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【 CASE REPORT 】

Successful Treatment of Systemic Sclerosis-related Pericarditis with Mycophenolate Mofetil and Low-dose Prednisolone

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Abstract:
We herein report a case of systemic sclerosis (SSc)-related pericarditis successfully treated with mycophenolate mofetil (MMF) and low-dose prednisolone (PSL). The patient was a 72-year-old woman with anti-centromere antibody. Her clinical manifestations were Raynaud phenomenon, bilateral pleural effusion, pericardial effusion and skin tightness. Based on the findings of exudative pericardial effusion with the absence of pulmonary arterial hypertension from the results of the cardiac catheter and pericardiocentesis, she was diagnosed with SSc-related pericarditis and treated with PSL10 mg and MMF 1 g per day, leading to the complete resolution of pericarditis. These findings suggested that MMF and low-dose PSL were effective for SSc-related pericarditis.

Key words: systemic sclerosis, pericarditis, mycophenolate mofetil

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Introduction

Systemic sclerosis (SSc) is an intractable autoimmune disease characterized by vasculopathy, fibrosis and immune dysregulation (1). Pericardial involvement is seen in 33-72% of patients with SSc, but clinically symptomatic pericardial effusion is present in only 5-16% of patients with SSc (2-5). Although pericarditis is a clinical manifestation of SSc that induces pericardial effusion, data on the treatment of symptomatic pericarditis in patients with SSc are limited due to the low incidence (6, 7).

We herein report a case of SSc-related pericarditis and scleroderma successfully treated with mycophenolate mofetil (MMF) and low-dose prednisolone (PSL).

Case Report

A 72-year-old-woman was referred to the Department of Dermatology in our hospital due to a right plantar ulcer and Raynaud phenomenon. She was treated with topical medication, and her right plantar ulcer improved. Scleroderma was not clearly noted on a medical examination in the Department of Dermatology, but anti-centromere antibody turned out to be positive one month before the referral to our department. Although her heart size on chest radiography was a bit larger than that taken six months earlier (Fig. 1a, b), she had no marked symptoms.

At the first visit to our department, the findings were as follows: body temperature, 37.2°C; blood pressure, 131/88 mmHg; heart rate, 99 beats/min; and SpO_2, 99% (room air). A physical examination showed bilateral coarse crackles on inspiration and scleroderma in the abdomen and both lower legs with a Modified Rodnan Skin Score (mRSS) of 20/51, indicating that scleroderma was rapidly proceeding. No lower extremity edema was noted. Laboratory investigations showed mildly elevated levels of C-related protein (CRP) and B-type natriuretic peptide (BNP). Other auto-antibodies, including anti-Scl-70 and anti-ribonucleic acid (RNA) polymerase III, were all negative (Table 1). Chest radiography and computerized tomography revealed bilateral pleural effusion and pericardial effusion (Fig. 1c, 2). Thoracentesis re-

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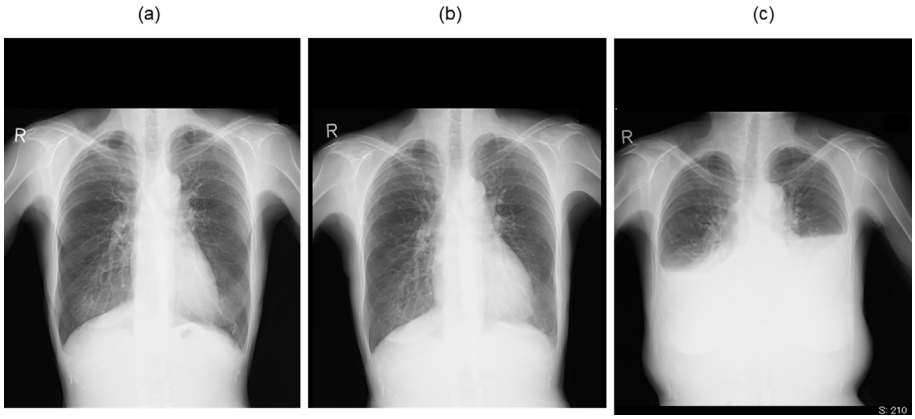

Figure 1. **Chest radiography. Pictures were taken seven months (a) and one month (b) before referral to our department. Picture (c) was obtained at the first visit to our department.**

Table 1. **Laboratory Data.**

<Complete blood count>		<Chemistry>		<Immunology>	
WBC	6,720 /μL	TP	6.1 g/dL	CRP	0.50 mg/dL
Neut	76.8 %	Alb	3.3 g/dL	ANA	>160×
Lym	13.0 %	T.Bil	0.8 mg/dL	Pattern	Centromere
Mono	5.7 %	AST	29 U/L	C3	102 mg/dL
Eos	2.1 %	ALT	41 U/L	C4	20 mg/dL
RBC	413×10^4 /μL	LDH	177 U/L	CH50	>60.0 U/mL
Hb	12.7 g/dL	ALP	204 U/L	IgG	1,284 mg/dL
Ht	38.8 %	γ-GTP	51 U/L	IgA	126 mg/dL
Plt	38.0×10^4 /μL	CPK	81 U/L	IgM	61 mg/dL
		UA	4.6 mg/dL	Scl-70	2.6 U/mL
<Coagulation>		BUN	9 mg/dL	Centromere	>500
PT-INR	1.14 INR	Cr	0.61 mg/dL	RNA polymerase III	<5
APTT	28.8 s	Na	139 mEq/L	ds-DNA	<10 IU/mL
D-dimer	2.1 μg/mL	K	3.9 mEq/L	Sm	1.5 U/mL
		Cl	105 mEq/L	SS-A	<1.0 U/mL
<Urine>		Ca	9.1 mg/dL	PR3-ANCA	<0.5 IU/mL
Sugar	(-)	IP	3.2 mg/dL	MPO-ANCA	<0.5 IU/mL
Protein	(-)	AMY	53 U/L	CCP	<0.5 U/mL
OB	(±)	P-AMY	36 U/L	RF	6 U/mL
WBC	(-)	BNP	42.9 pg/mL	ARS	<5.0
		TnI	<10.0 pg/mL		

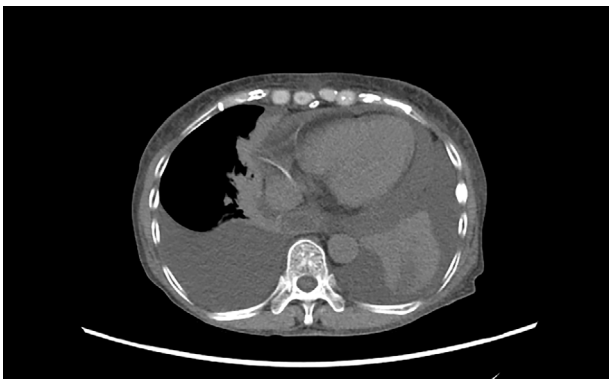

Figure 2. **Computed tomography. Chest CT showed bilateral pleural effusion and pericardial effusion.**

vealed transudative pleural effusion according to Light's criteria (Table 2). An electrocardiogram was normal, but echocardiography showed all-around pericardial fluid compressing the left ventricle (Fig. 3), and the ejection fraction was 66%. In addition, the maximum tricuspid regurgitation pressure gradient (max TRPG) was 21 mmHg. A cardiac catheter test revealed an elevated right atrium pressure (18 mmHg) and a loss of the normal "y" descent of the jugular venous pressure waveform, indicating that cardiac tamponade was induced by pericardial effusion. Before pericardiocentesis, the mean pulmonary artery pressure (mPAP) had been 26 mmHg, but it was reduced to 24 mmHg after the drainage of the pericardial effusion, suggesting that it did not meet the criteria of pulmonary arterial hypertension (PAH) (8). The pericardial effusion was exudative, and neither malignant nor infectious findings were shown on peri-

cardial effusion (Table 2). Taken together, pericarditis induced cardiac tamponade, contributing to the occurrence of right heart failure, followed by the development of bilateral pleural effusion.

These clinical, serological and biochemical findings helped us diagnose diffuse cutaneous SSc and SSc-related pericarditis. Despite the paucity of evidence regarding the treatment of SSc-related pericarditis, we selected oral PSL (10 mg per day) and MMF (1 g per day) as therapeutic drugs because of previous reports describing the efficacy of PSL for pericarditis and of MMF for scleroderma (6, 9). Since MMF for SSc is an off-label use, we explained the need to use MMF to treat the disease to this patient and members of her family, subsequently getting their approval. The risk factors associated with scleroderma renal crisis have been reported to include PSL (≥15 mg per day), rapid progression of skin disease and SSc at an early stage (10, 11), so we started treatment with 10 mg per day of PSL. The pericardial and pleural effusion rapidly disappeared, and the scleroderma likewise showed improvement. PSL was successfully tapered and ceased two months after being started as a therapeutic drug. At the time of writing (four months after initiating treatment), her symptoms have not recurred, and scleroderma has only been noted on the dorsum of both feet and lower legs (mRSS 10/51). Chest radiography and echocardiography showed the complete disappearance of pleural effusion and cardiac enlargement (Fig. 4).

Table 2. Data from Pleural and Pericardial Effusion.

[Pleural effusion]		[Pericardial effusion]	
<Chemistry>		<Chemistry>	
pH	7.692	TP	4.4 g/dL
TP	2.1 g/dL	Alb	2.8 g/dL
Glu	122 mg/dL	Glu	110 mg/dL
LDH	65 U/L	LDH	125 U/L
Alb	1.3 g/dL	Cell	237 /μL
		Neut	1.0 %
<Culture>	<Cytology>	Lym	94.0 %
Negative	No malignancy	Mo	5.0 %
		<Culture>	<Cytology>
		Negative	No malignancy

Discussion

Pericardial involvement is usually clinically silent and benign in SSc (6). In many cases, the presence of slight pericardial effusion does not induce clinical symptoms or possess any prognostic significance (12). Clinically symptomatic pericardial effusion is a rare cause of hospital admissions in SSc, and 74% of admitted patients with clinically symptomatic pericardial effusion suffered from PAH (13); however, the mPAP in this case did not meet the criteria of PAH. Given the lack of malignant and infectious findings in the exudative pericardial fluid or on the cardiac catheter, we considered the pericardial effusion to have been induced by SSc-related pericarditis.

Pericardial effusion usually occurs after the manifestations of other clinical features of SSc (6). However, large amounts of pericardial effusion, including those with development of tamponade, have been described prior to skin thickening and the establishment of the SSc diagnosis (14, 15). In the present case, the patient's heart was slightly larger on chest radiography at the most recent evaluation than it had been six months earlier, despite a lack of scleroderma, suggesting that pericarditis may have occurred prior to the establishment of scleroderma in this patient. We should consider pericardial effusion of unknown origin as a sign supporting a diagnosis of SSc.

No randomized clinical trial has provided evidence supporting the treatment of cardiac involvement in patients with SSc, so evidence concerning the treatment of SSc-related pericarditis is scarce. Given reports of cases with SSc in which steroids and immunosuppressive drugs were not effective for SSc-related pericarditis (16-18) and in which steroids may have caused progression to constrictive peri-

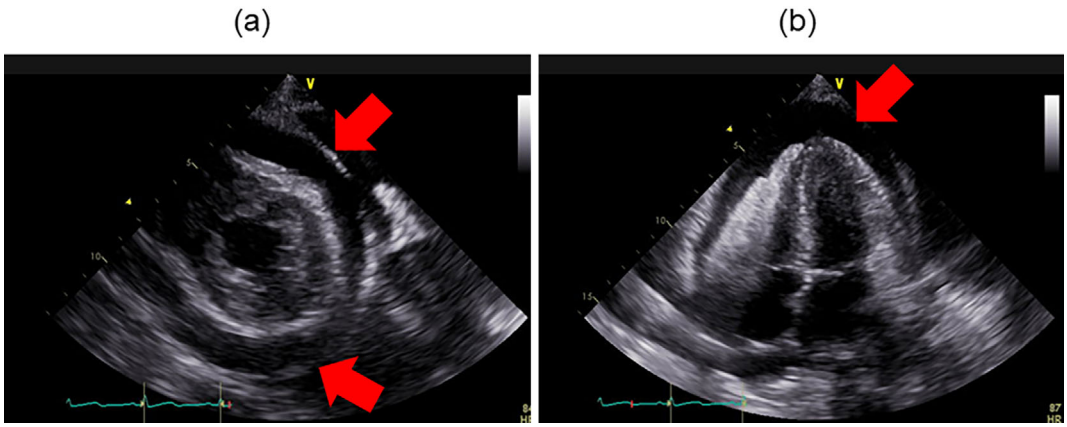

Figure 3. Echocardiography. Echocardiography revealed all-around pericardial effusion (a) and compression of the left ventricle (b). Red arrows show pericardial effusion.

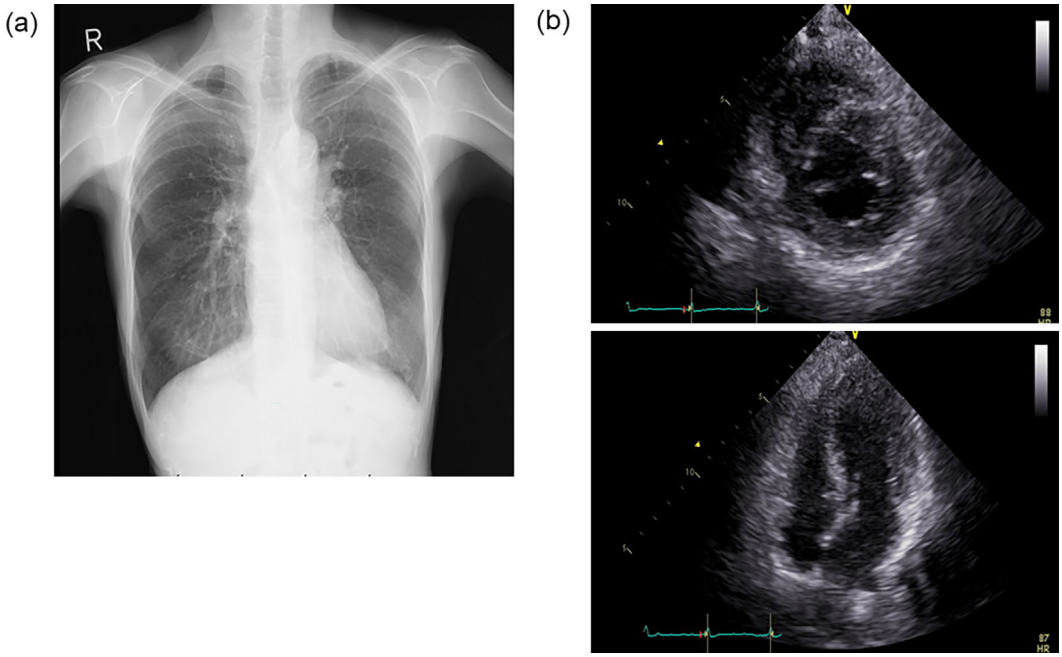

Figure 4. **Chest radiography and echocardiography. Chest radiography (a) and echocardiography (b) showed the complete resolution of pleural and pericardial effusion after treatment.**

Table 3. **Characteristics of Patients with SSc-related Pericarditis.**

sex	Age at SSc diagnosis (years)	Age at pericarditis diagnosis (years)	Time from SSc diagnosis to pericarditis diagnosis (years)	Type of SSc	auto-antibody	treatment	outcome	reference
F	42	42	Not described	Diffuse	Scl-70	CS+CYC	Recovery	[18]
F	37	37	Not described	Diffuse	Scl-70	CS	Recovery	[18]
F	61	61	Not described	Limited	Centromere	CS+RTX+TAC	Recovery	[18]
F	75	75	Not described	Diffuse	Scl-70	CS	Recovery	[19]
F	33	33	Not described	Diffuse	ND	CS	Recovery	[21]
F	Not described	33	1 year	Limited	ND	Drainage	Recovery	[31]
F	Not described	57	16 years	Limited	ND	Drainage	Recovery	[32]
F	Not described	54	2 years	Limited	ANA	Drainage	Recovery	[33]
F	56	74	18 years	Not described	Centromere	Drainage	Recovery	[34]
F	72	72	Pericarditis potentially prior to SSc diagnosis	Diffuse	Centromere	CS+MMF	Recovery	This case
M	40	40	Pericarditis prior to SSc diagnosis	Not described	Scl-70	CS+IVIg	Death	[14]
F	Not described	64	7 years	Limited	ND	CS	Death	[17]
F	Not described	38	2 years 4 months	Diffuse	Scl-70	Diuretics	Death	[17]
F	Not described	70	2 years 9 months	Diffuse	RNA poly I/III	Diuretics	Death	[17]
F	Not described	71	13 years	Diffuse	Scl-70	Diuretics	Death	[17]
M	Not described	41	3 years	Diffuse	Scl-70	Diuretics	Death	[17]

carditis (14), using steroids in patients with SSc-related pericarditis is a matter that demands careful consideration. However, it was reported that steroids were effective for SSc-related pericarditis in some cases (13, 18-21), and there was a case in which the infiltration of perivascular inflammatory cells was found (20). In addition, inflammatory cells, including lymphocytes, infiltrate the affected organs of patients with early SSc (22, 23). Furthermore, symptomatic pericarditis was recommended to be treated by low-dose PSL and colchicine as a first-line treatment option, with MMF as a second-line treatment option (24). Notably, colchicine is effective for treating recurrent pericarditis and has been reported to reduce the rate of incessant or recurrent pericarditis (25, 26), suggesting that colchicine may be a viable additional option in cases when pericarditis flares up in the future.

Scleroderma was not detected one month before the referral in this patient but was clearly shown at the first visit to

our department, suggesting that we diagnosed SSc at an early stage in this case. Indeed, almost all of the cells infiltrating the pericardial fluids were lymphocytes in this patient (Table 2), suggesting that anti-inflammation and immunosuppressive therapies would be effective in this case. MMF was also reported to be effective on scleroderma of SSc in previous reports (7, 27). Given these findings, we decided to treat this case with MMF and low-dose PSL.

MMF reversibly inhibits inosine-5'-monophosphate dehydrogenase (IMPDH), the metabolic enzyme that catalyzes the critical step in guanine nucleotide biosynthesis used in the proliferation of T and B lymphocytes (28, 29). In addition, the type II isoform of IMPDH, which predominates in proliferating T and B lymphocytes, is about four times more sensitive to inhibition by mycophenolic acid (MPA), the prodrug of MMF, than is the type I isoform, which is generally expressed constitutively at low levels (30). MMF has been generally accepted as a standard therapeutic drug for SSc (24).

Intriguingly, MMF and low-dose PSL were effective for treating pericarditis as well as scleroderma in this case. The characteristics of patients with SSc-related pericarditis are shown in Table 3 (14, 17-19, 21, 31-34). Patients have been treated in a variety of ways, including using steroids and immunosuppressive drugs or with pericardial drainage, but the accumulation of more cases with SSc-pericarditis will be required to determine an appropriate treatment. As reflected in Table 3, to our knowledge, there has never been a report of MMF and low-dose PSL being effective for SSc-related pericarditis.

In the present case, pericarditis was completely resolved by treatment, followed by the disappearance of pleural effusion in addition to the improvement of scleroderma. PSL was tapered smoothly, and the resolution of pericarditis was maintained even after finishing PSL, implying the possibility that MMF was effective. MMF and low-dose PSL may be viable options for treating SSc-related pericarditis.

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

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