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CASE REPORT

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# Scleroderma renal crisis in a patient with anticentromere antibody-positive limited cutaneous systemic sclerosis

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**Abstract** We have encountered a 68-year-old Japanese woman with limited cutaneous systemic sclerosis who developed de novo onset of accelerated hypertension and renal dysfunction; thus we diagnosed scleroderma renal crisis. Anticentromere antibody alone was identified, and not anti-DNA topoisomerase I antibody, anti-RNA polymerase antibodies, anti-Th/To antibodies, or antiribonucleoprotein antibodies, even with use of immunoprecipitation assay. She was successfully treated with angiotensin-converting enzyme inhibitor. This case, scleroderma renal crisis with detection of anticentromere antibody, is thought to be extremely uncommon.

**Key words** Anticentromere antibody · Limited cutaneous systemic sclerosis · Scleroderma renal crisis

## Introduction

Scleroderma renal crisis is defined as the new onset of severe hypertension and/or rapidly progressive renal dysfunction in patients with systemic sclerosis.[1,2] Scleroderma renal crisis mostly occurs in patients with diffuse cutaneous scleroderma. There is a high risk of renal crisis in systemic sclerosis patients who have rapidly progressive widespread skin thickening in their first 2–3 years of disease. Conversely, this renal complication is thought to be rare in patients with the limited form of the disease.

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Various autoantibodies, such as anti-DNA topoisomerase I, anticentromere, and anti-RNA polymerase I/III antibodies, are detected in systemic sclerosis patients, and these are known to correlate with clinical manifestations of this disease.[1,3,4] Anti-DNA topoisomerase-I antibody is associated with diffuse cutaneous involvement, interstitial pulmonary disease, and renal and other visceral organ involvement, whereas anticentromere antibody is associated with limited cutaneous scleroderma. Anti-RNA polymerase I/II/III antibodies are found in patients with diffuse cutaneous scleroderma, who have a higher prevalence of renal and cardiac complications. Our report describes unique development of scleroderma renal crisis in a patient with anticentromere antibody-positive limited cutaneous systemic sclerosis.

## Case report

A 68-year-old Japanese woman was admitted to our hospital because of onset of severe hypertension and renal dysfunction. One year previously, at age 67, she had been diagnosed as having limited cutaneous scleroderma and primary biliary cirrhosis in another hospital because of the presence of sclerodactyly, a several-year history of Raynaud's phenomenon, reflux esophagitis, severe persisting pruritus, elevated serum alkaline phosphatase, antinuclear antibody (1:1280; discrete speckled nuclear staining), anticentromere antibody, and antimitochondria antibody;[1,5] thus she had started to be treated with proton pump inhibitor and ursodeoxycholic acid. She had a 20-year history of hypertension, which had been well controlled, around 130/80 mmHg, with calcium antagonist. She had not been noted to have any renal dysfunction or urinary abnormalities (serum creatinine, 0.66 mg/dl). One month prior to the admission, however, she had reported headache and dizziness, and she was observed in a local hospital to have severe hypertension (200/110 mmHg), renal dysfunction, and proteinuria; thus she was referred to our hospital.

On admission, she was alert but in mild distress. Her blood pressure was 214/102 mmHg, and pulse 72 beats/min and regular. Physical examination of the heart, lung, and abdomen, and the neurological examination were unremarkable except sclerosis of the skin on her fingers and toes. Arthritis, digital pitting scars, nailfold bleeding, and tendon friction rubs were absent. Modified Rodnan total skin thickness score was 6 points.[6] Ophthalmologic examination did not reveal any abnormalities in the retina.

Results of laboratory examination revealed the following findings. The urine was positive for protein with daily excretion at 1.73 g, and the sediments contained 2-2 red blood cells/high-power field, but no white blood cells or granular casts. Hematocrit was 37.0%; hemoglobin, 12.9 g/dl; white blood cells, 6600/μl; and platelets, 217000/μl. Peripheral blood smear, coagulation screen, and the level of haptoglobin were normal. Total protein was 6.5 g/dl; albumin, 3.1 g/dl; alanine aminotransferase, 34 IU/l; aspartate aminotransferase, 48 IU/l; lactate dehydrogenase, 453 IU/l (normal range, 100–210); alkaline phosphatase, 485 IU/l (110–340); total bilirubin, 0.45 mg/dl; and creatine kinase, 77 IU/l. Blood urea nitrogen was 13 mg/dl; creatinine, 1.28 mg/dl; Na, 139 mEq/l; K, 3.4 mEq/l; Cl, 102 mEq/l; Ca, 8.3 mg/dl; phosphorus, 2.8 mg/dl; and uric acids, 5.5 mg/dl. A chest X-ray film and a chest computed tomography scan showed normal lung fields without cardiomegaly, and echocardiography showed normal pulmonary arterial pressure. Neither kidney atrophy nor obstruction of the urinary tracts was found in abdominal echography. Plasma renin activity was 19 ng/ml per hour (normal range, 0.3–3.0), and aldosterone level was 20 ng/dl (normal range, 2–9). The serum was positive for antinuclear antibody (1:320; discrete speckled nuclear staining), anticentromere antibody (156, normal value <10) and antipyruvate dehydrogenase antibody, but was negative for anti-UI-ribonucleoprotein (RNP) antibody, anti-Ro antibody, anti-La antibody, anti-DNA topoisomerase I antibody, and myeloperoxidase-antineutrophil cytoplasmic antibody. No other autoantibodies (e.g., Anti-RNA polymerase I/II/III antibodies) were identified with RNA-immunoprecipitation and protein immunoprecipitation.[4]

As she had a sudden onset of severe hypertension with the elevated plasma renin activity, she was diagnosed as having scleroderma renal crisis with limited cutaneous scleroderma. Therefore, treatment with angiotensin-converting enzyme inhibitor, captopril, 75 mg per day, was started, and she became normotensive within 5 days. Her serum creatinine levels were not markedly increased (1.63 mg/dl), and the proteinuria was reduced to 0.7 g per day. Because her clinical manifestations improved during the 1-month hospitalization, she was discharged. Six months later, she continues to be treated with enalapril, 20 mg per day, and to be normotensive with serum creatinine concentration of 1.49 mg/dl and trace amounts of proteinuria. Scleroderma skin changes remained limited to the skin on her fingers and toes.

## Discussion

We have described a patient with anticentromere antibody-positive limited cutaneous systemic sclerosis who developed scleroderma renal crisis. Our patient presented limited skin sclerosis with Raynaud's phenomenon, persisting severe systemic pruritus, elevated alkaline phosphatase level, and positive anticentromere and antimitochondria antibodies, which are consistent with limited cutaneous scleroderma-primary biliary cirrhosis overlap syndrome.[1,5,7] Further, she also presented de novo onset of accelerated arterial hypertension with elevated plasma renin activity and renal dysfunction without active nephritic urinary sediments; thus we diagnosed scleroderma renal crisis, and treated her with angiotensin-converting enzyme inhibitor, controlled her blood pressure, and stopped the progression of renal failure.

Scleroderma renal crisis usually occurs relatively early in the course of disease, usually within the first 5 years.[2,8] Black et al. have shown that the incidence of scleroderma renal crisis was 12.4% in patients with diffuse cutaneous scleroderma and 1.6% in those with limited cutaneous scleroderma.[2] Further, in Steen and Medsger's study of 145 patients with scleroderma renal crisis, 128 patients had diffuse skin involvement proximal to the elbows or on the trunk.[8] Eighteen patients had less extensive skin disease, but they showed features suggestive of the early stage of diffuse cutaneous scleroderma, including tendon friction rubs, anti-DNA topoisomerase I antibody, or anti-RNA polymerase III antibody.[8] Conversely, the occurrence of renal crisis has been reported to be rare in patients with limited cutaneous scleroderma.[1,2,8] Thus, the most important risk factor for renal crisis is thought to be widespread skin thickening in the first 2–3 years of disease.

Autoantibodies in systemic sclerosis are not known to have any role in the pathogenesis of the disease, but they have been shown to be associated with very specific clinical features, organ involvements, and survival outcomes.[3] Therefore, the determination of autoantibodies may be useful for assessing the prognosis, the follow-up, and the treatment of patients with systemic sclerosis. Anti-RNA polymerase III antibody has been reported to be strongly associated with renal crisis.[3] Several studies of limited cutaneous scleroderma have described that renal crisis occurred in the patients who had such autoantibodies as anti-RNA polymerase III antibody, anti-Th/To antibodies, or anti-U1/U3 RNP antibodies.[8–13] Katrib et al. have reported three patients with anticentromere antibody-positive limited cutaneous systemic sclerosis who developed renal failure, but these patients showed normal blood pressure, active urinary sediments, positive antineutrophil cytoplasmic antibodies, and crescentic glomerulonephritis,[12] indicating that these cases were not classical scleroderma renal crisis. A case has been reported of a patient with scleroderma and primary biliary cirrhosis overlap who had fatal scleroderma renal crisis, but she had massive gastrointestinal bleeding and had no anticentromere antibody,[13] suggesting that this case was also not typical scleroderma renal crisis. To our knowledge,

there are few reports of renal crisis associated with anticentromere antibody.

Our patient was not identified as having any autoantibodies (i.e., anti-DNA topoisomerase I antibody, anti-RNA polymerase antibodies, anti-Th/To antibodies, or antiribonucleoprotein antibodies) except anticentromere antibody, even with use of the immunoprecipitation assays. Patients with limited cutaneous scleroderma, especially those with anticentromere antibody, are generally thought to have a good prognosis, with the notable exception of those few patients who have complications such as malabsorption syndrome or primary biliary cirrhosis, or who develop pulmonary hypertension 10–20 years after the onset.[1] We do not accurately know the time of onset of our patient's disease, but we do know that she had a several-year history of Raynaud's phenomenon, and she showed mild liver dysfunction and no pulmonary hypertension; thus we speculate that she had been afflicted for less than 5 years. Therefore, we think that our case, scleroderma renal crisis with the presence of anticentromere antibody in the early course of limited cutaneous scleroderma, is extremely uncommon.

Scleroderma renal crisis is a fatal complication, but it can be effectively managed when hypertension is aggressively controlled with angiotensin-converting enzyme inhibitor.[2,8] Our study indicates that close monitoring of blood pressure is necessary for the management of patients with scleroderma, even those with limited cutaneous systemic sclerosis associated with anticentromere antibody.

## References


1. Gilliland BC. Systemic sclerosis (scleroderma) and related disorders. In: Fauci AS, editor. Harrison's rheumatology. New York: McGraw-Hill; 2006. p. 111–32.
2. Black CM, Sayegh MH, Rose BD. Systemic sclerosis (scleroderma) renal disease. In: Rose BD, editor. *UptoDate*, CD-ROM: version 14.1. Wellesley, MA: UptoDate; 2006.
3. Steen VD. Autoantibodies in systemic sclerosis. Semin Arthritis Rheum 2005;35:35–42.
4. Kuwana M, Kaburaki J, Okano Y, Tojo T, Homma M. Clinical and prognostic associations based on serum antinuclear antibodies in Japanese patients with systemic sclerosis. Arthritis Rheum 1994;37: 75–83.
5. Kaplan MM. Clinical manifestation, diagnosis, and natural history of primary biliary cirrhosis. In: Rose BD, editor. *UptoDate*, CD-ROM: version 14.1. Wellesley, MA: UptoDate; 2006.
6. Brennan P, Silman A, Black C, Bernstein R, Coppock J, Maddison P, et al. Reliability of skin involvement measures in scleroderma. The UK Scleroderma study group. Br J Rheumatol. 1992;31:457–63.
7. Akiyama Y, Tanaka M, Takeishi M, Adachi D, Mimori A, Suzuki T. Clinical, serological and genetic study in patients with CREST syndrome. Intern Med 2000;39:451–6.
8. Steen VD, Medsger TA Jr. Long-term outcomes of scleroderma renal crisis. Ann Intern Med 2000;133:600–3.
9. Gunduz OH, Fertig N, Lucas M, Medsger TA Jr. Systemic sclerosis with renal crisis and pulmonary hypertension. Arthritis Rheum 2001;44:1663–6.
10. Mitri GM, Lucas M, Fertig N, Steen VD, Medsger TA Jr. A comparison between anti-Th/To-and anticentromere antibody-positive systemic sclerosis patients with limited cutaneous involvement. Arthritis Rheum 2003;48:203–9.
11. Iwamoto M, Tamura K, Ozawa T, Nakamura N, Konishi K, Mizuri S, et al. Scleroderma renal crisis with limited cutaneous sclerosis and positive anti-RNA polymerase antibody. Clin Exp Nephrol 2000;4:152–5.
12. Katrib A, Sturgess A, Bertouch JV. Systemic sclerosis and antineutrophil cytoplasmic autoantibody-associated renal failure. Rheumatol Int 1999;19:61–3.
13. Szigeti N, Fabian G, Czirjak L. Fetal scleroderma renal crisis caused by gastrointestinal bleeding in a patient with scleroderma, Sjogren's syndrome and primary biliary cirrhosis overlap. J Eur Acad Dermatol Venereol 2000;16:276–9.