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CASE REPORT

A Critical Care Standpoint in the Diagnosis of Scleroderma Renal Crisis

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Abstract

Typical or atypical presentations of rare diseases may be confounded by co-morbidities in critically-ill patients. It is imperative to diagnose and treat appropriately, despite this difficulty. Scleroderma renal crisis mimics many other conditions, and can be potentially fatal if not caught early enough. Particularly, in critically-ill patients with multiple pathologies, it can be difficult to distinguish scleroderma renal crisis from other diseases, such as thrombotic thrombocytopenic purpura (TTP), hypertensive emergency, posterior reversible encephalopathy syndrome (PRES), or atypical hemolytic uremic syndrome (HUS). Herein, a patient who presented with encephalopathy and seizures was initially treated for thrombotic thrombocytopenic purpura, but was ultimately diagnosed with scleroderma renal crisis. Given her numerous laboratory abnormalities, such as thrombocytopenia, hemolytic anemia, kidney and liver dysfunction, and elevated inflammatory markers, various differentials were considered. During her hospitalization, she suffered a cardiac arrest, seizures, nosocomial infections and worsening kidney disease requiring dialysis, making the final diagnosis of scleroderma renal crisis a diagnosis of exclusion. Subsequently, the management of a patient with multiple co-morbidities and confounding laboratory abnormalities difficult to treat. This article highlights these intricacies and formulates the thought process behind the diagnosis of Scleroderma Renal Crisis.

Keywords: Atypical HUS, PRES, Scleroderma renal crisis, TTP, Seizure disorder, Renal failure, Thrombocytopenia

1. Introduction

Scleroderma renal crisis is a life-threatening disease that can lead to renal failure.[1] This may manifest in approximately 10% of scleroderma patients and common clinical features include kidney dysfunction as well as hypertensive emergency.[1] It is thought that multiple insults to the kidneys cause arteriolar narrowing, injury of the endothelium and proliferation of the intimal cells.[1] Decreased blood flow to the kidneys results in worsening hypertension.[1] Angiotensin-converting enzyme (ACE) inhibitors are the gold-standard treatment for this condition and can significantly reduce overall associated mortality.[1] If untreated, patients may develop end-stage renal failure and require hemodialysis.[1] This disease is often confused with other conditions, but is important to consider in a patient who develops significantly worsening hypertension and concomitant renal failure. We present a complex case of a critically-ill patient who was eventually diagnosed with scleroderma renal crisis, requiring hemodialysis.

2. Case presentation

2.1. History of presenting illness and ED course

A 54-year-old post-menopausal Asian female with a past medical history of seizure disorder presented to the Emergency Department (ED) with generalized weakness, dizziness, diplopia, nausea and vomiting that started 1 h prior to arrival. She also reported heavy vaginal bleeding and fevers over the past week, as well as daily seizures despite medication compliance with levetiracetam and

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phenytoin. On arrival, her vitals were 227/158 mmHg, 131 beats per minute and she was saturating 70% on room air. She was in mild acute distress, had scattered rhonchi bilaterally and exam was otherwise notable for sclerodactyly of the forearms, hands and lower extremities, but no other lesions or rashes were found. Laboratory studies were significant for leukocytosis with segmented neutrophilia, normocytic anemia, thrombocytopenia with decreased platelet estimation, schistocytes, ovalocytes, and target cells on the peripheral smear. Hyponatremia, hypokalemia, acute kidney injury, high anion gap metabolic acidosis and lactic acidosis were also noted (Table 1). A chest radiograph (CXR) demonstrated diffuse pulmonary edema bilaterally. Computerized tomography (CT) of the head without contrast revealed only an 18 mm (mm) lytic lesion of the left parietal bone, enlarged from imaging upon previous hospitalizations. She was initially treated with non-invasive positive pressure ventilator support and a nicardipine infusion. However, the patient became unresponsive, bradycardic and required intubation. There was also concern for seizure-like activity post-intubation, and her blood pressure remained elevated.

2.2. Initial hospital course

She was admitted to the Intensive Care Unit (ICU) with working diagnoses of hypertensive emergency with possible posterior reversible encephalopathy syndrome (PRES) versus a cerebrovascular event, possible status epilepticus with acute hypoxic respiratory failure and pulmonary edema, as well as thrombotic thrombocytopenic purpura (TTP). An electroencephalogram (EEG) was negative for active seizures, and she was maintained on levetiracetam and fosphenytoin. On the first night of hospitalization, the patient went into pulseless electrical activity arrest for approximately 8 min before resuscitation was achieved.

2.3. Hospital course continued

She was continued on a nicardipine infusion for persistent hypertension, and underwent emergent plasma exchange and steroids for possible TTP versus atypical hemolytic uremic syndrome (aHUS) while a diagnostic work up was pending (Table 2). Hematology was consulted and she was given methylprednisolone 1000 mg daily for 5 days without improvement. ADAMTS-13 returned at 60%, which was more compatible with aHUS and she was subsequently treated with eculizumab. A magnetic resonance image (MRI) did not show evidence of ischemia, which would typically be present in aHUS and thus Hematology concurred that this may in fact be a different diagnosis. To further support this, her platelet count improved already (but not normalized) with therapeutic plasma

*Table 1. **Admission laboratory studies.** Comprehensive metabolic panel and complete blood count with reference ranges.*

Comprehensive Metabolic Panel	Value (Reference Range)	Complete Blood Count	Value (Reference Range)
Brain Natriuretic Peptide	>4000 pg/mL (1-100)	White Blood Cells	18.6 x10^3/mm3 (4.5-11)
Creatinine Kinase	212 unit/L (30-223)	Red Blood Cells	3.74 x10^6/mm3 (4-5.33)
Troponin-I High sensitivity	569 pg/mL (3-17)	Hemoglobin	11.0 g/dL (12-16)
Random Cortisol	34.9 mcg/dL	Hematocrit	32.5 % (36-46)
Sodium	126 mEq/L (135-145)	MCV	86.9 fL (80-100)
Potassium	2.9 mEq/L (3.5-5.0)	MCH	29.4 pg (26-32)
Chloride	95 mEq/L (98-107)	MCHC	33.8 g/dL (31-37)
Bicarbonate	16 mEq/L (21-31)	RDW	15.2 % (0.5-16.5)
Glucose	294 mg/dL (70-110)	Platelets	66 K/mm3 (140-440)
Calcium	7.0 mg/dL (8.6-10.3)	MVP	No range (7.4-10.4)
Blood Urea Nitrogen	51 mg/dL (7-23)	Neutrophil Auto	77.9 % (36-75)
Creatinine	2.96 mg/dL (0.60-1.30)	Lymph Auto	9.1 % (24-44)
Total Bilirubin	1.1 mg/dL (0.3-1.1)	Monophil Auto	7.4% (4-10)
Total Protein	5.4 g/dL (6.4-8.4)	Eosinophil Auto	0.1% (0-5)
Albumin	2.9 g/dL (3.5-5.7)	Basophil Auto	0.9% (0-2)
Alkaline phosphatase	51 unit/L (34-104)	Immature Granulocytes	4.8% (0-0.6)
Aspartate aminotransferase	103 unit/L (13-39)	Segmented Neutrophils	62% (36-75)
Alanine aminotransferase	80 unit/L (7-52)	Bands Manual	28% (0-10)
Phosphorous	7.9 mg/dL (2.5-5.0)	Lymphocyte Manual	6% (22-44)
Direct Bilirubin	0.40 mg/dL (0-0.2)	Monocyte Manual	4% (4-10)
Hemoglobin A1c	5.1% (4-6)	Eosinophil Manual	0% (0-5)
Magnesium	1.9 mg/dL (1.7-2.5)	Basophil Manual	0% (0-2)
Serum Osmolality	289 mOsm/kg (283-299)		
Lactic acid	9.8 mmol/L (0.5-2.2)		
Total phenytoin level	<2.5 mcg/mL (10-20)		
T4 free	1.07 ng/dL (0.61-1.12)		
Thyroid stimulating hormone	3.876 mcIntUnit/mL (0.450-5.330)		

Table 2. ***Diagnostic workup of thrombocytopenia and bleeding.*** *Hematological laboratory studies with reference ranges.*

Lactate dehydrogenase	1,100 unit/L (140-271)
Prothrombin Time	16.2 seconds (12.2-14.9)
International Normalized Ratio	1.3 (critical high >4.0)
Partial Thromboplastin Time	27 seconds (21.3-35.1)
Fibrinogen	367 mg/dL (183-503)
D-dimer Quantitative	2.31 mcg/mL FEU (normal high 0.50-critical high >1.0)
Iron Level	32 mcg/dL (50-212)
Transferrin	197 mg/dL (205-362)
Total Iron Binding Capacity	294 mcg/dL (250-400)
Iron Saturations	11% (15-50)
Ferritin	273.0 ng/mL (14-233)
Platelet Estimation	Decreased
Hypochromia	None
Polychromia	Slight
Microcyte	Slight
Macrocyte	Slight
Burr Cells	None
Helmet Cells	Few
Ovalocytes	Few
Schistocyte	Few
Spherocyte	Few
Target Cell	Few
Teardrop Cell	None
Reticulocyte Count	3.53% (0.5-2)
Absolute Reticulocyte	0.1381 x106/mm3
Reticulocyte Hef	35.8 pg (29-38)
IRF	18.6 % (2.7-5.7)
Haptoglobin	10 (33-346)

exchange and this is also not typical with aHUS. Subsequently, eculizumab was stopped after 3 treatments, and another diagnosis was entertained. Hematology recommended discontinuing steroids, however given the high doses she initially received, she was started on a prednisone taper over the course of 10 days, with a starting dose of 50 mg daily. At this time, the patient remained hypertensive requiring clonidine, amlodipine, labetalol, isosorbide dinitrate and a nicardipine drip. In addition to this, nephrology recommended adding intravenous enalaprilat 1.25 mg, 1 mL solution every 6 h, while further evaluation for scleroderma renal crisis versus glomerulonephritis was pursued (Table 3).

2.4. Final diagnosis

Results included a positive ANA, but negative SCL 70 and dsDNA. C3 was within normal limits but C4 was slightly decreased. As scleroderma antibodies are not highly sensitive and other etiologies had been excluded, Rheumatologists concluded that a scleroderma renal crisis was the most likely diagnosis. When enalaprilat was commenced, her blood pressure significantly improved, her platelets and anemia normalized, and her baseline creatinine

Table 3. ***Rheumatological and vasculitis workup.*** *Laboratory studies with reference ranges.*

Rheumatoid factor	11.3 IntlUnit/mL (0-14)
C3 Complement	99 mg/dL (87-190)
C4 Complement	16 mg/dL (18-55)
ADAMTS13 Activity	60.6% (Normal Low > 66)
ANA	Positive
Anti-DNA Double Stranded Antibody	Negative
Anti-Jo-1	Negative
Antichromatin A	Negative
Antiribosomal P	Negative
pANCA	Negative
Cardiolipin IgA	Negative
Cardiolipin IgG Antibody	Negative
Cardiolipin IgM Antibody	Negative
Centromere B Antibody	Negative
CH50 Complement	Negative
Cytoplasmic cANCA	Negative
Glomerular Basement Membrane Antibody	Negative
Nucleolar Pattern	1:320 (high)
Speckled Pattern	1:320 (high)
Scleroderma-70 Antibody	Negative
RNP Antibody	Negative
Smith Antibody	Negative
Sjogrens SSA and SSB Antibodies	Negative

was slightly better than on admission. However, it was likely diagnosed too late causing irreversible renal damage warranting permanent dialysis. Her mentation post-cardiac arrest still fluctuated and ultimately, she required tracheostomy and PEG placement in lieu of this. She was maintained on oral captopril 12.5 mg every 8 h, amlodipine 20 mg daily, clonidine 0.3 mg/24-h transdermal patch once per 7 days, and oral labetalol 600 mg every 8 h for blood pressure control after departing the intensive care unit. Rituximab was withheld given her fragility, complexity, and risk for nosocomial infections. She ultimately required hemodialysis and is currently still recovering inpatient. Unfortunately, as she was very frail and her hospital course was so complicated, she was never optimized clinically for a biopsy of the kidneys. She remained hospitalized for three months and eventually succumbed to her disease after another cardiac arrest.

3. Discussion

Given our patient's complex presentation and multi-organ system involvement, interdisciplinary input and close communication was required to make the correct diagnosis. The differential for this patient was broad. PRES would have explained her hypertension, seizures, and encephalopathy but would not have addressed the multiple metabolic and hematologic abnormalities. Multiple myeloma

was considered given her anemia, renal injury and lytic lesions but the electrophoresis was negative.[2,3] Use of phenytoin may have led to kidney injury and neurotoxicity, however, alone would not have explained the hematological abnormalities. Other differentials, such as microthrombi secondary to microangiopathic hemolytic anemia (MAHA), TTP or aHUS were considered.[4]

TTP is diagnosed based on the presence of thrombocytopenia, MAHA and exclusion of other etiologies of thrombocytopenia.[5] A platelet count of 30K/mm^3 or greater provides strong evidence that the diagnosis is not TTP.[4] The ADAMTS13 level is typically deficient in patients with the inherited form of TTP, but can be low to normal in those with the acquired form.[6] TTP is diagnostic with an ADAMTS13 level less than or equal to 0.1U/mL[7]. The PLASMIC score is utilized for suspected TTP, with scores between 0 and 4 representing low probability, scores of 5 representing intermediate probability, and scores between 6 and 7 representing high probability of the disease.[8] A recent study concluded that a PLASMIC score of $\geq$5 provides both high negative predictive value and sensitivity, and should be utilized for screening.[8] With clinical signs of thrombotic microangiopathy, plasma exchange therapy should be initiated promptly given the severity of TTP, and when patients do not respond to this therapy, aHUS should be considered.[4] Given the patient's PLASMIC score of 6 and DAT negativity, TTP was less likely.[4,7] Additionally, her heart failure and acute kidney injury could have been solely from hypertensive emergency.[4,7] In TPP, platelets tend to be lower than 50,000 K/mm3 and serum creatinine less than 2.0 mg/dL, making her clinical picture less attributable to TTP.[7]

When the ADAMTS13 level returned greater than 60 IU/mL, our focus shifted to aHUS.[4,7] With aHUS, patients may also have MAHA, elevated LDH, and thrombocytopenia; although, platelet counts may be normal in up to 20% of patients.[4] Treatment requires management of hypertension and hemodialysis if necessary. Eculizumab should also be initiated promptly to preserve kidney function.[4] If untreated, aHUS can lead to ESRD in 50% of patients.[4] Additionally, there was no evidence of ischemia on imaging to correlate to the diagnosis of aHUS and the platelets were slightly improved after plasma exchange, which further supports another diagnosis. Overall, however, her clinical condition was relatively the unchanged after plasma exchange, steroids and eculizumab, and thus other differentials such as scleroderma renal crisis were considered. Use of maintenance fosphenytoin may have increased metabolism of the medications used up to this point, as it is a cytochrome p450 inducer, however, it is unlikely to have caused a lack of response completely as one would expect to see some improvement in the hematological abnormalities, mentation, blood pressure and renal function. The diagnosis of scleroderma renal crisis explained the MAHA, renal failure and hypertension.[1] In comparison to TTP and aHUS, renal failure in these patients is generally more progressive, and there is also non-nephrotic proteinuria.[9] Auto-antibody markers such as Scl-70 or centromere B antibodies may be positive; however, are not highly sensitive.[9,10] Anti-centromere antibodies (ACA) confer a sensitivity of 33% and a specificity of 99.9% when compared to healthy control patients, and anti-Scl-70 antibodies are 20.2% sensitive and 100% specific.[10] After excluding other differentials through diagnostics, laboratory and genetic testing, it appeared that scleroderma renal crisis was the most likely diagnosis. Moreover, the patient's renal function improved with the addition of an angiotensin-converting-enzyme inhibitor (ACEi) and dialysis, but treatment was likely initiated too late.[1] Captopril is the medication of choice but was unfortunately unavailable at our institution at the time of diagnosis, and she was started on enalapril intravenously.[1,9] Once captopril could be obtained, she was maintained on an oral regimen of this. Lastly, steroids worsen kidney function in scleroderma renal crisis and may have been the case in our patient, who received steroids for suspected TTP.[9] Previous studies have demonstrated that approximately 60% of patients also received corticosteroids at the time of presentation, prior to their diagnosis of scleroderma renal crisis.[9] Unfortunately, despite therapy, 66.6% of patients with scleroderma renal crisis will require hemodialysis and possibly renal transplant.[9]

From a critical care standpoint, it was important to treat the suspected TTP, which is a fatal diagnosis if left untreated. The diagnosis of scleroderma renal crisis was a diagnosis of exclusion and was delayed while other more sinister diagnoses were evaluated for. Ultimately, a biopsy of the kidneys to confirm the diagnosis is recommended, however our patient expired prior to this procedure.

4. Conclusion

The appropriate evaluation and treatment for the critically-ill patient can be very difficult especially with increasing multi-organ system dysfunction. In this case, it was difficult to discern the etiology of her thrombocytopenia, encephalopathy, seizures, progressive hypertension and renal dysfunction.

This case highlights the intricate complexities encountered in a Critical Care setting for a unique patient with a rare disorder.

Consent statement

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Author affiliation

Ariana Tagliaferri and Brooke Kania are the article guarantors. Ariana Tagliaferri and Brooke Kania performed the literature review and wrote the manuscript. All authors assisted in the collection of the patient's clinical data. All authors took part in the medical management of the patient and edited the final manuscript for submission. All work was performed at St. Joseph's University Medical Center at the following address: St. Joseph's University Medical Center, Department(s) of Critical Care and Internal Medicine, 703 Main Street, Paterson, NJ, 07503, USA, (973) 754-2000.

Disclosure of interest

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