Pulmonary Hypertension in Systemic Lupus Erythematosus: Evaluation of Clinical Characteristics and Response to Immunosuppressive Treatment

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ABSTRACT. ***Objective***. To clarify the clinical features of systemic lupus erythematosus (SLE) complicated with pulmonary hypertension (PH) and to evaluate the efficacy of immunosuppressive treatment.

Methods. Case records were reviewed for 194 patients with SLE who were admitted to Aoyama Hospital of Tokyo Women's Medical University between 1992 and 1999. There were 12 patients with PH [8 SLE and 4 SLE + systemic sclerosis (SSc) overlap syndrome]. These patients were compared with 59 age and sex matched patients with SLE for clinical characteristics and laboratory findings. The efficacy of treatments for PH was also evaluated.

Results. In our cohort of 194 patients with SLE, 6.2% had PH. The plasma thrombin-antithrombin III complex and plasma D-dimer levels were significantly higher in patients with PH compared with those without PH. Eight patients with PH (4 SLE and 4 SLE + SSc) were treated with corticosteroids (CS) ± cyclophosphamide (CYC). Right ventricular systolic pressure (RVSP) was improved in 7 of 8 patients. In 6 of 7 responders to the therapy, the treatment was started as soon as they were diagnosed with PH. PH relapsed in 2 patients treated with oral CS ± CS pulse therapy, but their RVSP was decreased again by immunosuppressive treatment.

Conclusion. CS ± CYC was effective for PH associated with SLE. Immunosuppressive treatment should be performed during the early stage of PH to improve prognosis. (J Rheumatol 2002; 29:282–7)

Key Indexing Terms:
PULMONARY HYPERTENSION SYSTEMIC LUPUS ERYTHEMATOSUS
CORTICOSTEROIDS CYCLOPHOSPHAMIDE IMMUNOSUPPRESSIVE TREATMENT

Pulmonary hypertension (PH) has a profound influence on the prognosis of patients with connective tissue diseases[1-10]. In systemic lupus erythematosus (SLE), the prognosis of patients with PH has been reported to be very poor and the mean durations of survival from the onset of PH were within 2 years[1-3,5,6,10-13]. In some patients, PH is caused by thrombosis/embolism of large branches of the pulmonary arteries, valvular heart diseases, or severe pulmonary fibrosis (PF). However, the causes of most SLE associated PH have not yet been clarified.

Several immunopathological mechanisms of SLE associated PH have been proposed. These include vasoconstriction or Raynaud's phenomenon[1,2,11,12,14-18], vasculitis[12,15,16], thrombosis or thromboembolism[12,15,16], anti-RNP antibody[5], and anticardiolipin antibody or lupus anticoagulant[1,9,19-21]. To investigate the immunopathology of SLE associated PH, we compared clinical and laboratory features of SLE patients with and without PH.

Various drugs have been used for SLE associated PH, such as vasodilators, anticoagulants, corticosteroids (CS), and immunosuppressants. Treatments with vasodilators and anticoagulants were generally disappointing[1,22,23], while the efficacy of CS and/or immunosuppressants on SLE associated PH is controversial[1,15,22,24-28].

MATERIALS AND METHODS

Patients. Medical records were reviewed for all patients who were admitted to Aoyama Hospital of Tokyo Women's Medical University between 1992 and 1999. One hundred ninety-four patients with SLE were identified. All SLE patients were classified according to the American Rheumatism Association (ARA) criteria[29]. The diagnosis of PH was as described below. In the medical records between 1992 and 1999, there were 12 patients with PH, including 8 SLE and 4 SLE + systemic sclerosis (SSc) overlap syndrome. Fifty-nine age and sex matched SLE patients without PH were chosen from the medical records. These patients had undergone the same clinical evaluation including chest radiograph, electrocardiogram, and Doppler echocardiography as patients with PH except for cardiac catheterization. Antiphospholipid syndrome (APS) was diagnosed according to international workshop criteria[30]. The latest information for the 12 SLE

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associated PH patients was obtained from their medical records in April 2001.

Evaluation of PH by Doppler echocardiography. All patients were evaluated by echocardiography using commercial systems (SONOS 1000, Hewlett-Packard, Andover, MA, USA). All studies were performed by skilled cardiologists, recorded on videotape for subsequent review, and read by several cardiologists experienced in echocardiography. All studies estimated tricuspid regurgitation using a validated standard technique with a 2 dimensional echocardiogram and Doppler method[1,3,4,7,8,31]. To estimate right ventricular systolic pressure (RVSP), the maximum transtricuspid pressure gradient was calculated using the modified Bernoulli equation[31,32]. An estimate of right atrial pressure, 10 mm Hg, was added to the pressure gradient to calculate RVSP, which was considered equal to the RVSP in the absence of right ventricular outflow obstruction[7]. PH was diagnosed when RVSP was > 40 mm Hg at rest. Several patients with PH were also examined by right heart catheterization to evaluate the efficacy of drugs against PH.

Comparison of clinical features and laboratory findings. We retrospectively compared clinical and laboratory features of SLE patients with and without PH. We compared the percentages of the following clinical features: cough, dyspnea, pulmonary infarction (PI), arthritis, Raynaud's phenomenon, fever, butterfly rash, serositis, and central nervous system (CNS) lupus. PI was diagnosed when a patient showed clinical symptoms such as chest pain, dyspnea, and hemosputum, as well as segmental defects by lung perfusion scintigraphy. CNS lupus included both lupus psychosis and organic brain syndrome. Laboratory findings compared between patients with and without PH included hemoglobin level, lymphocyte counts, platelet counts, serum lactate dehydrogenase (LDH) level, plasma thrombin-antithrombin III complex (TAT) level, plasma D-dimer level, serum complement level, and serum immune complex (IC) level (C1q binding assay). Autoantibodies including anti-double-stranded DNA (dsDNA) antibody (Ab), anti-Sm Ab, anti-U1 ribonucleoprotein (RNP) Ab, anticardiolipin-ß$_2$ glycoprotein I complex Ab (anti-CL-ß$_2$GPI Ab), lupus anticoagulant (LAC), and myeloperoxidase antineutrophil cytoplasmic Ab (MPO-ANCA) were also examined. To compare cardiopulmonary function, % vital capacity (%VC), % diffusing capacity for carbon monoxide (DLCO), arterial blood oxygen pressure (PaO_2), RVSP, and ejection fraction on Doppler echocardiography were studied. The pulmonary function test was carried out according to American Thoracic Society standards.

Analysis of treatment of PH. We analyzed the efficacy of immunosuppressive treatment for SLE associated PH. Pre-RVSP and post-RVSP were defined as RVSP before and after the treatment, respectively. The delta RVSP ratio (ΔRVSPr) was calculated from the following formula: (post-RVSP – 40)/(pre-RVSP – 40). The criteria for the efficacy of the treatment of PH were as follows: markedly effective when post-RVSP was ≤ 40 mm Hg; moderately effective when post-RVSP > 40 mm Hg and ΔRVSPr < 0.5; slightly effective when ΔRVSPr was between 1.5 and 0.5, but clinical signs and symptoms disappeared; no change, when ΔRVSPr was between 1.5 and 0.5, and clinical signs and symptoms neither disappeared nor deteriorated; deteriorated, when ΔRVSPr was ≥ 1.5 or clinical signs and symptoms deteriorated.

Statistical analysis. For comparison of clinical and laboratory features, Fisher's direct probability test or Mann-Whitney U test was used. Odds ratio and 95% confidence interval (95% CI) were also calculated. Results were considered significant when p values were ≤ 0.05.

RESULTS

Characteristics of SLE patients with PH. Patient profiles are summarized in Table 1. Twelve patients were diagnosed as PH. None of the 12 PH patients showed either ischemic heart disease or severe valvular heart disease that could result in PH. Four patients with PH showed the overlap syndrome of SLE + SSc (3 limited cutaneous type and one diffuse cutaneous type SSc). Two of 12 patients with PH and 4 of 53 SLE patients without PH were also classified with APS. In our cohort of 194 SLE patients, 6.2% had PH.

Table 1. Patient profiles.

Diagnosis	PH	Number of Cases (%*)	Age, yrs, mean ± SD	M/F
SLE	+	12** (6.2%)	38.3 ± 14.2	1/11
	–	59	33.7 ± 11.5	6/53

*Percentage of patients with PH. ** Three SLE + limited cutaneous type SSc and one SLE + diffuse cutaneous type SSc cases were included.

The results of the comparison of clinical features and laboratory tests are shown in Tables 2 and 3. The percentages of cough and dyspnea were significantly higher in PH patients (Table 2). There were significant differences in the plasma TAT level, plasma D-dimer level, PaO_2, and RVSP between patients with and without PH (Table 3).

Response of PH patients to immunosuppressive treatment. Among the 12 patients with PH, 8 had signs and symptoms of right heart failure (Table 4). These 8 patients with PH and right heart failure included 4 SLE and 4 SLE + SSc, and they were initially treated with calcium channel blocker, oral prostaglandin I_2, anticoagulants and/or diuretics for 2 to 3 weeks.

Immunosuppressive treatment was initiated because PH patients did not respond to these conventional drugs. RVSP (mean ± SD) before the immunosuppressive treatment was

Table 2. Comparison of clinical features between SLE patients with and without PH.

	PH (+) (%)	PH (–) (%)	Odds Ratio (95% CI)
Cough	6/12 (50.0)*	3/59 (5.1)*	16.1 (3.4–77.1)
Dyspnea	9/12 (75.0)*	6/59 (10.2)*	22.3 (5.0–100.3)
Pulmonary infarction	1/12 (8.3)	1/59 (1.7)	
Arthritis	9/12 (75.0)	40/59 (67.8)	
Raynaud's phenomenon	7/12 (58.3)	19/59 (32.2)	
Fever	6/12 (50.0)	44/59 (74.6)	
Butterfly rash	4/12 (33.3)	29/59 (49.2)	
Serositis	5/12 (41.7)	15/59 (25.4)	
CNS lupus	1/12 (8.3)	2/59 (3.4)	
Anti-dsDNA Ab	8/12 (66.7)	46/59 (78.0)	
Anti-Sm Ab	4/12 (33.3)	8/59 (13.6)	
Anti-U1 RNP Ab	8/12 (66.7)	25/58 (43.1)	
Anti-CL-β_2GPI Ab	1/11 (9.1)	7/53 (13.2)	
Lupus anticoagulant	2/12 (16.7)	2/55 (3.6)	
MPO-ANCA	1/6 (16.7)	3/28 (10.7)	

*p < 0.01 by Fisher's exact probability test. CNS: central nervous system; Anti-dsDNA: anti-double-stranded DNA; Ab: antibody; Anti-U1 RNP: anti-U1 ribonucleoprotein; Anti-CL-β_2GPI: anti-cardiolipin-β_2 glycoprotein I complex; MPO-ANCA: myeloperoxidase antineutrophil cytoplasmic antibody.

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Table 3. Comparison of laboratory findings between SLE patients with and without PH.

	PH (+)	PH (–)
TAT, ng/ml	21.1 ± 15.5**	11.2 ± 25.1
D-dimer, mg/ml	13.1 ± 17.2*	3.9 ± 9.6
PaO_2, mm Hg	73.8 ± 20.9*	90.2 ± 14.7
RVSP, mm Hg	55.5 ± 10.7***	26.9 ± 4.3
%VC	81.7 ± 15.1	90.8 ± 16.5

Values are expressed as mean ± SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, Mann-Whitney U test. TAT: thrombin-anti-thrombin III complex; PaO_2: arterial blood oxygen pressure; RVSP: right ventricular systolic pressure; % VC: % vital capacity.

60.8 ± 9.0 mm Hg (range 51–74) for these 8 patients with PH. Five of the 8 patients were also evaluated by cardiac catheterization, and their findings agreed well with those of Doppler echocardiography (Table 4). The characteristics of these 8 patients with SLE associated PH were as follows. The mean age was 36.1 ± 13.5 years old. The mean and median values of disease duration between the diagnosis of SLE and PH were 27.3 ± 35.2 months and 9 months, respectively (range 1–96 mo). The mean and median values of the duration between the diagnosis and treatment of PH were 0.63 ± 1.8 months and 0 months, respectively (range 0–5 mo). One of the 8 patients (Patient 8 in Table 4) had PI of the first branch of the left pulmonary artery.

We evaluated the response of SLE associated PH to immunosuppressive treatment according to the described criteria (Table 4). One patient (Patient 1) was treated with oral CS alone, 4 (Patients 2–5) with oral CS and steroid pulse therapy, and 3 (Patients 6–8) with oral CS and cyclophosphamide (CYC). Four patients (Patients 1, 2, 5 and 8), 3 (Patients 3, 6, and 7), and one (Patient 4) showed marked, moderate, and slight effectiveness, respectively. RVSP did not change in one case (Patient 4), but her clinical symptoms were ameliorated. Two patients (Patients 1 and 3) later relapsed. The treatments of the relapsed cases are shown in Table 5. Both patients were successfully treated with CS and CYC.

It has been reported that severe reduction in the DLCO as well as the increased ratio of functional vital capacity (FVC) to DLCO would be excellent predictors of PH[33]. In this study, PH patients 1, 2, 4, and 5, without pulmonary fibrosis (PF) by chest computed tomography, showed recovery of DLCO or %VC along with the improvement of PH after immunosuppressive treatment (Table 4). These findings suggest that not only DLCO but also %VC would be an

Table 4. Characteristics and response to immunosuppressive treatment of SLE associated PH.

Patient	Age, Sex	Diagnosis	Right Heart Failure	PA Thrombosis	Treatment: Oral CS, mg (Maximum PSL/day)	Treatment: CS Pulse, mPSL or CYC	RVSP, mm Hg: Before	RVSP, mm Hg: After	PAP, mm Hg	%DLCO/%VC: Before	%DLCO/%VC: After	Effectiveness	Relapse	Followup Duration, mo	Prognosis
1	22 F	SLE	+	–	PSL 50	ND	51	29	ND	47.9/77.1	52.5/86.1	+++	Yes	36	Alive
2	50 F	SLE	+	–	PSL 60	mPSL pulse: 1000 mg ×3	ND	28	68/25 (39)	47.9/52.5	77.1/86.1	+++	No	124	Deceased
3	20 F	SLE	+	–	PSL 40	mPSL pulse: 500 mg ×3	59	48	56/24 (37)	ND/ND	ND/74.3	++	Yes	31	Alive
4	43 F	SLE+SSc(D)	+	–	PSL 60	mPSL pulse: 500 mg ×3	59	56	78/33 (51)	ND/53.8	ND/72.3	+	No	42	Alive
5	24 F	SLE+SSc(L)	+	–	PSL 60	mPSL pulse: 1000 mg ×3	62	35	73/29 (45)	68.4/66.2	87.1/95.4	+++	No	22	Alive
6	33 F	SLE+SSc(L)	+	–	PSL 30	Oral CYC:50 mg/ every other day	74	46	57/23 (37)	ND/ND	80.9/92.0	++	No	61	Alive
7	56 F	SLE+APS	+	–	PSL 35	CYC pulse: 300 mg ×4	110	44	ND	ND/ND	ND/ND	++	No	34	Alive
8	41 F	SLE+SSc(L)	+	+	PSL 40	Oral CYC: 50 mg/day	51	29	ND	ND/ND	ND/ND	+++	No	24	Alive
9	54 F	SLE	–	–	PSL 60	ND	46	37	ND	ND/ND	ND/ND	NA	No	50	Alive
10	63 F	SLE	–	–	PSL 60	ND	46	21	ND	ND/ND	ND/ND	NA	No	68	Alive
11	31F	SLE	–	–	PSL 40	ND	41	35	ND	119.0/97.0	74.3/85.0	NA	No	37	Alive
12	29 M	SLE+ APS +RA	–	–	PSL 40	ND	46	33	ND	ND/97.8	ND/ND	NA	No	26	Alive

PA thrombosis : pulmonary arterial thrombosis diagnosed by lung perfusion scintigraphy; CS: corticosteroids; CYC: cyclophosphamide; PSL: prednisolone; mPSL: methylprednisolone; RVSP: right ventricular systolic pressure by echocardiography; PAP: main pulmonary arterial pressure before treatment by right heart catheterization, systolic/diastolic (mean); %DLCO: % diffusing capacity for CO; %VC: % vital capacity.
Effectiveness: +++: markedly effective; ++: moderately effective; +: slightly effective; –: deteriorated; NA: not applicable. Followup duration: Duration from the improvement of PH to April 2001 for all except Patient 2 or to deceased day for Patient 2. SLE: systemic lupus erythematosus; SSc(D): diffuse type SSc; SSc(L): limited type SSc; APS: antiphospholipid syndrome; RA: rheumatoid arthritis; ND: not done.

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Table 5. Treatment of relapsed PH cases.

Patient	Age/Sex	Diagnosis	First Tx	Duration 1, mo	2nd Tx	Duration 2, mo	3rd Tx	RVSP after Tx, mm Hg	Prognosis
1	22 F	SLE	Oral CS alone (PSL: max 50 mg)	4	Oral CS + CS pulse + CYC (PSL: max 100 mg) (mPSL pulse:300 mg ×3, 500 mg ×2) (CYC pulse: 300–500 mg ×9)			28	Alive
3	20 F	SLE	Oral CS + CS pulse (PSL: max 40 mg) (mPSL pulse: 500 mg ×3)	15	Oral CS + CS pulse (PSL: max 60 mg) (mPSL pulse: 500 mg ×3)	9	Oral CS + CYC (PSL: max 28 mg) (CYC: oral 50 mg/day)	44	Alive

First Tx: first immunosuppressive treatment of PH; Duration 1: duration between first treatment and first relapse of PH; 2nd Tx: immunosuppressive treatment after first relapse of PH; Duration 2: duration between 2nd treatment and 2nd relapse of PH; 3rd Tx: immunosuppressive treatment after 2nd relapse of PH; RVSP after Tx: RVSP after last immunosuppressive treatment of PH; SLE: systemic lupus erythematosus; CS: corticosteroids; CYC: cyclophosphamide; PSL: prednisolone; mPSL: methylprednisolone.

excellent marker of drug efficacy for SLE associated PH in the absence of severe PF.

One of 8 patients with PH (Patient 2) died during the followup period. The cause of death was sepsis derived from severe infection of the left leg. By April 2001, when the last findings were obtained, all but the deceased patient showed improvement of their RVSP. We tapered prednisolone (PSL) slowly and maintained PSL at > 10 mg per day. Patients 1 and 7 did not receive additional CYC pulse or oral CYC after the improvement of RVSP. Patient 3 discontinued oral CYC after the improvement of relapsed PH because of the onset of hemorrhagic cystitis, and has not shown relapsed PH. Patients 6 and 8 are still taking oral CYC (Tables 4, 5).

The remaining 4 PH cases (Patients 9–12), including one patient with APS, did not have right heart failure and these 4 cases were observed without any specific treatments for PH (Table 4). RVSP (44.9 ± 2.3 mm Hg) before the CS treatment of these patients was significantly lower than those of 8 PH patients with right heart failure ($p < 0.01$, Mann-Whitney U test). RVSP for these 4 patients did not deteriorate during the followup period.

DISCUSSION

The most important finding of our study was the favorable efficacy of immunosuppressive treatment against PH. In 7 of 8 patients, CS ± CYC was moderately or markedly effective (Table 4). The immunosuppressive treatment was also effective for the relapsed cases (Table 5). There are some reported cases of SLE associated PH who were successfully treated with immunosuppressants[22,24,25,27,28]. Goupille, *et al*[25] reported that PH markedly improved with high doses of CS in a patient with SLE. In that study, PH and SLE were diagnosed simultaneously. Dahl, *et al*[28] also reported that a 20-year-old female patient with mixed connective tissue disease associated PH was successfully treated with CS pulse therapy and intravenous CYC. The treatment was started immediately after she had been diagnosed with PH. These findings suggest the partially reversible inflammatory lesions contributed to the increased pulmonary vascular resistance in SLE or mixed connective tissue disease associated PH. Poor responses of SLE associated PH to immunosuppressants, however, have also been reported[1,15,26]. There has been no study focusing on the relationship between the efficacy of treatment for PH and the duration from onset of PH to the treatment. In patients with long standing PH whose pathological changes of pulmonary vessels have already become irreversible, immunosuppressive treatment for PH may not be effective. In our patients, 6 of 7 responders to immunosuppressive treatment were treated immediately after the diagnosis of PH. The present findings and the previous observations of those with SLE associated PH suggest that treatment of PH with CS and/or CYC during the reversible phase of the disease would be important for good prognosis. Immunosuppressive drugs may inhibit the production of cytokines and/or chemokines as well as the expression and/or activation of adhesion molecules of pulmonary vascular endothelial cells and of infiltrating lymphocytes. The drugs may also repair the endothelial cell dysfunction and improve the hypercoagulability in PH, especially during the early stage of the disease.

The percentage of PH in SLE has been reported as 0.5 to 14%[1,2,5,14,19], which is similar to the present findings (Table 1). In our institute, almost all SLE patients were admitted to Aoyama Hospital once to evaluate organ involvement irrespective of their disease activity. Therefore, the percentage of PH in SLE patients (6.2%) does not overestimate the true value. With the use of sensitive diagnostic techniques such as Doppler echocardiography, the percentage of PH in SLE has been recognized to be higher than previously described[14,34]. Regarding the accuracy of diagnosis of PH by Doppler echocardiography, Currie, *et al*[31] and Simonson, *et al*[14] reported a significant correlation between Doppler estimated and catheter measured right ventricular systolic pressure. Our findings also confirm the accuracy of Doppler echocardiography for the diagnosis of PH (Table 4).

One of 12 patients with SLE associated PH (Patient 8)

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had definite PI by lung perfusion scintigraphy when she was diagnosed with PH. In the other 11 patients, there was no underlying disease except SLE that can cause PH. In the postmortem examination of SLE patients with PH, fibrous intimal thickening, subintimal fibrosis, hypertrophy of the media, plexiform lesion, angiomatoid lesions of the muscular arteries, periarteriolar and perivenular lymphocytic infiltrates, and small fibrin thrombi obliterating the small vessels have been reported[2,4,15,35]. These findings indicate that endothelial cell damage of pulmonary arteries or arterioles would lead to irreversible fibrotic and obliterating changes to the vessels. Among the present 12 SLE associated PH patients, one (Patient 8) could be classified as thromboembolic PH and others as plexogenic PH. It was reported that plasma TAT and D-dimer levels were elevated in thrombotic microangiopathy[36]. We observed that plasma TAT and D-dimer levels were increased in SLE with PH (Table 3). These findings suggest that microangiopathy of pulmonary arteries and/or arterioles would be important for the immunopathogenesis of PH in SLE.

The diagnosis of PH is often delayed and by the time this diagnosis has been made, irreversible changes have already taken place. Most treatments are not effective for these patients. Hence, it is quite important to diagnose SLE or SLE + SSc overlap associated PH during its early stage by regular screening, using chest radiographs, Doppler echocardiography and/or spirometry.

Our findings suggest that a trial of immunosuppression may be advantageous in patients with SLE associated PH. High dose corticosteroid with or without cyclophosphamide would be a treatment of choice for the immunosuppression. Early diagnosis by Doppler echocardiography and intensive treatment is most important for improved prognosis of patients with SLE associated pulmonary hypertension.

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