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【 CASE REPORT 】

Anticentromere Antibody-positive Scleroderma Renal Crisis Requiring Dialysis

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Abstract:
A 70-year-old man with prior Raynaud's phenomena developed hypertension and renal insufficiency. Raynaud's phenomena, finger skin thickening, interstitial lung disease, and positive anticentromere antibody findings indicated systemic sclerosis (SSc). Based on the presence of SSc, severe hypertension with rapidly progressive renal failure, and proliferative and obliterative arteriolar vasculopathy, scleroderma renal crisis (SRC) was diagnosed. Despite good blood pressure control with antihypertensive drugs, hemodialysis was initiated and could not be withdrawn owing to unimproved renal dysfunction. Although SRC in anticentromere antibody-positive limited cutaneous SSc is extremely rare, some patients may develop SRC, and their renal prognosis may be poor.

Key words: scleroderma renal crisis, anticentromere antibody, systemic sclerosis

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Introduction

Scleroderma [systemic sclerosis (SSc)] is a complex disease in which extensive fibrosis, vascular alterations, and positive findings for autoantibodies against various cellular antigens are among the principal features (1). Scleroderma renal crisis (SRC) is a rare complication characterized by malignant hypertension and acute renal failure. Although the prognosis improves with the introduction of angiotensin-converting enzyme (ACE) inhibitors for malignant hypertension (2), nearly half of patients need dialysis (3). SSc has two major subgroups in the commonly accepted classification of scleroderma: limited cutaneous scleroderma and diffuse cutaneous scleroderma (1). SRC often occurs during the rapid progression of skin thickening in the early stage of diffuse cutaneous SSc. SRC with limited SSc is extremely rare; it occurs in less than 2% of the population (4). Furthermore, there are only few reports on renal crisis associated with anticentromere antibody (5-7).

We herein report a case of SRC in a patient with anticentromere antibody-positive limited cutaneous SSc undergoing renal biopsy.

Case Report

A 70-year-old man was admitted to our hospital because of renal dysfunction and hypertension. He had a 10-year history of Raynaud's phenomenon and had received regular follow-ups and medication therapies for dyslipidemia for 2 years.

Seven months before admission, his creatinine (Cr) level had been 1.04 mg/dL; as such, his renal function was almost normal. Since his systolic blood pressure increased to 180 mmHg 5 months previously, irbesartan and amlodipine were started. Thereafter, the Cr level deteriorated to 1.5 mg/dL. Despite the adjustment of the antihypertensive drug, his renal function deteriorated rapidly, and the Cr level had been 2.4 mg/dL 3 months previously and 3.8 mg/dL 2 months previously. Since the Cr level increased to 6.91 mg/dL 2 weeks prior to admission, he was referred to our hospital.

On admission to our hospital, he was alert; his pulse rate was 79 beats/min; and his blood pressure was 168/83 mmHg. He had skin thickening of the fingers, i.e. puffy fin-

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Table 1. Laboratory Findings on Admission

Urinalysis		Blood cell count		Blood chemistry		Immuno-serological	
urinometry	1.011	WBC	10,100 /μL	TP	8.1 g/dL	CRP	10.27 mg/dL
pH	5.5	RBC	308×10^4 /μL	Alb	4.5 g/dL	IgG	1,350 mg/dL
Protein	2+	Hb	9.4 g/dL	BUN	76 mg/dL	IgA	226 mg/dL
Occult blood	+-	HCT	27.2 %	Cr	8.41 mg/dL	IgM	88 mg/dL
RBC	1-3/HPF	MCV	88 fL	UA	9.7 mg/dL	IgE	33.6 IU/mL
WBC	<1/HPF	Plt	32.9×10^4 /μL	Na	129 mEq/L	CH50	64.6 /mL
cast	(-)	Coagulation test		Cl	91 mEq/L	C3	122 mg/dL
		PT-Sec	11.7 s	K	4.7 mEq/L	C4	50.6 mg/dL
Urinary chemistry		APTT	32.7 s	Ca	9.1 mg/dL	anti-nuclear antibody	1,280 times
UP	0.5 g/day	Fib	559 mg/dL	iP	6 mg/dL	(centoromere type)	
NAG	16.6 IU/gCr	D-dimer	2.7 μg/mL	CK	73 IU/L	anti-centromere	131 IU/mL
β2MG	31,716 μg/gCr	FDP	7.3 μg/mL	AST	14 IU/L	antibody	
				ALT	13 IU/L	anti-CCP antibody	<0.6 IU/mL
		Endocrine		LDH	206 IU/L	anti-ds-DNA antibody	<10 IU/mL
		plasma renin	>20 ng/mL/h	ALP	226 IU/L	anti-RNP antibody	(-)
		activity		Glu	112 mg/dL	anti-Smith antibody	(-)
		aldosterone	608 pg/mL	HbA1c	5.6 %	anti-SS-A antibody	4 times
				KL-6	330 IU/mL	anti-SS-B antibody	(-)
				SP-D	<17.2 ng/mL	anti-Scl-70 antibody	(-)
						rheumatoid factor	8 IU/mL
						anti-GBM antibody	(-)
						MPO-ANCA	<1.0 IU/mL
						PR3-ANCA	<1.0 IU/mL
						anti-RNA polymerase IIII antibody	(-)

RBC: red blood cell, WBC: white blood cell, UP: urinary protein, NAG: N-acetyl-β-D-glucosaminidase, β2MG: β2microglobulin, Hb: hemoglobin, HCT: hematocrit, MCV: mean corpuscular volume, Plt: blood platelet, PT: prothrombin time, APTT: activated partial thromboplastin time, Fib: fibrinogen, FDP: fibrin/fibrinogen degradation products, TP: total protein, Alb: albumin, BUN: blood urea nitrogen, Cr: creatinine, UA: uric acid, Na: sodium, Cl: chloride, K: potassium, Ca: calcium, iP: inorganic-phosphate, CK; creatine phosphokinase, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, Glu: glucose, HbA1c: hemoglobin A1c, KL-6: sialylated carbohydrate antigen, SP-D: surfactant protein-D, CRP: C-reactive protein, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, IgE: immunoglobulin E, CH50: complement homolytic complement activity, C3: complement C3, C4: complement C4, anti-CCP antibody: anti-cyclic citrullinated peptide antibody, anti-ds-DNA antibody: anti-double stranded deoxyribonucleic acid antibody, anti-RNP antibody: anti- ribonucleoprotein antibody, anti-SS-A antibody: anti- sjögren's syndrome -A antibody, anti-SS-B antibody: anti-Sjögren's syndrome-B antibody, anti-Scl-70 antibody: anti-topoisomerase antibody, anti-GBM antibody: anti-glomerular basement membrane antibody, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase-3 anti-neutrophil cytoplasmic antibody, anti-RNA polymerase IIII antibody: anti- ribonucleic acid polymerase IIII antibody

gers, but no fingertip lesions or telangiectasia. His modified Rodman's total skin thickness score (mRSS) was 1 (mild). A chest examination revealed bilateral fine rales in the lower zone. The findings of the physical examination of the heart and abdomen and neurological examination were unremarkable.

Regarding the relevant laboratory data on admission (Table 1), the urine showed positive findings for protein with daily excretion at 0.51 g, and the sediment contained 1-3 red blood cells/high-power field but no white blood cells or granular casts. The hematocrit level was 27.2%; hemoglobin level, 9.4 g/dL; white blood cell count, 10,100/μL; and platelet count, 329,000/μL. The total protein level was 8.1 g/dL; albumin level, 4.5 g/dL; alanine aminotransferase level, 13 IU/L; aspartate aminotransferase level, 14 IU/L; lactate dehydrogenase level, 206 (normal range, 115-245) IU/L; alkaline phosphatase level, 226 (115-359) IU/L; total bilirubin level, 0.3 (0.3-1.2) mg/dL; and creatine kinase level, 73 (62-287) IU/L. The blood urea nitrogen level was 76 (8-22) mg/dL; Cr level, 8.41 (0.6-1.0) mg/dL; Na level, 129 (136-147) mEq/L; K level, 4.7 (3.6-5.0) mEq/L; Cl level, 91 (98-109) mEq/L; Ca level, 9.1 (8.5-10.2) mg/dL; P level, 6.0 (2.4-4.3) mg/dL; and uric acid level, 9.7 (3.7-7.0) mg/dL. The autoimmune profile indicated an antinuclear antibody level of 1:1,280 (centromere type; normal, <1:40), and the anticentromere antibody level was 131 (<10) IU/mL. The test findings for anti-DNA topoisomerase I antibody, anti-UI-ribonucleoprotein antibody, anti-double-stranded DNA antibody, anti-single-stranded DNA antibody, anti-RNA polymerase IIII antibodies, anti-Sm antibodies, anti-mitochondrial antibodies M2, and rheumatoid factor were all negative. Although he had already taken angiotensin receptor antagonists when he was hospitalized, his plasma renin activity was >20 (0.3-5.4) ng/mL/h, and his aldosterone level was 608 (39-307) pg/mL.

Chest X-ray showed normal lung fields without cardi-

Table 2. Summary of Case Reports of Anticentromere Antibody-positive Scleroderma Renal Crisis (SRC).

Reference	Age (y)	Sex	Raynaud's phenomenon	Steroid use	Diffuse skin thickening	Duration of scleroderma	Cr at first visit (mg/dL)	BP on admission (mmHg)	Anti-centromere antibody	Anti-Scl-70 antibody	Anti-RNA polymerase III antibody	Treatment	Kidney biopsy	Renal outcome
[7]	83	F	+	-	-	four years	4.5	205/95	+	-	+	ACEI	-	Maintenance hemodialysis
[7]	89	F	-	-	-	no data	1.5	180/100	+	-	-	ACEI	-	CKD
[5]	68	F	+	N/A	-	several years	1.28	214/102	+	-	-	ACEI	-	CKD
[6]	79	F	+	N/A	-	six months	2.5	170/100	+	no data	no data	ACEI	-	CKD
Present case	70	M	+	-	-	ten years	8.41	168/83	+	-	-	ACEI	+	Maintenance hemodialysis

BP: blood pressure, Cr: creatinine, F: female, M: male, ACEI: angiotensin converting enzyme inhibitor, N/A: not available, CKD: chronic kidney disease

omegaly; however, chest computed tomography (CT) showed a reticular shadow in the lower lung field on both sides, which was a finding indicative of interstitial pneumonia, and dilation of the esophagus; the presence of reflux esophagitis was suspected. Abdominal CT and kidney echogram showed a slightly decreased left kidney size and a normal right kidney size without hydronephrosis. Echocardiography showed a mild elevation of the right ventricular systolic pressure of 47 mmHg, and mild pulmonary hypertension was suspected. He had hypertensive retinopathy with dot hemorrhaging, which is classified as group 3 under the Keith-Wagener criteria.

The presence of Raynaud's phenomena, skin thickening of the fingers, interstitial lung disease, and positive anticentromere antibody finding indicated limited cutaneous SSc (8). As he had severe hypertension with rapidly progressive renal failure, he was clinically diagnosed with SRC. However, SRC in anticentromere antibody-positive limited cutaneous SSc is extremely rare; a renal biopsy was therefore scheduled for the differentiation of other renal diseases. The renal biopsy was performed while the patient was being treated with antihypertensive drugs, including enalapril, doxazosin, and nifedipine. However, he was started on hemodialysis on the 14th day of admission because of a deteriorating kidney function.

The renal biopsy specimen contained 17 glomeruli, 1 of which demonstrated global sclerosis (Figure). On light microscopy, one site included an artery corresponding to the arcuate arteries to the interlobular arteries, and mucoid intimal thickening was observed. Most arterioles had narrowing of the lumen, and intimal or wall thickening was observed but did not resemble an onion skin. Although the glomerular changes were poor, wrinkling of the basement membrane was observed in some areas. The interstitium was generally open due to fibrosis, and the tubules were generally atrophied. Immunofluorescence microscopy revealed no deposition of IgG, IgA, IgM, C3, or C1q.

The renal disturbance was considered to have been caused by scleroderma and hypertension in the histological findings along with the clinical findings, and the antihypertensive therapy was continued. The blood pressure was reduced to less than 140 mmHg by antihypertensive therapy, including ACE inhibitors. However, his urine volume gradually decreased, and hemodialysis could not be withdrawn.

Discussion

SRC with anticentromere antibody is extremely rare, and there have been only a few reports of SRC in patients with anticentromere antibody-positive limited cutaneous SSc. To our knowledge, this is the first report to describe the pathological findings of SRC in a patient with anticentromere antibody-positive limited cutaneous SSc. Through a comprehensive search in Medline and Web Japan Medical Abstracts Society, we identified only four reported cases of anticentromere antibody-positive SRC (5-7) and compared the fea-

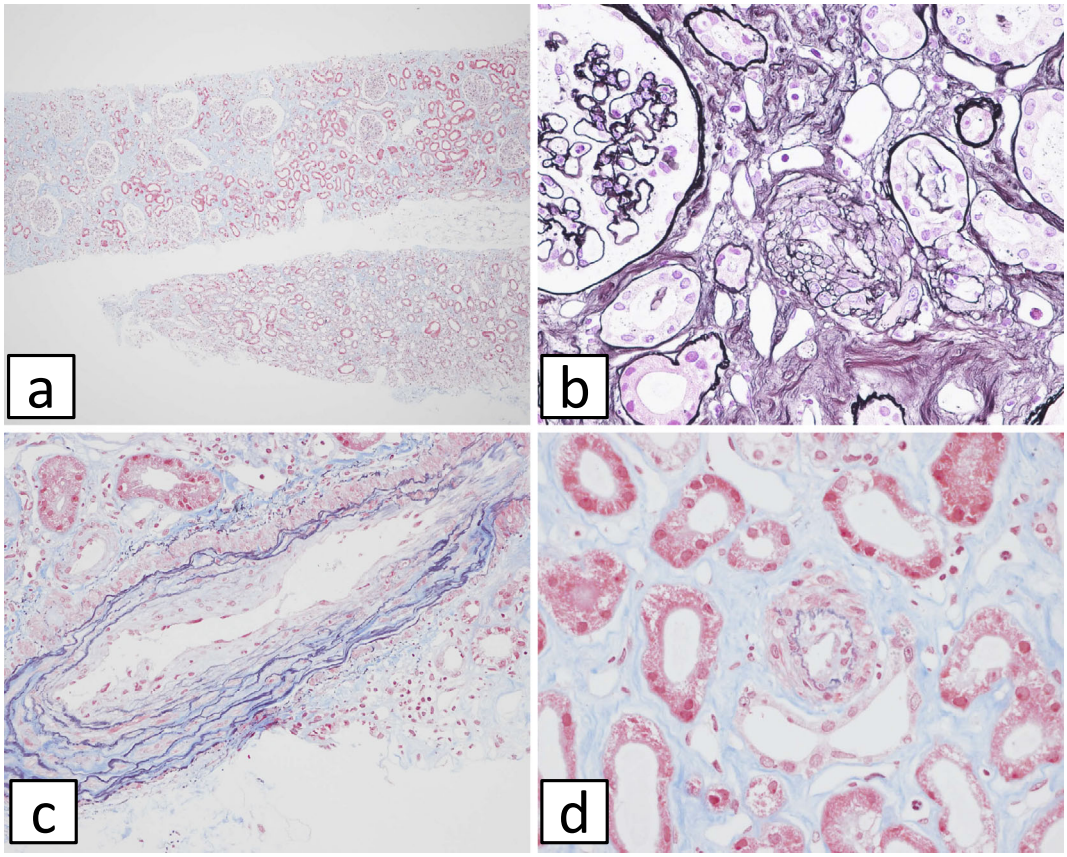

Figure. **Kidney biopsy findings. a: Two samples were collected. Cortex:medulla=1:1. There were 17 glomeruli, including 1 with global sclerosis. The interstitium was generally open due to fibrosis, and the tubules were generally atrophied (Masson-Noguchi staining, ×40). b: The glomerular changes were poor; however, wrinkling of the basement membrane was observed in a few areas. The arterioles showed narrowing of the lumen (Periodic acid methenamine silver staining, ×100). c: An artery corresponding to the arcuate arteries to the interlobular arteries with mucoid intimal thickening (Elastica-Masson staining, ×100). d: Arterioles with narrowing of the lumen and intimal thickening (Elastica-Masson staining, ×100).**

tures of these cases with those of the present case (Table 2).

All patients received treatment with ACE inhibitors, and only one patient received hemodialysis. His Cr level and that of the present case were high, which might suggest that the Cr level at the initial diagnosis affects the renal prognosis. Anticentromere antibody was originally associated with the calcinosis, Raynaud's phenomenon, esophageal hypompotility, sclerodactyly, and telangiectasia (CREST) variant of SSc. When compared with other patients who exhibit speckled or nucleolar antinuclear antibody patterns, those with anticentromere antibody have major organ system involvement significantly less frequently and have a better prognosis (9). However, two of five SRC patients with anticentromere antibody received maintenance hemodialysis, suggesting that some patients may develop end-stage renal failure. There have been no reports of death, even in cases of end-stage renal failure, which is consistent with the notion that anticentromere antibody-positive patients have a good prognosis. Therefore, although the renal prognosis of SRC with anticentromere antibody may not be good, it is not life-threatening.

All four previous cases and the present patient were Asians, suggesting that Asians may more easily develop SRC in anticentromere antibody-positive SSc than other races. The frequency of autoantibodies in SSc and clinical symptoms are known to have racial differences, and clinical symptoms and severity may differ among patients, even if they have the same antibody (10). Similarly, racial differences may influence the onset of anti-centromere antibody-positive SRC.

A renal biopsy is not necessary to confirm the diagnosis of classical SRC. Practically, such biopsies are recommended when doubt exists regarding the etiology of renal dysfunction, or alternatively, to exclude the presence of other pathologic conditions (11). The hallmark of SRC is proliferative and obliterative arteriolar vasculopathy with hypertensive vascular damage, thrombotic vascular occlusion, glomerular ischemic collapse, onion skinning, intimal myoid accumulation, and adventitial fibrosis (11). Early vascular changes can manifest as the intimal accumulation of myxoid material, and onion-skin lesions develop later. As the present patient did not have a typical course of SRC, we conducted

a renal biopsy to establish a diagnosis and evaluate the activities better. Small vessel changes predominated and caused vascular narrowing; however, onion-skin lesions were not observed. Because there were no advanced lesions in the tissue, we attempted to improve his renal function by continuing the antihypertensive therapy, including ACE inhibitors. However, he remained on dialysis.

We considered two reasons as possible causes for his end stage kidney disease despite the fact that no advanced vascular lesions were observed. First, the patient showed severe interstitial fibrosis and expansion of the interstitium, which may have exacerbated the poor renal function. Second, despite the high Cr value, there were no serious findings regarding the histopathology, suggesting that other sites may have had more serious lesions. However, the exact cause is unknown.

The diagnosis of acute kidney failure with SSc is not always obvious, and the differential diagnosis is important. Hypovolemia can mimic SRC and may be provoked by dehydration, third-space sequestration in case of gut involvement, and intestinal paresis from the use of diuretics or nonsteroidal anti-inflammatory drugs (NSAIDs), cardiac failure, and/or arrhythmia. On admission, the present patient did not have symptoms of dehydration, a history of the use of diuretics or NSAIDs, or cardiac failure or arrhythmia. Some risk factors have been identified as predictive of the occurrence of SRC, including an SSc duration of <4 years, diffuse and rapidly progressive skin thickening, new anemia, and new cardiac events (12, 13). Anti-RNA polymerase III antibody is another major risk factor of SRC. Important associations of anti-RNA polymerase III antibodies include an increased risk of renal crisis, systemic hypertension, synovitis, myositis, joint contractures, and malignancy within a 5-year timeframe before or after the onset of SSc. Although roughly 60% of patients with SRC have anti-topoisomerase antibodies, the presence of these antibodies is not specific to SRC (4). In contrast, SSc-specific anti RNA polymerase III antibodies are independently associated with SRC development (14, 15). Exposure to corticosteroids (CSs) before the onset of SRC is also reported as another major risk factor of inducing SRC (16). In the present case report, the patient had a 10-year history of Raynaud's phenomenon, limited skin lesions, and negative findings for anti-topoisomerase antibodies or anti RNA polymerase III antibodies. Furthermore, he had never received CS therapy before the onset of SRC. Therefore, he did not have a typical course of SRC.

In summary, SRC in patients with anticentromere antibody-positive limited cutaneous SSc is extremely rare. The precise pathophysiology remains uncertain. A kidney biopsy may be an important tool for obtaining information on the renal pathology and making a differential diagnosis, guiding the treatment. Although the most common treatment protocol includes ACE inhibitor administration, the renal prognosis may be poor. Further case reports are needed to improve our understanding of both the etiopathology and the clinical course of this condition.

The authors state that they have no Conflict of Interest (COI).

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