424. Pub Med PMID: 24092682.
2. **Ostojić P, Damjanov N**. Different clinical features in patients with limited and diffuse cutaneous systemic sclerosis. *Clin Rheumatol*. 2006 Jul;25(4):453-7. Epub 2006 Apr 28. PubMed PMID: 16261285.
3. **Preston IR, Hill NS**. Evaluation and management of pulmonary hypertension in systemic sclerosis. *Curr Opin Rheumatol*. 2003 Nov;15(6):761-5. Review. PubMed PMID: 14569207.
4. **Valentini G, Della Rossa A, Bombardieri S, Bencivelli W, Silman AJ, D'Angelo S, Cerinic MM, Belch JF, Black CM, Bruhlmann P, Czirják L, De Luca A, Drosos AA, Ferri C, Gabrielli A, Giacomelli R, Hayem G, Inanc M, McHugh NJ, Nielsen H, Rosada M, Scorza R, Stork J, Sysa A, van den Hoogen FH, Vlachoyianno-**

poulos PJ. European multicentre study to define disease activity criteria for systemic sclerosis. II. Identification of disease activity variables and development of preliminary activity indexes. *Ann Rheum Dis*. 2001 Jun;60(6):592-8. PubMed PMID: 11350848; PubMed Central PMCID: PMC1753669.

5. **Penn H, Howie AJ, Kingdon EJ, Bunn CC, Stratton RJ, Black CM, Burns A, Denton CP**. Scleroderma renal crisis: patient characteristics and long-term outcomes. *QJM*. 2007 Aug;100(8):485-94. Epub 2007 Jun 29. PubMed PMID: 17601770.
6. **Teixeira L, Mouthon L, Mahr A, Berezné A, Agard C, Mehrenberger M, Noël LH, Trolliet P, Frances C, Cabane J, Guillevin L; Group Français de Recherche sur le Sclérodermie (GFRS)**. Mortality and risk factors of scleroderma renal crisis: a French retrospective study of 50 patients. *Ann Rheum Dis*. 2008 Jan;67(1):110-6. Epub 2007 Jun 8. PubMed PMID: 17557890.
7. **Steen VD, Costantino JP, Shapiro AP, Medsger TA Jr**. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme (ACE) inhibitors. *Ann Intern Med*. 1990 Sep 1;113(5):352-7. PubMed PMID: 2382917.
8. **Walker JG, Ahern MJ, Smith MD, Coleman M, Pile K, Rischmueller M, Cleland L, Roberts-Thomson PJ**. Scleroderma renal crisis: poor outcome despite aggressive antihypertensive treatment. *Intern Med J*. 2003 May-Jun;33(5-6):216-20. PubMed PMID: 12752889.
9. **Steen VD**. Scleroderma renal crisis. *Rheum Dis Clin North Am*. 2003 May;29(2):315-33. Review. PubMed PMID: 12841297.
10. **Rahman M, Shad F, Smith MC**. Acute kidney injury: a guide to diagnosis and management. *Am Fam Physician*. 2012 Oct 1;86(7):631-9. PubMed PMID: 23062091.
11. **Akoglu H, Atilgan GK, Ozturk R, Yenigun EC, Gonul II, Odabas AR**. A "silent" course of normotensive scleroderma renal crisis: case report and review of the literature. *Rheumatol Int*. 2009 Aug;29(10):1223-9. doi: 10.1007/s00296-008-0807-1. Epub 2008 Dec 2. Review. PubMed PMID: 19048256.
12. **Bose N, Chiesa-Vottero A, Chatterjee S**. Scleroderma renal crisis. *Semin Arthritis Rheum*. 2015 Jun;44(6):687-94. doi: 10.1016/j.semarthrit.2014.12.001. Epub 2014 Dec 11. Review. PubMed PMID: 25613774.
13. **Cannon PJ, Hassar M, Case DB, Casarella WJ, Sommers SC, LeRoy EC**. The relationship of hypertension and renal failure in scleroderma (progressive systemic sclerosis) to structural and functional abnormalities of the renal cortical circulation. *Medicine (Baltimore)*. 1974 Jan;53(1):1-46. PubMed PMID: 4808710.
14. **Steen VD, Medsger TA Jr**. Long-term outcomes of scleroderma renal crisis. *Ann Intern Med*. 2000 Oct 17;133(8):600-3. PubMed PMID: 11033587.
15. **Moore SC, Desantis ER**. Treatment of complications associated with systemic sclerosis. *Am J Health Syst Pharm*. 2008 Feb 15;65(4):315-21. doi: 10.2146/ajhp070024. Review. PubMed PMID: 18238768.
16. **Steen VD, Medsger TA Jr, Osial TA Jr, Ziegler GL, Shapiro AP, Rodnan GP**. Factors predicting development of renal involvement in progressive systemic sclerosis. *Am J Med*. 1984 May;76(5):779-86. PubMed PMID: 6372452.
17. **Shanmugam VK, Steen VD**. Renal disease in scleroderma: an update on evaluation, risk stratification, pathogenesis and management. *Curr Opin Rheumatol*. 2012 Nov;24(6):669-76. Review. PubMed PMID: 22955019; PubMed Central PMCID: PMC4048657.
18. **DeMarco PJ, Weisman MH, Seibold JR, Furst DE, Wong WK, Hurwitz EL, Mayes M, White B, Wigley F, Barr W, Moreland L, Medsger TA Jr, Steen V, Martin RW, Collier D, Weinstein A, Lally E, Varga J, Weiner SR, Andrews B, Abeles M, Clements PJ**. Predictors and outcomes of scleroderma renal crisis: the high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. *Arthritis Rheum*. 2002 Nov;46(11):2983-9. PubMed PMID: 12428241.
19. **Denton CP, Lapadula G, Mouthon L, Müller-Ladner U**. Renal complications and scleroderma renal crisis. *Rheumatology (Oxford)*. 2009 Jun;48 Suppl 3:iii32-5. doi: 10.1093/rheumatology/ken483. Review. PubMed PMID: 19487221.

Submitted January 8, 2019