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Case Report

Scleroderma Renal Crisis with Normal Blood Pressure: A Diagnostic Dilemma Solved by Renal Biopsy

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Abstract

Systemic sclerosis is an autoimmune disorder involving skin, gastro-intestinal tract, lungs, kidneys and heart and can present with a variety of manifestations like esophageal dysmotility, pulmonary fibrosis, hypertension and renal dysfunction. Scleroderma renal crisis is a dreaded complication of systemic sclerosis presenting as rapidly progressive renal dysfunction and accelerated hypertension. However around 10% of the patients with this condition have normal blood pressure which makes it difficult to diagnose early and have poor outcome. Here we present a case of normotensive scleroderma renal crisis in a 48 year old female, who presented with clinical signs of systemic sclerosis and unexplained renal dysfunction. The diagnosis was made with the help of immunological profile and renal biopsy, but the renal function of the patient did not improve and she remains dialysis dependent.

Keywords: Systemic Sclerosis; Scleroderma Renal Crisis; Normotensive Scleroderma Renal Crisis; Rapidly Progressive Renal Failure; Onion Skinning of Arterioles; Autoantibodies

Abbreviations

SS: Systemic Sclerosis; SRC: Scleroderma Renal Crisis; TMA: Thrombotic Microangiopathy; GBM: Glomerular Basement Membrane; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; LDH: Lactate Dehydrogenase; PAS: Periodic Acid-Schiff; JMS: Jones Methenamine Silver; H And E: Hematoxylin and Eosin

Introduction

Systemic sclerosis (SS) also known as scleroderma is an autoimmune disease of unknown etiology and characterized by fibrosis and thickening of skin and systemic involvement including gastrointestinal tract, lungs, kidneys and heart [1,2]. It is more common in females and in the third to fifth decade of life. Diffuse systemic sclerosis and limited cutaneous systemic sclerosis are the two subsets of SS based on the extent of skin and systemic involvement. Oesophageal dysmotility, pulmonary fibrosis, arterial hypertension and hypertensive heart failure are some of the systemic manifestations of SS [3]. Renal complications are common in patients of SS ranging from 45-60% and include azotemia, proteinuria and hypertension [4,5]. About 10% of the patients develop scleroderma renal crisis (SRC), a rapidly progressive oliguric renal failure due to immune mediated vascular endothelial injury [3,6]. Although majority of patients with SRC have accelerated hypertension but around 10% of them have normal blood pressure and hence become difficult to diagnose. Here we present a challenging case of normotensive SRC, and the role of renal biopsy in clinching the diagnosis.

Case Presentation

A 48-year-old non diabetic, non-hypertensive and euthyroid female presented with history of decreased urine output, progressively worsening shortness of breath and nausea for last 10 days. On further enquiry she gave history of generalized weakness, pain in bilateral wrist and metacarpophalangeal joints of her hands with difficulty in clenching her fists and opening her mouth for last 2 years. She did not consult any physician for her complaints and used to take over the counter analgesics for pain relief.

On examination her blood pressure was 105/70 mm of Hg, pulse rate 84/minutes. There was pallor and bilateral pedal edema along with skin hyperpigmentation and tightening. Her oral aperture was markedly narrow and did not permit more than two fingers to pass. There was no joint tenderness or swelling in her hands, no ulcers or gangrene in her digits and no history of Reynod's phenomenon. She had bilateral basal crepitations on auscultation in her chest. Rest of the physical examination was uneventful.

Baseline investigations revealed Hemoglobin 8.4 gm/dL, platelets 1.2 lakh/mm^3, and peripheral smear had 2% schistocytes. Serum sodium was 131 mmol/L, potassium 4.3 mmol/L, urea 127 mg/dL, creatinine 6.7 mg/dL, lactate dehydrogenase (LDH) 537 IU/L and serum haptoglobin was 0.47 g/L (normal range 0.5-2.2 g/L). Urine routine examination showed bland urine sediments and 24 hours quantitative urine protein was 343 mg. Ultrasound of abdomen showed normal sized kidneys with slightly raised cortical echogenicity and maintained cortico-medullary differentiation. Chest X-ray revealed dilated upper lobe vessels, slightly increased cardiothoracic ratio (0.6) and prominent septal (Kerley) lines. Echocardiography showed left ventricular ejection fraction of 65% with normal wall motion. From the history and physical examination, we suspected SS. Initial investigations gave somewhat a thrombotic microangiopathy (TMA) like picture but was not very specific. We kept SRC as our first differential, but her normal blood pressure made us hesitant to make a diagnosis of SRC. Our second differential was acute interstitial nephritis due to over-the-counter analgesic use. In view of pedal edema, renal dysfunction, chest X-ray findings, and normal echocardiography, we attributed her shortness of breath to volume overload due to rapidly progressive renal failure, and it improved on initiation of hemodialysis.

Immunological workup was done for the patient and the results are summarized in table 1.

Anti-nuclear antibody (ANA)	Positive, 4+ intensity, speckled pattern
Anti double stranded DNA (dsDNA)	Negative
Anti-Smith	Positive, 1+ intensity
Anti Sjogren's syndrome related Antigen A (Anti-SS-A)	Negative
Anti Sjogren's syndrome related Antigen B (Anti-SS-B)	Negative
Anti-ribonucleoprotein (Anti-RNP)	Negative
Anti-topoisomerase 1 (Anti-SCL 70)	Positive, 4+ intensity
Anti-Jo	Negative
Anti-myeloperoxidase antibody (Anti-MPO)	Negative
Anti-proteinase 3 antibody (Anti-PR3)	Negative
Anti-Glomerular basement membrane (Anti-GBM)	Negative
Complement 3 (g/L)	1.36 (0.9 - 1.80 g/L)
Complement 4 (g/L)	0.34 (0.10 - 0.40 g/L)
Rheumatoid Factor	Negative
Serum Immunoglobulin A (IgA)	2.13 (0.87 - 3.94 g/L)
Serum Immunoglobulin G (IgG)	18.5 (5.5 - 17.2 g/L)
Serum Immunoglobulin M (IgM)	1.07 (0.37 - 2.86 g/L)

Table 1: Details of immunological workup of the patient.

The presence of skin thickening and autoantibodies (Scl-70) confirmed the diagnosis of diffuse systemic sclerosis according to the ACR/EULAR 2013 criteria [7].

Renal biopsy was done in view of rapidly progressive renal dysfunction. In light microscopy there were 26 glomeruli, out of which 5 were globally sclerosed. Remaining glomeruli showed mesangiolysis and ischaemic glomerular basement membrane wrinkling. There were intracapillary fibrin thrombi along with shrinkage of glomerular tuft and capillary loop collapse (Figure 1). In the vascular compartment there was fibrous intimal thickening and arteriolar onion skinning (Figure 2 and 3). Interstitium showed moderate fibrosis and tubular atrophy (Figure 4). Direct Immunofluorescence was negative for IgM, IgG, IgA, C3, C1q, kappa and lambda. Electron microscopy showed normal glomerular architecture and no electron dense deposits. The renal biopsy was suggestive of acute TMA with hypertensive vascular changes.

Figure 1: Light microscopy of renal histopathology showing (A) Mesangiolysis (black arrow) and ischaemic wrinkling of GBM in PAS stain (B) Shrinkage of glomerular tuft with capillary loop collapse - blood less glomeruli in PAS stain (C) Ischaemic wrinkling of GBM prominent in JMS stain (D) Intra-capillary fibrin thrombi (black arrow) in MT stain.

Figure 2: Light microscopy of renal histopathology showing fibrous intimal thickening (black arrow) in H and E stain (A) and in Masson's Trichrome stain (B).

Thus, we made the diagnosis of normotensive SRC and proceeded to look for other organ involvement of SS. Echocardiography, magnetic resonance imaging of bilateral wrist and small joints of hands and endoscopy were done which came out to be normal.

Figure 3: Light Microscopy of renal histopathology showing (A) arteriolar onion skinning (yellow arrow) in JMS stain (B) narrowing of arteriolar lumen (black arrow) in H and E stain.

Figure 4: Light microscopy of renal histopathology showing (A) moderate interstitial fibrosis of around 30% in low power 100X (B) tubular simplification (black arrow), loss of brush borders and tubular atrophy in high power of 400X.

High resolution computed tomography thorax revealed subpleural fibro-reticular and ground glass opacities in bilateral lung parenchyma. Pulmonary function tests were done which came to be normal for age [forced vital capacity (FVC) 64%, forced expiratory volume at first second (FEV1) 77%, FEV1/FVC 99%].

Dialysis was initiated in our patient, as she had uremic symptoms. Her dyspnea and nausea improved after intensive hemodialysis. Angiotensin converting enzyme inhibitor (ACEI) was started at low dose with strict monitoring of blood pressure and electrolytes. Her urine output did not improve and she remained dialysis

dependent. Second immunosuppressant was planned in view of early lung involvement and two doses of injection Rituximab, one gram each dose, was given two weeks apart. She is currently dialysis dependent and under close follow up of nephrology, rheumatology and chest medicine.

Discussion

SRC usually manifests as rapidly progressive oliguric renal failure in presence of accelerated hypertension. The pathogenesis of SRC is poorly understood, and probably mediated by both immunological and non-immunological pathways [8]. Initial endothelial injury is caused by autoantibody mediated endothelial cell apoptosis and overactivation of T-Helper lymphocytes type-2 and B lymphocytes which triggers a cascade of reactions ultimately leading to excess cytokine production, mainly interleukin (IL) - 4, IL-13 and IL-17 [9,10]. It is followed by endothelial cell proliferation and excess collagen deposition which leads to narrowing of vessel lumen, formation of microthrombi and renal hypoperfusion [10]. This leads to excess secretion of renin, leading to vasospasm and worsening renal ischaemia, thus causing rapid renal dysfunction and accelerated hypertension [3]. However, normotensive SRC is mediated by over production of potent vasoconstrictor endothelin-1 and over expression of its receptor endothelin-B [11]. Another hypothesis is early involvement of heart in some patients of SS, which leads to hypotension and hence BP do not rise in these group of patients during an episode of SRC [2].

The risk factors for development of SRC include diffuse disease, positive anti-topoisomerase III antibody test, onset of scleroderma within the previous 1 year, drugs such as prednisone at doses > 15 mg/day, cyclosporine within the preceding 3 months, contractures at the large joints, new-onset anaemia, new heart failure and pericardial effusion [12]. In our patient, absence of hypertension and previous history of immunosuppression led to the diagnostic dilemma.

The diagnosis of SRC is based on the presence of clinical features of SS together with lab investigations - hemolytic anemia, thrombocytopenia, schistocytes on peripheral blood, elevated LDH and low haptoglobin. The urine examination is usually normal, but may be associated with sub-nephrotic proteinuria and microscopic hematuria. However, these findings are not confirmatory of SRC and can be found in a variety of other clinical conditions like - malignant hypertension, thrombotic thrombocytopenia purpura, atypical hemolytic uremic syndrome, drug toxicity, radiation nephritis, antiphospholipid antibody syndrome and chronic transplantation rejection. Presence of autoantibodies and renal biopsy helps to differentiate between these close differentials. In our patient there was history of skin tightening and narrowing of oral aperture, bland urine sediment, evidence of TMA like picture in blood investigations and anti-SCL 70 positivity.

The renal biopsy, the predominant picture is that of thrombotic microangiopathy and small vessel changes predominate over glomerular pathology. Histologic manifestations may vary during the course of the disease [13]. In the vascular compartment, early changes can manifest as intimal accumulation of myxoid material, thrombosis, and/or fibrinoid necrosis while Onion-skin lesions develop later. Fibro-intimal sclerosis with or without adventitial fibrosis may be the only manifestation of chronic ongoing damage or organization resulting from previous episodes of acute injury. Acute glomerular changes can occur primarily or often develop secondary to the vascular injury and reduction in renal perfusion. Primary glomerular changes appear to be related to glomerular endothelial injury and manifest as endothelial swelling and glomerular capillary thrombosis in early phase while basement membrane double contours and glomerulosclerosis, may develop later [14]. Secondary glomerular changes may result in ischemic glomerular collapse. Juxta Glomerular hyperplasia, a histologic sequel of increased renin production can be observed microscopically in some patients [15]. Tubulointerstitial changes, are frequently manifested as ischemic acute tubular injury, tubular atrophy and interstitial fibrosis. In our patient we found fibrous intimal thickening with onion skinning, mesangiolysis with ischaemic GBM thickening and tubular atrophy with moderate interstitial fibrosis, indicating that the disease had progressed well beyond the early stages.

Immunofluorescence (IF) 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 [1]. In our patient IF was negative, but most of the glomeruli were bloodless with intracapillary fibrin thrombi and ischemic collapse.

Normotensive SRC has worse renal outcome and overall prognosis than hypertensive SRC. It is attributed to the prolonged subclinical renal injury which go undetected for a long time [16]. Also, the clinical improvement seen in hypertensive SRC patients on addition of ACEI/ARBS is less prominent in normotensive SRC patients, mechanism of which is still not very clear, but could be due to its non-renin mediated pathogenesis [2].

The treatment of SRC comprises of ACEI/ARBS as the first line agent in both normotensive and hypertensive groups, along with adequate supportive care like BP control, avoiding nephrotoxic drugs etc [17]. Sudden and excessive decreases in blood pressure should be avoided because excessive reduction in renal perfusion may lead to acute tubular necrosis. Plasma exchange can be tried in severe TMA and Eculizumab has also been tried in some patients on experimental basis [1]. Despite all these measures around 33 - 50% of patients have poor outcome - death or dialysis dependence [2,18]. In our patient also, despite treatment with ACEI and Rituximab, the renal function did not improve and the patient remained dialysis dependent.

Conclusion

Normotensive SRC comprises of a distinct subset of SRC, which is much more difficult to treat and has a worse prognosis. It should be suspected in all patients of SS having unexplained renal dysfunction, with or without hypertension. The outcome depends on early diagnosis and initiation of therapy with ACEI/ARBs. Clinicians must have high level of suspicion and awareness to the signs and symptoms to diagnose such cases promptly. Despite adequate therapy most of the patients eventually land in end stage kidney disease and become dialysis dependent.

Conflict of Interest

There is no financial interest or any conflict of interest.

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