Case Report: Scleroderma Renal Crisis Presenting as Thrombotic Microangiopathy

Olgu Sunumu: Trombotik Mikroanjiopati ile Başvuran Skleroderma Renal Kriz

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ABSTRACT

Scleroderma is a systemic autoimmune disease of unknown origin characterized by excessive deposition of collagen and other connective tissue macromolecules in multiple organs. It can cause thrombotic microangiopathy. Scleroderma renal crisis is a major complication of this disorder. We aimed to present a case that presented with thrombotic microangiopathy findings and was diagnosed as scleroderma renal crisis.

A 56-year-old female patient presented with hypertension and thrombotic microangiopathy signs. After examination and renal biopsy, scleroderma renal crisis with thrombotic microangiopathy was diagnosed. A routine hemodialysis program and an angiotensin converting enzyme inhibitor was started

Scleroderma renal crisis should be kept in mind in patients presenting with malignant hypertension and thrombotic microangiopathy.

KEY WORDS: Scleroderma, Renal crisis, Thrombotic microangiopathy, Hemodialysis

ÖZ

Skleroderma, bir çok organda kollajen ve diğer bağ dokusu makromoleküllerinin aşırı birikimi ile karakterize, kökeni bilinmeyen, sistemik otoimmün bir hastalıktır. Trombotik mikroanjiopatiye neden olabilir. Renal kriz, sklerodermanın majör bir komplikasyonudur. Biz de, trombotik mikroanjipati bulgularıyla ile prezente olan ve skleroderma renal kriz tanısı koyulan bir olguyu sunmak istedik.

56 yaşında kadın hasta, hipertansiyon ve trombotik mikroanjiopati bulgularıyla başvurdu. Tetkikler ve renal biyopsi sonrasında trombotik mikroanjipatinin eşlik ettiği skleroderma renal kriz tanısı koyuldu. Hasta rutin hemodiyaliz programına alındı ve anjiotensin konverting enzim inhibitörü başlandı.

Malign hipertansiyon ve trombotik mikroanjiopati ile başvuran hastalarda skleroderma renal kriz tanısı akılda tutulmalıdır.

ANAHTAR SÖZCÜKLER: Skleroderma, Renal kriz, Trombotik mikroanjiopati, Hemodiyaliz

INTRODUCTION

Scleroderma is a systemic autoimmune disease of unknown origin characterized by excessive deposition of collagen and other connective tissue macromolecules in multiple organs. Scleroderma renal crisis (SRC) is a major complication of this disorder. SRC is characterized by malignant hypertension and oligo/anuric acute renal failure, and occurs in approximately 5% of patients with scleroderma (1,2).

Systemic rheumatic disorders such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and antiphospholipid syndrome (APS) can cause thrombotic microangiopathy (3). We aimed to present a case that presented with thrombotic microangiopathy findings and was diagnosed as scleroderma renal crisis.

CASE

A 56-year-old female patient with no other history of chronic disease except

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diabetes mellitus presented to the emergency room with the complaints of widespread body pain and fatigue. Arterial blood pressure was 180/100 mmHg. Serum urea, creatinine and potassium levels were found to be increased on initial blood chemistry. The patient was hospitalized and hemodialysis was started immediately. On physical examination, three-positive pretibial edema and bilateral crackles in lungs were noticed. The remainder of the physical examination was normal. Laboratory tests revealed leukocytes: 12,000/uL, hemoglobin: 7.7 g/dL, platelets: 85000 /L, urea 201 mg /dL, creatinine 12.6 mg/dL, potassium 6.5 mmol /L, sodium 134 mmol/L albumin 2.8 g/dL, lactate dehydrogenase (LDH): 785 U/L. The bilirubin levels were normal. Erythrocyte sedimentation rate and C-reactive protein (CRP) were found to be increased. Iron parameters were consistent with anemia of chronic disease and ferritin level was found to be increased possibly due to acute phase response. Vitamin B12 and folic acid levels were both in normal range. Direct and indirect Coombs tests were negative. Peripheral blood smear performed to explain the etiology of anemia and thrombocytopenia. Platelets were enough and clustered. There were 2 or 3 fragmented erythrocyte and burn cell in every area (Figure 1). Thrombotic thrombocytopenic purpura (TTP) could not be ruled out and plasmapheresis was started after the blood sample had sent for ADAMTS 13 activity.

Anti-nuclear antibody (ANA) was positive in a titer of 1/2560 with a homogeneous and nucleolar patern in the evaluation of the etiology of renal failure. P-ANCA (perinuclear anti-neutrophil cytoplasmic antibody), C-ANCA (cytoplasmic anti-neutrophil cytoplasmic antibody), anti-dsDNA (anti-double stranded DNA) and viral parameters were negative. Complement levels were in the normal range. Proteinuria was 8 g/day on one occasion. Size and thickness of parenchyma of the right and left kidneys were normal in ultrasonography. The echogenecity of the right kidney was found to be slightly increased to grade 1. The echogenecity of the left kidney was normal. A mild pericardial effusion with no pressing sign was noticed in transthoracic echocardiography. There was no pathological view except an increasing cardiothoracic ratio in chest X-ray. High-resolution computed tomography without intravenous contrast enhancement performed for the differential diagnosis of connective tissue disease and fibrotic densities that were observed in left paracardiac and posterobasal of the lower lobe of the left lung. There were signs of severe restriction on the pulmonary function test. A grade three hypertensive retinopathy was noticed with ophthalmoscopic examination.

Since ADAMTS 13 activity was detected to be normal, plasmapheresis was terminated after three cycles, and TTP was ruled out. The decrease in the levels of LDH and normalization of the thrombocytopenia without treatment ruled out atypical hemolytic uremic syndrome.

Consequently, renal biopsy was performed to clarify the etiology of acute renal failure and thrombocytopenia. Thrombotic microangiopathy in two glomerules and fibrinoid necrosis and myxoid degeneration of major vascular structures in one glomerule were seen in the biopsy specimen (Figure 2, 3).

Considering the presence of these findings and clinical data, connective tissue disorders accompanied by thrombotic microangiopathy were thought of in the differential diagnosis. The items in the differential diagnosis included antiphospholipid syndrome, atypical HUS, TTP and scleroderma. Antiphospholipid antibody was negative. Atypical HUS and TTP had been excluded with ADAMTS 13 activity and laboratory findings. Anti-SCL-70 antibodies (anti-topoisomerase) were analyzed by the ELISA method and found to be increased to 200 RU/ml. Ultimately, a scleroderma renal crisis was diagnosed.

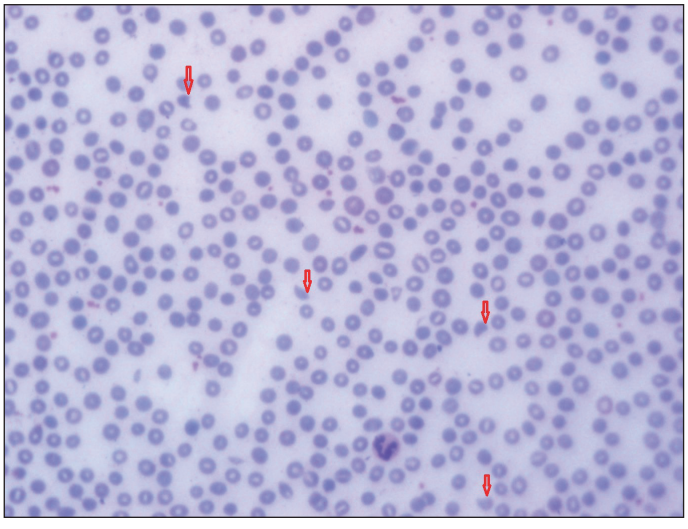

Figure 1: *Fragmented erythrocytes (schistocytes) marked with red arrows.*

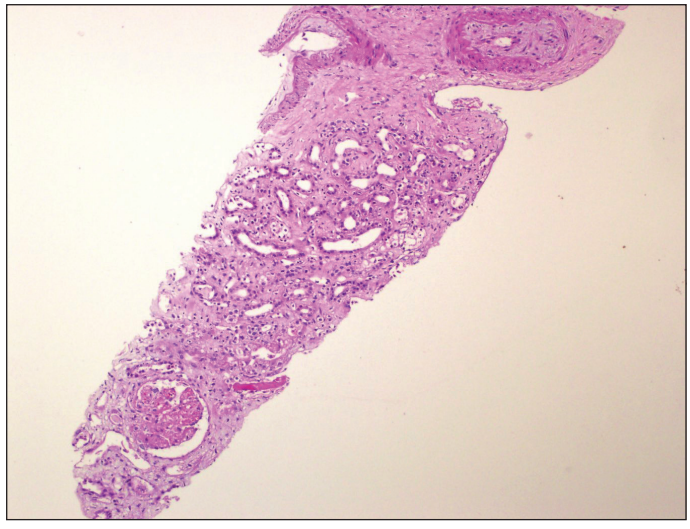

Figure 2: *Mucoid intimal thickening in arteries with large diameter, excessive congestion in a glomerule and fibrin thrombus.*

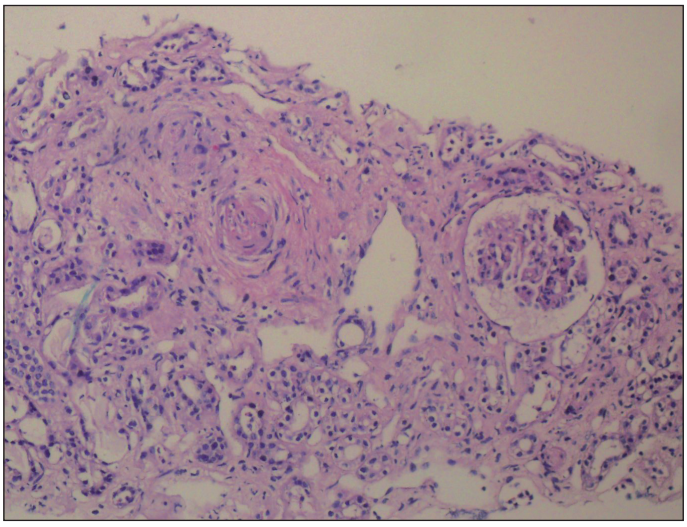

Figure 3: *Fragmented red blood cells on a blood vessel wall in the middle of picture and concentric lamellar fibrosis.*

Immunosuppressive therapy was not considered due to the findings of thrombotic microangiopathy in the renal biopsy. Angiotensin converting enzyme inhibitor (ACEI) was started as ramipril 5 mg/day. A routine hemodialysis program was arranged as three times a week, and blood pressure was in normal range during hospitalization. The patient was discharged.

DISCUSSION

Scleroderma is separated into generalized and localized forms. Systemic sclerosis is used synonymously with the generalized form of scleroderma. The extent of skin involvement and the accompanying pattern of internal organ involvement define the basis for the classification of systemic sclerosis and there are five subtypes (4):

- Diffuse cutaneous SSc
- Limited cutaneous SSc
- SSc without scleroderma, in which patients have only internal organ involvement
- Environmental
- Overlap syndromes

Since, our patient had interstitial and restrictive lung disease, and positive serum autoantibodies for Scl-70 without skin involvement on admission, the diagnosis was consistent with SSc without scleroderma.

Renal involvement is common in SSc. It has been found in 60 to 80 percent of SSc patients in autopsy studies (5). The most serious renal manifestation is renal crisis (SRC). SRC was reported in 5 to 20 percent of patients with diffuse cutaneous SSc (6). It was reported in 86 percent of patients with diffuse cutaneous SSc, 10 percent with limited cutaneous SSc and 4 percent in the other forms in another study (7).

SRC is characterized by acute renal failure and sudden onset of hypertension. The urine microscopy is usually normal. Hypertension generally manifest with ocular signs such as hypertensive retinopathy. In a review, 85 percent of 145 patients with SRC had new-onset diastolic hypertension. The mean peak blood pressure was 178/102 mmHg (8,9). Interestingly, no hypertension was noticed in10 percent of patients with SRC in another study (10). These patients have a worse renal outcome and higher mortality (10). Our patient had hypertension with retinopathy and acute renal failure on admission.

Serum autoantibodies can predict the risk for SRC. A rapid progression is associated with the presence of anti-ARN-polymerase III and anti-topoisomerase I antibodies (Scl-70). Scl-70 antibodies are found in about 40% of patients with diffuse cutaneous SSc and 10% of patients with limited cutaneous SSc. Anti-RNA polymerase III autoantibodies were detected in 59 percent of 96 patients (11,12). We found positive anti-Scl-70 by the ELISA method.

The histopathologic finding is intimal proliferation and thickening, narrowing and obliteration of the vascular lumen with concentric “onion-skin” hypertrophy. In a review of renal biopsies from 17 patients with SRC, both a higher number of thrombosed blood vessels and severe glomerular ischemic collapse was reported (13,14). There was fibrinoid necrosis and myxoid degeneration on major vascular structures in the biopsy specimen of our patient. Also, there was thrombotic microangiopathy in two glomerules.

Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and scleroderma renal crisis (SRC) all present with features of thrombotic microangiopathy. Therefore, distinguishing these entities are very important (15). We distinguished these conditions with ADAMTS 13 activity and laboratory findings.

ACE inhibitors are vital in preventing the development of SRC. A prospective cohort study of 108 patients with SRC seen between 1972 and 1987 found the following benefits in patients treated continuously with ACE inhibitors (mostly captopril). This study showed that using ACEI was associated with higher rate of recovery of renal function, discontinuing dialysis and higher survival rate at one year (16, 17). Combination therapy with plasmapheresis and ACEI may be associated with better renal survival. In a single-center retrospective review, half of 20 patients with SRC with associated microangiopathic hemolytic anemia were treated with plasma exchange therapy in combination with ACE inhibitors. Combination therapy was associated with better renal survival rate at one year than only ACEI treatment (80 and 45 percent) (18).

Despite treatment with ACE inhibitors, approximately 20 to 50 percent of patients with SRC require dialysis. However, as discussed in the following section, an appreciable proportion of these patients recover sufficient renal function to discontinue

dialysis. If indicated, either hemodialysis or continuous peritoneal dialysis is an effective therapy for ESRD due to SRC (9). However, survival on dialysis in patients with SRC is worse than in other forms of ESRD. In a study from the United States Renal Data System (USRDS) that included 364,000 patients with ESRD on maintenance dialysis, 820 had scleroderma. Two-year survival was significantly lower in patients with scleroderma (49 percent versus 64 percent in all other patients) (19). We had performed plasmapheresis until excluding TTP. After the diagnosis of SRC, we started a routine hemodialysis program and ACEI treatment.

CONCLUSION

We presented a case of scleroderma renal crisis that presented with thrombotic microangiopathy. Scleroderma renal crisis should be kept in mind in case of malignant hypertension with thrombotic microangiopathy.

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