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ORIGINAL ARTICLE

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Pulmonary-renal syndrome in systemic sclerosis: a report of three cases and review of the literature

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Abstract We describe three cases of acute renal failure with diffuse alveolar hemorrhage, which is designated pulmonary-renal syndrome (PRS), in systemic sclerosis (SSc) and review the literature to better define this rare but severe complication of SSc. The clinical course of three SSc patients with acute renal failure and concomitant diffuse alveolar hemorrhage are reported, and the literature published between 1967 and 2005 is reviewed following a PubMed search. Including our cases, a total of 19 SSc patients with acute renal failure and concomitant diffuse alveolar hemorrhage have been reported. Pulmonary-renal syndrome developing in SSc patients can be categorized clinicopathologically into three entities: PRS with thrombotic microangiopathy, PRS with small vessel vasculitides accompanied with SSc, and D-penicillamine-induced Goodpasture-like syndrome. Patients with scleroderma PRS with thrombotic microangiopathy, to which group our all patients belong, often developed diffuse alveolar hemorrhage after receiving high-dose corticosteroid therapy. Pulmonary-renal syndrome is a fatal complication of SSc and results from different pathogenic processes. Prompt differential diagnosis between the subsets is critical, because therapeutic strategy may differ in the use of high-dose corticosteroid and plasma exchange between the subsets of PRS. Clinical courses of the patients with PRS with thrombotic microangiopathy suggest that high-dose corticosteroid therapy is a trigger of diffuse alveolar hemorrhage in patients with diffuse SSc with signs of thrombotic microangiopathy.

Key words Acute renal failure · Diffuse alveolar hemorrhage · Scleroderma · Scleroderma renal crisis · Thrombotic microangiopathy

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Introduction

Systemic sclerosis (SSc; scleroderma) is a chronic disorder of connective tissues characterized by inflammation, fibrosis, and degenerative changes in the blood vessels, skin, and visceral organs, notably the gastrointestinal tract, lung, heart, and kidney.[1] Scleroderma renal crisis (SRC), originally defined as accelerated hypertension and rapidly progressive renal failure, is well known as one of the life-threatening complications of SSc.[2–4] Early intervention with angiotensin-converting enzyme inhibitors (ACE-I) has dramatically improved the outcome in patients with this complication.[5] Helflich et al. reported that patients with SRC without elevated blood pressure, which occurred in about 10% of SRC patients in their series, sometimes presented with severe and acute lung disease, such as diffuse alveolar hemorrhage (DAH), and had a grave prognosis.[3] This combination, DAH and acute renal failure, has been called pulmonary-renal syndrome (PRS). In this report, we describe a series of SSc patients who presented with PRS in our hospital, review the previous literature, and discuss the clinical and pathological features of this rare but devastating complication of SSc.

Patients and methods

We reviewed the inpatient medical records of patients admitted to the Rheumatology Unit of the Nagoya City University Hospital from 1996 through 2005 to identify the SSc

patients who had acute renal failure and DAH in the same hospitalization period. We identified four SSc patients with acute renal failure and DAH in the same hospitalization period from 135 consecutive admissions of 68 patients with SSc. The clinical course of one of these (Case 4) was previously reported.[6] All patients met the classification criteria of the American Collage of Rheumatology criteria for SSc.[7] Medline/PubMed was searched using the keywords *systemic sclerosis*, *pulmonary hemorrhage*, *renal failure*, *renal crisis*, and *Goodpasture syndrome*, and the extracted articles and their citations were also reviewed to identify SSc patients who had concomitant acute renal failure and DAH.

Case reports

Case 1

A 63-year-old woman with a 7-year diagnosis of diffuse SSc with interstitial pneumonia and anti-Scl-70 positivity was admitted to this hospital because of progressive dyspnea, malaise, and dysphagia of 3 months' duration. She had had psoriatic arthritis from the age of 30 years. Three years before admission, high-dose corticosteroid therapy including pulse methylprednisolone (mPSL) was instituted for the treatment of interstitial pneumonia associated with SSc and was effective without severe adverse events except for steroid-induced diabetes. Seven months before admission, while she was on prednisolone (PSL) 12.5 mg/day, edematous skin change re-emerged and 100 mg/day of D-penicillamine (DPC) was started. Multiple digital ulcers and polyarthritis developed. Three months before admission, pericardial effusion and right pleural effusion emerged. On admission, she was taking 7.5 mg/day of PSL. Temperature was 36.8ºC, pulse 96 beats/min and regular, and blood pressure 116/64 mmHg. Indurative skin thickening with edematous changes in the face, extremities, and anterior chest, and digital ulcerations with flexion contractures in the fingers were observed. Pericardial friction rub and bibasilar fine crackles were heard. Laboratory data on admission were as follows: white blood cells (WBC) 6600/μl, hemoglobin 8.6 g/dl with increased count of schistocytes, platelet count 107×10^3/μl, fibrinogen 382 mg/dl, fibrin/fibrinogen degradation produces (FDP) 6.5 μg/ml, D-dimer 4.8 μg/ml, blood urea nitrogen 22.0 mg/dl, creatinine 0.9 mg/dl, lactate dehydrogenase (LDH) 463 U/l, normal transaminases, C-reactive protein (CRP) 1.19 mg/dl, haptoglobin <10 mg/dl, CH_{50} 31.5 U/ml, plasma renin activity 5.1 ng/ml per hour (normal range 0.3–2.9). The tests for antineutrophil cytoplasmic antibodies (ANCA), antiglomerular basement membrane (GBM) antibodies, direct/indirect Coombs tests, and anticardiolipins were all negative. The urine contained 2+ protein, granular, and leukocytic casts. Chest radiograph showed enlarged cardiac shadow, increased right pleural effusion, and worsening of interstitial shadow. Pericardiocentesis and drainage were performed because of the presence of cardiac tamponade, and revealed exudative effusion. Treatment with ACE-I and plasma exchange was started under the diagnosis of normotensive SRC with thrombotic microangiopathy (TMA); however, her renal function progressively deteriorated, and hemodialysis was required from day 22. For the treatment of refractory pericarditis and progressive interstitial pneumonia, she was treated with pulse mPSL (1 g daily for 3 days) from day 20 and thereafter with 40 mg/day of PSL. From the 37th hospital day, intractable recurrent pulmonary edema and diffuse edematous skin change developed, which required positive airway ventilation and a stringent negative fluid balance achieved by hemofiltration. On day 51, she was diagnosed clinically as having DAH from the findings as a concurrent emergence of diffuse consolidation in both lungs with bloody sputa, and deteriorating signs of TMA occurred from 4 days before. Methylprednisolone pulse therapy was reinstituted, but she died of respiratory failure on the same day.

Case 2

A 59-year-old woman with a 6-year diagnosis of diffuse cutaneous SSc was admitted because of rapidly progressive renal dysfunction, malaise, and dyspnea. Three years before admission she had received 40 mg/day of mPSL for the treatment of interstitial lung disease without adverse events. Five months before admission, edematous skin changes with itching re-emerged and 2 months before admission, she had started to receive 30 mg/day of PSL. On admission, she was taking 10 mg/day of PSL. Blood pressure 160/78 mmHg and afebrile state. Indurative skin changes extending to the anterior chest with edematous changes in the forearms and lower legs, and digital ulcers with flexion contractures of the fingers were observed. Slight systolic murmur and bibasilar fine crackles were heard. Laboratory data on admission were as follows: WBC 7700/μl, hemoglobin 9.1 g/dl with increased count of schistocytes, platelet count 118×10^3/μl, fibrinogen 429 mg/dl, D-dimer 1.6 μg/ml, blood urea nitrogen 29.0 mg/dl, creatinine 3.0 mg/dl, LDH 423 U/l, normal transaminases, CRP 2.06 mg/dl, haptoglobin <10 mg/dl, CH_{50} 35.6 U/ml, plasma renin activity 29.4 ng/ml per hour. The tests for ANCA, anti-GBM antibodies, direct/indirect Coombs tests, and anticardiolipin antibodies were all negative. The urinalysis showed 2+ of proteinuria and slight hematuria. Chest computed tomography (CT) scan showed worsening of interstitial pneumonia. Treatment with ACE-I, plasma exchange 2 times a week, and weekly 2 courses of pulse mPSL (1 g daily for 3 days) was started. Dyspnea and hypoxemia were temporally improved, though TMA and renal dysfunction deteriorated. On day 26, DAH, which was diagnosed from concurrent emergence of diffuse consolidation in lungs, bloody sputa, and anemia, emerged on the 9th day after cessation of plasma exchange and the 4th day after the last administration of the second course of pulse mPSL. Reinstitution of plasma exchange two times a week and single dose intravenous cyclophosphamide (500 mg/body) improved DAH and TMA, but renal function progressively deteriorated and hemodialysis was required 2 months after admission. Dosage of PSL was tapered. On day 68, DAH with deteriorating signs of TMA recurred on the 12th day after cessation of plasma exchange. Reinstitution of plasma

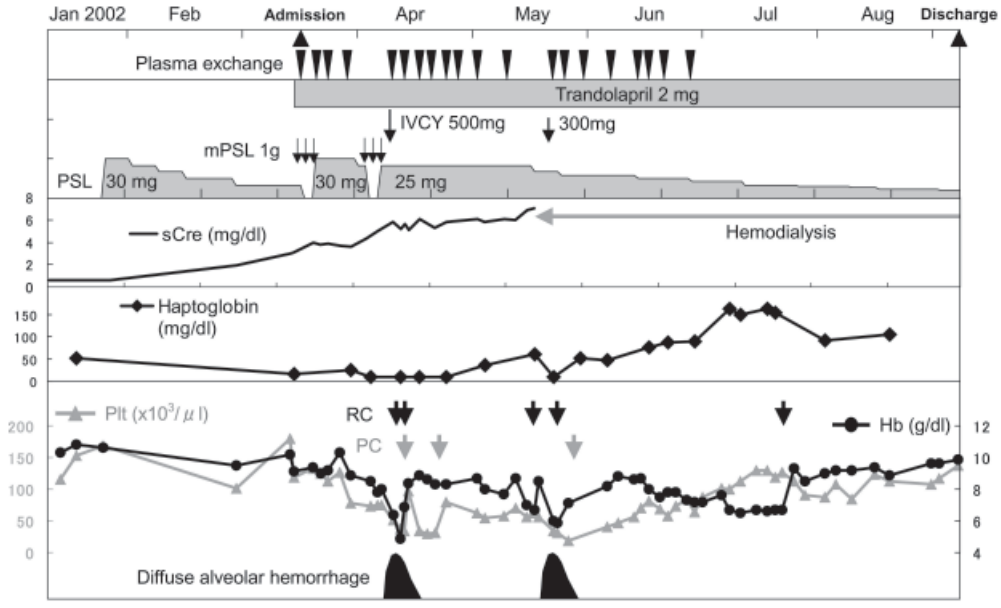

Fig. 1. Clinical course of Case 2. *Hb*, hemoglobin; *IVCY*, intravenous intermittent cyclophosphamide; *mPSL*, methylprednisolone; *PC*, concentrated platelet transfusion; *Plt*, platelet count; *PSL*, prednisolone; *RC*, concentrated red blood cell transfusion; *sCre*, serum creatinine

exchange two times a week and single-dose intravenous cyclophosphamide (300 mg/body) improved DAH and signs of TMA. Reducing corticosteroid, repeated plasma exchange, and intravenous cyclophosphamide stabilized TMA and she was deemed fit for discharge with peritoneal dialysis (Fig. 1).

Case 3

A 53-year-old woman with a 2-year history of diffuse type SSc was admitted to this hospital because of headache and renal dysfunction with severe hypertension. She had no visceral involvements at the initial visit and received 15 mg/day of PSL for the treatment of skin lesion and arthralgia without adverse events. Three months before admission, interstitial pneumonia emerged. Due to the lack of efficacy, PSL was tapered and discontinued, and 100 mg/day of DPC was started 1 month before admission. She discontinued taking DPC after 2 weeks because of general fatigue, and appetite loss occurred after taking DPC. These symptoms worsened even after discontinuation of DPC, and she was emergently admitted to this hospital. On admission, blood pressure was 224/113 mmHg, pulse 130 beats/min and regular. Generalized tonic seizures were intermittently seen. Retinal vasculature showed severe hypertensive changes. Indurative skin changes extending to the anterior chest with edematous changes in the forearms and lower legs were observed. Pericardial friction rub was heard. Laboratory data on admission were as follows: WBC 16 200/μl, hemoglobin 10.5 g/dl, platelet count 120 × 10^3/μl, fibrinogen 429 mg/dl, FDP 19 μg/ml, blood urea nitrogen 110 mg/dl, creatinine 5.3 mg/dl, LDH 1026 U/l, normal transaminases, CRP 2.06 mg/dl, haptoglobin <10 mg/dl, CH_{50} 35.6 U/ml, plasma renin activity 7.8 ng/ml per hour. Discontinuation of DPC and treatment with ACE-I, hemodialysis, and plasma exchange was promptly started. Treatment with ACE-I had to be discontinued because of drug fever due to several kinds of ACE-I. Treatment with PSL 40 mg/day was started on day 50. On day 60, she developed acute respiratory failure with diffuse pulmonary consolidation. Thrombocytopenia and microangiopathic hemolytic anemia deteriorated. Serum β-D-glucan level and cytomegalovirus antigenemia assay were negative. The tests for ANCA and anti-GBM were negative. The analysis of bronchoalveolar lavage fluid showed she had DAH. She was treated with mPSL pulse therapy and plasma infusion with a minor response. Diffuse lung disease recurred and additional courses of high-dose mPSL were administered. Thereafter pulmonary aspergillosis emerged. She died of multiple organ failure on day 100. Autopsy showed DAH and the histological pattern of organizing diffuse alveolar damage in the lung fields spared from the infection foci in the lungs and renal endoarteropathy, and fibrinoid necrosis without signs of glomerulonephritis in the kidneys. No pathological evidence of vasculitis was observed.

Literature review

Except for our four cases, we identified 15 previously reported cases of PRS associated with SSc in nine articles in the English and Japanese literature to date[3,8–15] (Table 1). By description, all cases met the American College of Rheumatology criteria for SSc. All patients whose demographic data were available from the literature ranged from 33 to 68 years of age (mean 49, median 47 years); 6 were women and 3 were men. In every case, the diagnosis of SSc preceded the diagnosis of PRS or DAH with renal dysfunction.

Among 15 SSc cases with PRS from the literature, 7 patients from two articles exhibited the signs of TMA.[3,8] Helflich et al. reported 6 cases with normotensive SRC complicating DAH. Increased count of schistocytes and

Table 1. Clinicopathological characteristics of the scleroderma patients with pulmonary-renal syndrome

No.	Age/ Sex	SSc type	Disease duration (years)	Antecedent D-PC	PLT < 100000	Schistocytes	ANCA	Histopathology		Prognosis	Follow-up period (months)	First author[Ref.]	Year
								Lung	Kidney				
1–6	NA	NA	NA	NA	6/6 Yes	5/5 Yes	NA	NA	NA	Died	<12	Helfrich[3]	1989
7	33F	D	<1	No	Yes	Yes	(–)	DAH	TMA	Died	2	Nanke[8]	2000
8	56F	L	22	No	No	No	NA	DAH	Pauci-immune crescentic GN	Died	0.6	Kumagai[10]	1983
9	47F	D	6	Yes	No	No	(+)	DAH, capillaritis	Pauci-immune crescentic GN	Died	<12	Endo[9]	1994
10	66F	D	5	No	No	No	(+)	NA	NA	Died	<12	Endo[9]	1994
11	44M	L	8	For 1 year	No	No	(–)	DAH, capillaritis,	Renal endoarteropathy	Died	1	Bar[11]	2001
12	56F	NA	2.75	1.5 g/day for 27 months	No	No	NA	NA	Crescentic GN, granular fibrin, C3 deposits	Survived	25	Devogelaer[12]	1987
13	68M	D	8	1 g/day for 30 months	No	No	NA	DAH	Focal segmental GN, granular fibrinogen deposits	Died	<1	Derk[13]	2003
14	38M	L	10	No	No	No	NA	NA	Crescentic GN, granular IgM, C3 deposits	Died	18	Hara[14]	1992
15	34F	L	0.5	0.5 g/day for 6 months	Yes	No	(–)	NA	NA	Died	<1	Phillips[15]	1998
16	63/F	D	8	0.1 g/day for 7 months	Yes	Yes	(–)	NA	NA	Died	3	Our Case 1	
17	59/F	D	7	No	Yes	Yes	(–)	NA	NA	Survived	24	Our Case 2	
18	53/F	D	2	0.1 g/day for 2 weeks	Yes	Yes	(–)	DAH, Organizing DAD, infectious pneumonia[a]	Renal endoarteropathy	Died	4	Our Case 3	
19	68F	D	0.6	No	Yes	Yes	(–)	DAH, Exudative DAD, fibrotic NSIP	TMA	Died	0.7	Our Case 4	2005

ANCA, antineutrophil cytoplasmic antibodies; D, diffuse cutaneous; DAD, diffuse alveolar damage; DAH, diffuse alveolar hemorrhage; D-PC, D-penicillamine; L, limited cutaneous; GN, glomerulonephritis NA, not available; PLT, platelet count; SSc, systemic sclerosis

[a] Aspergillus and cytomegalovirus pneumonia

thrombocytopenia (<100 000/μl) were observed in all patients whose data were available (5/5 and 6/6, respectively), and the results of ANCA and anti-GBM were not described. Five had a history of previous corticosteroid use. All six died within 1 year.[3] Nanke et al. reported another patient with PRS associated with SSc and microangiopathic changes.[8] She had early diffuse SSc with overlapping features of systemic lupus erythematosus and rheumatoid arthritis. She developed PRS with microangiopathic hemolytic anemia and thrombocytopenia (PLT 64×10^3/μl) after high-dose corticosteroid therapy including pulse mPSL (1 g/day for 3 days) and PSL 60–100 mg/day for 3 weeks, and died of massive pulmonary hemorrhage. Pathological evidence of TMA was observed in the kidney, spleen, and bone marrow. Brand pulmonary hemorrhage was noted, although a description of the presence of pulmonary capillaritis or diffuse alveolar damage was absent. Crescentic glomerulonephritis was not observed.[8]

In the eight patients from the remainder (7 articles), four patients had ANCA or pathological evidence of vasculitis. Two of them had diffuse SSc and MPO-ANCA. One of the MPO-ANCA positive patients had pulmonary capillaritis and pauci-immune glomerulonephritis.[9] In two patients with pathological evidences of small vessel vasculitis, one reported in pre-ANCA era had brand pulmonary hemorrhage and pauci-immune glomerulonephritis without granular deposits;[10] the other with negative results of ANCA had pulmonary capillaritis and renal endoarteropathy without glomerulonephritis.[11] In a patient with MPO-ANCA and two with pathological evidences of vasculitis, corticosteroid was administered for the treatment of PRS. None of these was treated by plasmapheresis or immunosuppressants. All four patients died within 1 year of administration.[9–11]

In the four patients other than those described above, two SSc patients with PRS have been reported as having Goodpasture-like syndrome elicited by high-dose DPC.[12,13] Each of them was treated with 1.5 g/day of DPC for 27 months[12] and 1.0 g/day for 30 months[13] before the onset of PRS. All of them lacked signs of TMA, positive results of ANCA. They also lacked anti-GBM antibodies, as did other patients with DPC-related Goodpasture-like syndrome having background diseases other than SSc. Histopathological examination of renal biopsy from these patients showed focal segmental glomerulonephritis with glomerular granular fibrinogen or fibrinogen and C3 deposits,[12,13] in contrast to typical findings of Goodpasture syndrome, which show linear deposition of immunoglobulin along the GBM.[16] One patient responded to the treatment with discontinuation of DPC, high-dose corticosteroid including pulse mPSL, and azathiopurine, and survived with mild renal dysfunction.[12]

Discussion

Pulmonary-renal syndrome is caused by a variety of conditions, including small vessel vasculitides, Goodpasture syndrome, systemic lupus erythematosus, antiphospholipid syndrome, environmental factors, and drugs.[17] Diffuse alveolar hemorrhage has been reported in the course of SRC, and Bar et al. proposed the term "scleroderma PRS" for this uncommon and fatal complication of SSc.[11]

However, the pathogenesis and inciting factors of PRS in SSc remain largely unknown; different pathologies are supposed to be included in the pathogenesis of PRS in SSc from the clinicopathological findings of the reviewed cases. The aim of this study is to describe the characteristics of PRS in SSc, to classify them from the clinicopathological features, and to provide important suggestions in the management of this devastating complication of SSc.

Distinct clinicopathological findings of reviewed cases and ours, such as the presence of schistocytes, MPO-ANCA, or pathological evidences of vasculitis, and prior history of high-dose DPC with glomerulonephritis and fine granular deposits, suggest PRS in SSc patients can be broadly categorized into three subsets: scleroderma PRS with TMA, scleroderma PRS with small vessel vasculitis, and Goodpasture-like syndrome induced by high-dose DPC therapy in scleroderma patients (Tables 1 and 2). Due to limited information, two cases could not be classified into these three subsets.[14,15]

The cases of scleroderma PRS with vasculitis can be further sub-categorized into the following two subsets: microscopic polyangiitis superimposed on SSc and small vessel vasculitis including pulmonary capillaritis with SRC (Table 2). Wutzl et al. reported a case of diffuse cutaneous SSc with microscopic polyangiitis, which presented DAH and crescentic glomerulonephritis with mild renal dysfunction.[18] Pulmonary-renal syndrome with MPO-ANCA in SSc should be classified as MPO-ANCA-related vasculitis or microscopic polyangiitis superimposed on SSc.

All of our patients presented an increased count of peripheral blood schistocytes, and can be categorized into scleroderma PRS with TMA. Although two of our patients had prior history of low-dose DPC therapy, the histopathological findings of the autopsied patient who developed hypertensive renal crisis shortly after starting DPC therapy were different from those of Goodpasture-like syndrome induced by high-dose DPC therapy.[13] Moreover, the dosage of DPC and duration of DPC therapy of the 14 reported Goodpasture-like syndrome cases related to DPC use irrespective of background diseases ranged 0.5 to 3.5 g/day (median, 1 g/day) and 7 to 84 months (median 31 months).[13] Thus, clinicopathological features of our two patients with preceding DPC use were different from those with DPC-related Goodpasture-like syndrome.

Scleroderma patients with PRS have a grave prognosis irrespective of subset of PRS.[3,6,8–15] Although the small number of cases precludes well-founded conclusions regarding management, therapeutic strategies for this devastating complication of SSc should be determined by consideration of the subsets of PRS. The important clues for the differential diagnosis and characteristic pathological findings of these three subsets of PRS associated with scleroderma are shown in Table 2. Edematous skin changes (4/4), overt pericardial effusion (4/4), malaise (4/4), and myopathy (3/4) were

Table 2. Clinicopathological findings in the subsets of pulmonary-renal syndrome in scleroderma

Subsets of PRS in SSc	Characteristic clinical features and laboratory findings		Major histopathologic findings	
			Lung	Kidney
PRS with TMA	Early diffuse SSc or re-emerging scleroderma Overt pericardial effusion Signs of TMA present: Increased schistocytes Low haptoglobin level Thrombocytopenia ($<100\,000/mm^3$) ANCA and anti-GBM usually negative High-dose corticosteroid use may be a trigger of acute renal failure and/or DAH		Diffuse alveolar damage without capillaritis	Microthrombi formations in glomerular vasculatures (Normotensive subset) Renal en doarteropathy (Hypertensive subset)
PRS with SVV	Signs of TMA absent	MPO-ANCA negative	Capillaritis	Renal endoarteropathy
		MPO-ANCA positive	Capillaritis	Pauci-immune CGN
D-PC-related Goodpasture-like syndrome	History of high dose D-PC therapy (≥ 0.5 g/day) Signs of TMA absent ANCA and anti-GBM usually negative		Bland hemorrhage with granular staining of GBM Capillaritis usually absent	CGN with no linear or granular staining of GBM

ANCA, antineutrophil cytoplasmic antibodies; CGN, crescentic glomerulonephritis; D-PC, D-penicillamine; GBM, glomerular basement membrane; Ig, immunoglobulin; MPO, myeloperoxidase; NA, not available; PRS, pulmonary-renal syndrome; SSc, systemic sclerosis; SVV, small vessel vasculitis; TMA, thrombotic microangiopathy

seen just before the onset of PRS with TMA in our patients. Decreased haptoglobin and thrombocytopenia preceded emergence of increased count of schistocytes in our cases of scleroderma. Pulmonary-renal syndrome with TMA,[6] haptoglobin and platelet count should be closely monitored in the suspected cases of scleroderma with TMA.

Therapeutic strategies may contain common and specific approaches on the basis of the subsets of PRS. In general, if the patient is taking DPC, it should be immediately withdrawn and accelerated hypertension or hypertensive SRC should be treated with ACE-I. ACE-I is also recommended for the management of normotensive SRC even if in a smaller dosage.[19] Two normotensive patients of ours were treated with low-dose ACE-I; treatment with hypertonic albumin solutions and catecholamine infusion was needed in one of them to maintain blood pressure. They showed severe edema and serosal effusion, which might have been caused by capillary leakage due to severe systemic microangiopathy. Although ACE-I may be life saving during acute normotensive SRC, efficacy of ACE-I has not been confirmed in our normotensive patients.

Other disease-modifying treatment options include plasma exchange, corticosteroids, and immunosuppressants. Plasma exchange is the most important component of treatment and may be indicated for all patients with suspected TMA,[20] and may be an effective measure for the treatment of scleroderma PRS with TMA. In a total of nine reported cases with thrombotic thrombocytopenic purpura (TTP) associated with SSc, all patients had been treated with the regimen including plasma exchange, and three of them were improved.[21]

The recent finding that deficiency of the von Willebrand factor cleaving protease, which is also known as ADAMTS13 (a disintegrin and metalloprotease domain, with thrombospondin type 1 motif 13), is involved in the pathogenesis of idiopathic TTP provided new insight into management of TMA.[22,23] Severe ADAMTS13 deficiency is associated with idiopathic TTP, good response to plasmapheresis, and low mortality. On the other hand, TMA with detectable ADAMTS13 activity was associated with poor response to plasmapheresis and a very high mortality.[24,25] Manadan et al. reported a case of TTP and limited SSc that exhibited undetectable ADAMTS-13 activity and a good response to plasmapheresis.[21] In contrast, two normotensive diffuse SSc patients of ours, Cases 1 and 4 (a previously reported case) whose ADAMTS-13 activity at the onset of PRS was decreased but at a detectable level (32% and 19%, respectively), showed poor response to plasmapheresis. Although it is sometimes very difficult to differentiate clinically between TTP with SSc and normotensive SRC, measurement of ADAMTS-13 activity might be a helpful measure to differentiate these two subsets of TMA associated with SSc, and eventually could become a good index to help in deciding whether plasmapheresis is indicated. Limited availability of accurate assays for ADAMTS-13 activity and little information about ADAMTS-13 activity in the TMA associated with SSc at present leads us to believe that plasma exchange should be initiated promptly in the treatment of scleroderma PRS with TMA.

High-dose corticosteroids have often been successfully used for the treatment of PRS associated with other autoimmune diseases, such as systemic vasculitis, systemic lupus erythematosus, and Goodpasture syndrome.[17] Because efficacy of early intervention with high-dose corticosteroid has been reported in some scleroderma patients who devel-

oped DAH or glomerulonephritis associated with the signs of small vessel vasculitis and DPC-induced glomerulonephritis,[12,26–28] high-dose corticosteroid may be effective for the treatment of scleroderma PRS with vasculitis, especially in MPO-ANCA positive cases, or Goodpasture-like syndrome. On the other hand, high-dose corticosteroid use (PSL ≥ 30 mg/day) has been suspected to be a risk factor or a trigger of SRC,[4] especially normotensive SRC, which often accompanies signs of TMA and DAH, in patients with early diffuse type SSc.[3] All of our patients and a patient reported by Nanke et al. were diffuse type SSc in the early stage or with progressive diffuse skin thickening, and developed DAH with deteriorating signs of TMA shortly after receiving high-dose corticosteroid therapy, such as mPSL pulse therapy (4 days to 4 weeks).[8] In contrast, from the review of nine SSc patients with TTP, high-dose corticosteroid has been successfully used with 3 of 4 patients with concomitant plasmapheresis without fatal adverse effects.[21] Those patients were all in the limited cutaneous SSc category. Although exact mechanisms remain unknown, more extensive and severe microvascular injury in diffuse SSc with high disease activity compared with limited SSc might account for the different response to high-dose corticosteroid. Clinical courses of scleroderma PRS with TMA suggest that high-dose corticosteroid use is a precipitating factor for developing DAH in diffuse SSc patients with signs of TMA. Therefore, we believe that high-dose corticosteroids should not be used in diffuse SSc patients with recent-onset SRC or prodromal signs of PRS with TMA, such as progressive (edematous) skin thickening, overt pericardial effusion, malaise, or myopathy. Preventive effects of antiplatelets, anticoagulants, or protease inhibitors for the treatment of disseminated intravascular coagulation against worsening of TMA after high-dose corticosteroid use were not confirmed in our patients.

Cyclophosphamide has been successfully used for the treatment of systemic vasculitis. There are suggestions that cyclophosphamide may be beneficial for the treatment of interstitial lung disease associated with SSc.[29] Although the efficacy of this drug for the treatment of PRS in SSc is uncertain, cyclophosphamide can be an option to treat PRS with vasculitis and to obtain immunosuppressive effects, in place of high-dose corticosteroids in PRS with TMA. Other treatment strategies supported by the evidence about the pathogenesis of PRS with TMA should be explored.

In conclusion, this report may help us to better understand one of the most devastating complications of SSc and may provide some suggestions about the management of PRS in SSc patients, especially the TMA-related subset. The use of high-dose corticosteroids in diffuse SSc patients at higher risk of PRS with TMA should be strongly discouraged. Further studies are needed to elucidate the pathogenesis of this disorder and to explore the effective therapeutic measures.

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