

Case Report

Scleroderma Renal Crisis Precipitated by Steroid Treatment in Systemic Lupus Erythematosus and Scleroderma Overlap Syndrome

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Abstract

Introduction: Connective tissue disorders can overlap in various ways. Patients may present with features of more than one specific disease without satisfying the diagnostic criteria and thereafter evolve into a specific disease entity. Occasionally, patients may fulfil simultaneously the diagnostic criteria of two or more diseases. Several cases of systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) overlap syndrome have been reported. SLE patients often develop lupus nephritis, the treatment of which is based on immunosuppression with corticosteroids (CS) and cytotoxic drugs. However, the use of high dose of CS has been associated with scleroderma renal crisis (SRC) in patient with SSc.

Case report: a 43-year-old woman presented to the nephrology department of the Military hospital in Rabat, Morocco, in August 2011 with progressive dyspnea and oliguria. She was diagnosed as SLE and scleroderma overlap syndrome based on clinical and serological markers. Renal biopsy showed lupus nephritis. Immunosuppression consisting of high-dose steroid and cyclophosphamide pulses was given. There was response to treatment but 15 days later the course of the disease was complicated by scleroderma renal crisis evidenced by elevated blood pressure, deteriorating kidney function, hemolysis and thrombocytopenia. The patient was treated with perindopril and rapid reduction of steroid doses. This was followed by correction of hemolysis and thrombocytopenia. Two months later, the patient was off dialysis, but had chronic renal insufficiency with an estimated GFR of 25 ml/minute.

Conclusion: This report describes the occurrence of SRC in a patient with lupus nephritis and SSc/SLE overlap syndrome who was treated by CS and cyclophosphamide.

Key words: Systemic Sclerosis; Lupus Erythematosus; Overlap Syndrome; Scleroderma Renal Crisis; Corticosteroids

The authors declared no conflict of interest

Introduction

Connective tissue disorders can overlap in various ways. Patients may present with features of more than one specific disease without satisfying the diagnostic criteria and thereafter evolve into a specific disease entity. Occasionally, patients may fulfil simultaneously the diagnostic criteria of two or more diseases [1]. Several cases of systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) overlap syndrome have been reported [2, 3]. SLE patients often develop lupus nephritis the treatment of which is based on immunosuppression with corticosteroids (CS) and cytotoxic drugs [4]. However the use of high doses of CS has been associated with scleroderma renal crisis (SRC) in patient with SSc [5]. This report describes the occurrence of SRC in a patient with lupus nephritis and SSc/SLE overlap syndrome who was treated by CS and cyclophosphamide.

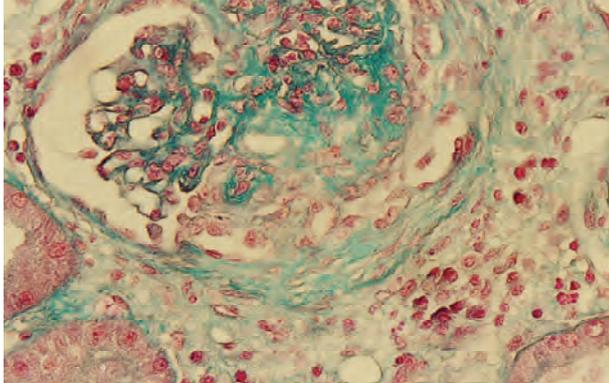
Case report

A 43 year old woman presented to the nephrology department of the Military hospital in Rabat, Morocco, in August 2011 with progressive dyspnea and oliguria. She had no history of systemic disease like diabetes or hypertension and had not taken any medications. She had five pregnancies and five living children. She did not report any joint pain but had the typical complaints of Raynaud's phenomenon. She had no fever or skin rash.

On admission, her blood pressure was 140/80 mmHg with a pulse rate of 70 beats/min. Clinical examination

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Figure 1: Photomicrograph of the renal biopsy showing global endocapillary proliferation in a glomerulus. Periglomerular infiltrating cells were also noted (trichrome stain)



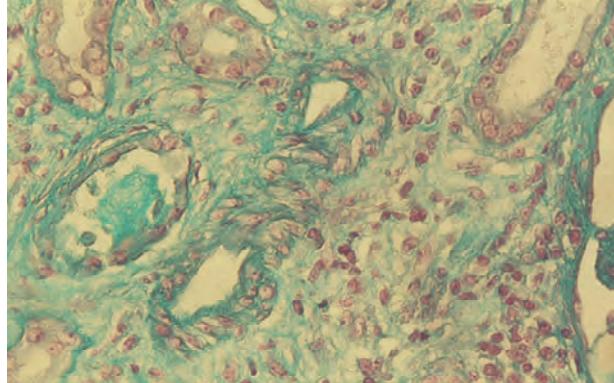
revealed pulmonary crackles and tightness of the skin over the face and hands. The rest of examination was normal.

Her urine dipstick examination revealed two crosses of protein and blood. 24-hour urine protein was 2 g/day. The blood urea and serum creatinine levels were 180 mg/dL and 9.9 mg/dL respectively, sodium 137 meq/L and potassium 4.8 meq/L. Her complete blood count revealed a hemoglobin of 9 g/dl, a platelet count of $272 \times 10^9/L$, and white blood cell count of $3000 \times 10^9/L$ with $700 \times 10^9/L$ lymphocytes. On admission she had no evidence of hemolysis with haptoglobin level of 1.6 g/L, LDH 145 units/L, total bilirubin 0.5 mg/dL and alanine transaminase 10 units/L. Her serum albumin was 3.1 mg/dL. She was hepatitis B surface antigen and anti-HCV antibody negative.

Autoantibody screening at that time detected elevated titers of antinuclear antibodies (using indirect immunofluorescence on HEP-2 cells; titer: 320, speckled nucleolar fluorescence), anti-double-stranded DNA (anti-dsDNA), anti-topoisomerase I antibodies (anti-Scl-70) and anti-ribonucleoprotein antibodies (anti-RNP). Anti-SSA, anti-SSB, anti-Smith, and anti-Jo1 antibodies were negative. Anticardiolipin, anti-beta 2 glycoprotein and lupus anticoagulant were also negative. Both serum complement factor 3 and 4 were markedly depressed.

A chest radiograph revealed cardiomegaly with pulmonary congestion. ECG showed normal sinus rhythm. A Doppler study of the renal arteries did not reveal any evidence of renal artery stenosis. Both kidneys were within the normal size range and showed normal corticomedullary differentiation. An echocardiogram showed normal ejection fraction and minimal pericardial effusion without pulmonary hypertension. Gastroesophageal endoscopy and manometry proved pangastritis and discrete esophageal

Figure 2: Photomicrograph of the renal biopsy showing normal extraglomerular renal vessels (trichrome stain)



hypomotility. In addition, capillaroscopy revealed capillary dropout. Electromyogram revealed minimal peripheral neuropathy. Chestscan, after correction of fluid overload, showed discrete bilateral interstitial syndrome.

The patient was diagnosed as systemic lupus erythematosus and scleroderma overlap syndrome. Renal biopsy was performed and it showed diffuse and global membranous glomerulonephritis with active and chronic lesions (Activity Index: 6, Chronicity Index: 2), classified as lupus nephritis stage V+ IV-G [A(6)/C(2)] according to the ISN/RPS classification (Fig-1). Minimal inflammatory cellular infiltration of interstitial tissue was also seen. The extraglomerular renal vessels were normal (Fig-2). Immunofluorescence showed diffuse immune deposits of IgG, IgM, IgA, C3 and C1q.

Immunosuppression was started consisting of high-dose steroid (methylprednisolone 640 mg for 3 days followed by prednisolone 60 mg) and cyclophosphamide pulses (600 mg per month) along with diuretics, proton pump inhibitors, amlodipine and vitamin D3 supplements. Hydroxychloroquine was not used because of the visual field impairment. The clinical course was favourable with resumption of diuresis and improvement of renal function (creatinine level dropped from 9.9 mg/dl to 6.0 mg/dl). However, at day 15 of immunosuppression, the evolution was complicated by scleroderma renal crisis. Her blood pressure was 180/100 mm Hg and investigations showed thrombocytopenia (platelet count $75 \times 10^3/L$), normocytic normochromic anemia with hemoglobin level of 7g/dl and the presence of schistocytes in peripheral blood. Haptoglobin level was markedly depressed and Coomb's test was negative. Her blood urea increased to 380 mg/dL and creatinine to 8.8 mg/dl, serum sodium was 133 meq/L, serum potassium was 5.9 meq/L, pH was 7.34 and the bicarbonate level was 18 meq/L.

She was consequently started on hemodialysis. The patient was treated with perindopril 10 mg/day with rapid reduction of steroid dose (10 mg every 15 days reaching a dose of 10 mg/day). This was followed by correction of hemolysis and thrombocytopenia. Two months later, the patient was weaned from dialysis, but had chronic renal insufficiency with an estimated GFR of 25 ml/minute according to the Modification of Diet in Renal Disease (MDRD) formula.

Discussion

Patients with connective tissue disorders can often be classified into a specific disease according to certain criteria. Occasionally, patients may have features of overlap between more than one disease. Overlap syndromes usually include polymyositis and either SLE or scleroderma. Coexistence of SLE with scleroderma is rare [1, 6]. In a large series of SSc patients who developed one or more additional autoimmune diseases, only (0.8%) of patient had coexistence of SLE [7]. Shared clinical features between scleroderma and SLE such as arthritis, Raynaud's phenomena, and renal involvement complicate the definition of leading conditions and dictate the use of additional diagnostic tools [8].

In patients with overlap syndromes, autoantibody profiles might be useful in diagnosis, predicting response to treatment and long-term prognosis [9]. Interesting serological findings were present in this case with positive anti-Scl-70, anti-dsDNA, and anti-RNP. High titers of anti-Scl-70 are highly specific for SSc but are present only in 10-15% of SSc patients. The average prevalence of anti-Scl-70 in SLE is less than 5%, and it's observed only in low titers [10]. Anti-dsDNA and anti-Sm antibodies are present in 70 and 30% of SLE patients respectively [1]. Anti RNP is more frequent (44%) in SSC/SLE overlap syndrome [10]. Coexistence of these antibodies is really rare [11].

Approximately 5 to 10% of patients with scleroderma develop renal crisis that mimics malignant hypertension, with rapidly progressive renal failure secondary to microvascular disease, vasospasm and tissue ischemia. Microangiopathic hemolytic anemia and thrombocytopenia can accompany scleroderma renal crisis [12]. Renal crisis may also occur in asclerodermic scleroderma [13]. Studies demonstrate that high levels of serum renin levels are associated with vasospasm and intrinsic renal vessel disease [12]. Hypertension (> 140/90 mmHg) in a scleroderma patient should be carefully evaluated because renal crisis is potentially reversible with appropriate management with angiotensin converting enzyme (ACE) inhibitors.

Histopathologically, there is concentric edematous intimal thickening of interlobular arteries and fibrinoid arteriolar necrosis causing elevation of plasma renin level with onset or aggravation of hypertension and rapid deterioration of renal function as a result of ischemic glomerulopathy. Variable changes may be seen in the glomeruli, in some cases thickening of glomerular capillary walls with a double contour appearance on silver or periodic acid-Schiff staining may be seen. Fibrinoid necrosis may also be seen [14]. Crescents are very rare and those seen are invariably small. Interlobular arteries show intimal thickening which is mucinous or finely fibrous. The thickening results in considerable reduction of the lumen [12]. The occurrence of this SRC may therefore be confused with other microangiopathies secondary to lupus, particularly antiphospholipid syndrome.

Lupus nephritis is a major cause of morbidity and mortality in patients with SLE. The general consensus is that 45-86% of lupus patients will develop clinically relevant nephritis at some time in the course of their illness [15]. The initial clinical presentation of lupus nephritis ranges from asymptomatic proteinuria discovered on routine urinalysis to the nephrotic syndrome with or without renal impairment. Histologic examination of a renal-biopsy specimen is a pivotal step in confirming the diagnosis and guiding therapy [16]. The histopathological patterns of lupus nephritis have been classified by the World Health Organization and, more recently, by the International Society of Nephrology/ Renal Pathology Society (ISN/RPS) [17]. Immunosuppressive therapy consists of glucocorticoids combined with a cytotoxic drug (cyclophosphamide, mycophenolate mofetil (MMF)) to achieve a prompt response [15]. In SSc/SLE patients who develop renal failure and hypertension, it is essential to distinguish between lupus nephritis and scleroderma renal crisis because the treatment is completely different [13]. Almost all current treatment regimens for lupus nephritis include steroids, usually pulses of high doses at induction and then tapering doses of oral steroids. However, SRC has been associated with the use of high doses or recently introduced corticosteroids.

The concern that corticosteroid use may exacerbate the clinical manifestations of SSc has been longstanding [18]. A case control study retrospectively reviewed the relationship of SRC to corticosteroid use in the six months preceding the onset of SRC [19]. This study suggested that recent use of prednisone in dosages exceeding 15 mg daily was significantly associated with the subsequent onset of SRC, whereas recent use of low-dose steroids (less than 15 mg daily) or continuous use of steroids for six months was not associated with increased risk of SRC.

Trang *et al* have found in a systematic review that 2% of all SSc patients and 4% of early diffuse scleroderma patients treated with CS developed SRC [5]. Anemia, new cardiac events (e.g. pericardial effusion or congestive heart failure), diffuse skin thickening, rapidly progressive skin thickening, large joint contractures, SSc disease duration more than 4 years, and the presence of anti-RNA polymerase III antibody may also increase the risk of RCS. Urinary abnormalities and elevations of serum creatinine or plasma renin preceding the onset of SRC have not been shown to predict SRC [20].

Concomitant lupus nephritis and SSc overlap syndrome may limit the use of high steroid doses in SLE and may advocate early use of cytotoxic drugs and other biological therapies. Reduction in steroid dose may be achieved with aggressive immunosuppression including novel biological therapies. Clinical trials and case studies have reported the efficacy and safety of rituximab and MMF in SLE. Rituximab may also significantly improved lung function tests and skin score one year after treatment in patients with SSC. It seems that in SSc/SLE overlap these therapies could be attractive for both conditions yet there are no data in the literature [8]. Also, possible exacerbation of SLE may limit the use of anti-TNF α agents in SSc/SLE overlap [21].

In this case the importance of corticosteroids in the treatment of lupus nephritis and the low risk of occurrence of renal crisis (2%) prompted us to use high doses of CS. However, after the onset of scleroderma renal crisis, the rapid reduction in CS dose and the use of angiotensin converting enzyme inhibitors together with cyclophosphamide improved the prognosis in this particular patient.

Conclusion

This observation underlines the importance of analyzing the benefits and risks of steroid treatment when lupus nephritis is associated with scleroderma in SLE/SSc overlap syndrome.

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