

# Successful Use of Intensive Immunosuppressive Therapy for Treating Simultaneously Occurring Cerebral Lesions and Pulmonary Arterial Hypertension in a Patient with Systemic Lupus Erythematosus

Ryu Watanabe<sup>1</sup>, Hiroshi Fujii<sup>1</sup>, Tsuyoshi Shirai<sup>1</sup>, Shinichiro Saito<sup>1</sup>, Akira Hatakeyama<sup>2</sup>, Koichiro Sugimura<sup>3</sup>, Yoshihiro Fukumoto<sup>3</sup>, Tomonori Ishii<sup>1</sup> and Hideo Harigae<sup>1</sup>

---

## Abstract

---

A 59-year-old woman who had been diagnosed with systemic lupus erythematosus (SLE) was admitted to our hospital due to paralysis in all of her limbs. The patient presented with dysarthria, cerebellar ataxia and hypoxia. Magnetic resonance imaging (MRI) revealed vasogenic edema in the brain stem and the cerebellum. She was diagnosed with neuropsychiatric lupus syndrome (NPSLE) and pulmonary arterial hypertension (PAH), and was successfully treated using immunosuppressive therapy. To our knowledge, this is the first reported case of simultaneously developing NPSLE and PAH.

**Key words:** cerebral lesion, pulmonary arterial hypertension, systemic lupus erythematosus

(Intern Med 53: 627-631, 2014)

(DOI: 10.2169/internalmedicine.53.0514)

---

## Introduction

---

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by the production of pathogenic autoantibodies which results in damage to multiple organs (1). Central nervous system (CNS) involvement is one of the major manifestations of SLE and occurs in approximately 15% to 75% of lupus patients (2). In 1999, a multi-disciplinary committee of the American College of Rheumatology published the nomenclature for neuropsychiatric lupus syndromes (NPSLE). The neuropsychiatric syndromes were divided into 19 different conditions which included the neurologic disorders of the central, peripheral and autonomic nervous system as well as the psychiatric syndromes (3). Although technological advances in neuroimaging have proved useful in monitoring brain damage, the diagnosis of NPSLE is difficult and requires a careful assessment. NPSLE still accounts for 4% to 16% of the deaths of lupus patients (4). Pulmonary arterial hypertension (PAH) is sometimes associ-

ated with connective tissue diseases (CTD) such as systemic sclerosis (SSc), mixed connective tissue diseases (MCTD) and SLE. The prevalence of PAH is estimated to be 0.5% to 17.5% in SLE patients (5, 6). PAH is also associated with a poor prognosis, and the three-year survival rate of SLE-PAH patients has only been reported as 75% (7). We herein describe a case of SLE that was simultaneously diagnosed with NPSLE and PAH. Although each of these manifestations may not be rare in SLE, this is the first reported case to have concurrently developed both complicating conditions. The patient was successfully treated with intensive immunosuppressive therapy.

---

## Case Report

---

A 59-year-old woman was admitted to our hospital due to paralysis in all of her limbs. She had previously been diagnosed with SLE based on polyarthralgia, facial rash and serological tests showing positivity for anti-nuclear antibody (ANA, ×160, speckled pattern) and anti-Smith antibody. Her

---

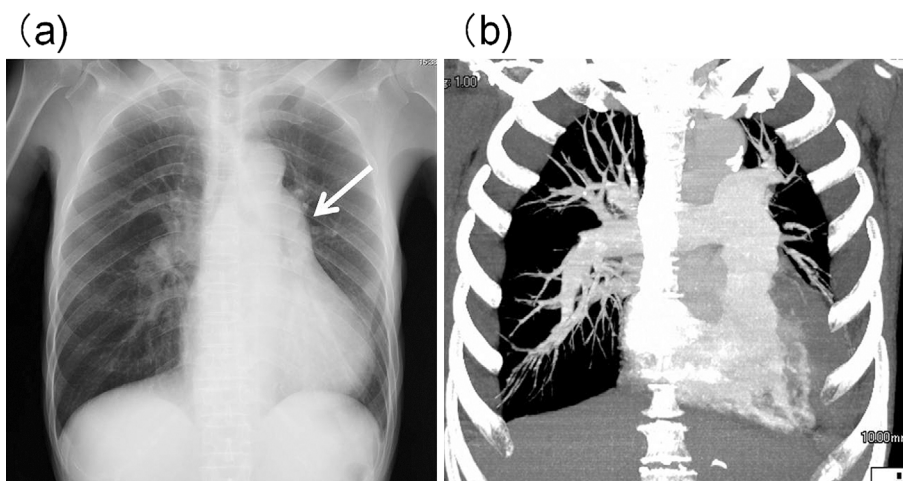
<sup>1</sup>Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Japan, <sup>2</sup>Division of Arthritis and Connective Tissue Diseases, Tohoku Rosai Hospital, Japan and <sup>3</sup>Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Japan

Received for publication March 4, 2013; Accepted for publication May 19, 2013

Correspondence to Dr. Hiroshi Fujii, hfujii@med.tohoku.ac.jp

**Table 1. Laboratory Findings of the Patient**

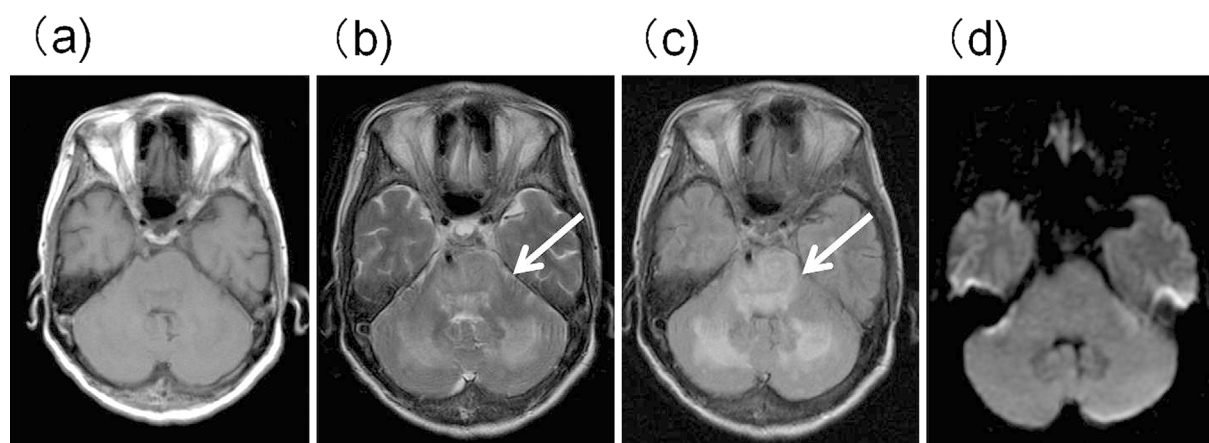
<u>Complete blood cell counts</u>			<u>Urinalysis</u>					
WBC	5,500	/μL	protein	(1+)		Na	133	mEq/L
Seg	90	%		0.8	g/g-cr	K	3.0	mEq/L
Lym	7	%	occult.blood.	(2+)		Cl	97	mEq/L
Mon	3	%	<sediment>			BUN	19	mg/dL
Eos	0	%	RBC	10-29	/HPF	Cr	0.6	mg/dL
Bas	0	%	Cast	10-29	/LPF	UA	4.8	mg/dL
RBC	454×10 <sup>4</sup>	/μL	<u>Biochemistry</u>			Ferritin	264	ng/mL
Hb	14.6	g/dL	T.Bil	1.4	mg/dL	CRP	1.1	mg/dL
MCV	94.8	fL	ALP	132	IU/L	C3	47	mg/dL
Hct	43	%	γ-GTP	30	IU/L	C4	5.8	mg/dL
Ret	0.6	%	AST	25	IU/L	CH50	25.4	U/mL
Plt	11.1×10 <sup>4</sup>	/μL	ALT	15	IU/L	ANA	80	fold
<u>Coagulation</u>			LDH	254	IU/L	dsDNA	6.1	IU/mL
PT:INR	0.96		TP	7.2	g/dL	Sm	133.1	index
APTT	30.6	sec	Alb	3.5	g/dL	RNP	179.3	index
Fbg	347	mg/dL	Haptoglobin	22.2	mg/dL	SS-A	97.1	index
D-Dimer	1.5	μg/mL	KL-6	604	U/mL	SS-B	9.0	index
LAC	1.2		BNP	162	pg/mL	β2GP1CL	< 1.3	U/mL
*LAC: lupus anticoagulant			HbA1c	6.1	%	Cardiolipin	6.0	U/mL

**Figure 1. The chest X-ray and CT findings upon admission. (a) The chest X-ray showed a protrusion of the left second arch (arrow). (b) Enhanced CT showed no signs of pulmonary embolism.**

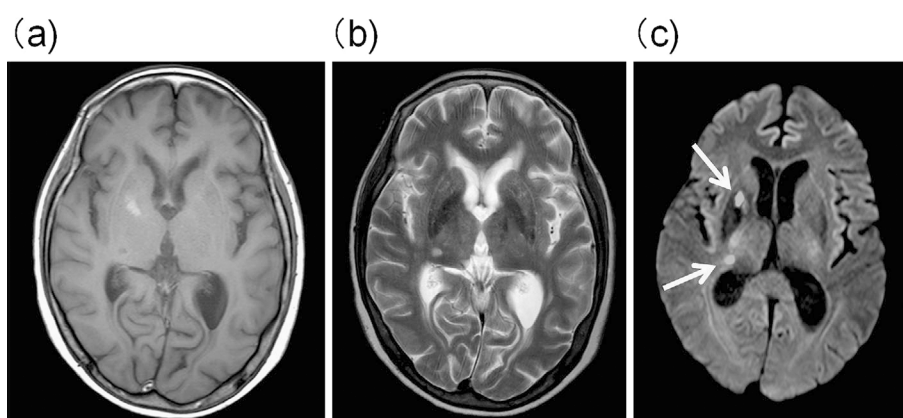
symptoms had been well controlled with low dose prednisolone (PSL) for the five years leading up to the current admission. Upon admission, her blood pressure was 178/108 mmHg, her body temperature was 37.8°C, her heart rate was 126 beats/min and her oxygen saturation level (SpO<sub>2</sub>) was 93%. A physical examination showed facial and palmar erythema and pretibial edema. A neurological examination revealed that her consciousness was slightly altered and her Glasgow Coma Scale (GCS) score was 14/15. In addition, dysarthria and cerebellar ataxia were also observed. Bilateral manual muscle testing (MMT) produced an upper limb score of 4/5 and lower limb score of 3/5. Laboratory tests demonstrated positive results for anti-RNP, anti-Smith and anti-SS-A antibodies as well as hypocomplementemia, an elevated brain natriuretic peptide (BNP) level and abnormal urinary findings (Table 1). Chest X-rays showed a protrusion of the left second arch of the cardiac silhouette and a

cardiothoracic ratio of 59.6% (Fig. 1a). Enhanced computed tomography (CT) revealed no evidence of either pulmonary embolism or interstitial pneumonia, but right ventricular hypertrophy and a small amount of pericardial effusion were observed (Fig. 1b). Echocardiography showed the ejection fraction to be normal (79.6%), but the tricuspid pressure gradient (TRPG) was elevated (50 mmHg). Pulmonary scintigraphy showed no signs of any blood flow defects.

Magnetic resonance imaging (MRI) of the brain revealed multiple high intensity signals in the brain stem and the bilateral cerebellum on a T2-weighted image (T2WI) and a fluid-attenuated inversion recovery (FLAIR) image (Fig. 2b, c). The T1-weighted images (T1WI) and diffusion-weighted images (DWI) of these lesions were almost normal, thus suggesting vasogenic edema (Fig. 2a, c). Cerebral blood flow scintigraphy showed a significant decrease in the flow to the bilateral cerebellum and the right frontal and



**Figure 2.** MRI findings of the brain stem and cerebellum upon admission. (a) T1WI. (b, c) T2WI and FLAIR. High intensity signals (arrow) were observed. (d) DWI.



**Figure 3.** MRI findings of the right thalamus and caudate nucleus one month after admission. (a) T1WI. (b) T2WI. (c) DWI. High intensity signals (arrow) were observed.

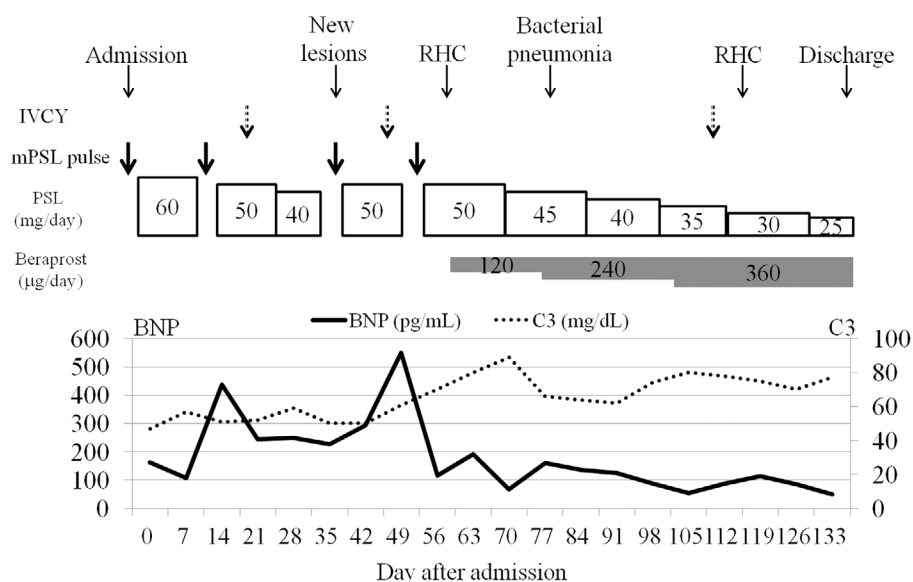
temporal lobes. An electroencephalogram (EEG) showed diffuse slow waves (8-10 Hz) with multiple bursts. An examination of the cerebrospinal fluid revealed normocytosis and a slightly increased concentration of total protein (50 mg/dL; normal, 10-40 mg/dL), but the IgG index was within normal limits (0.76). The SLE disease activity index (SLEDAI) (8) was 35. From these findings, we concluded that SLE-associated NPSLE and PAH had developed simultaneously in this patient.

Intravenous steroid pulse therapy followed by high dose PSL therapy (60 mg/day), intravenous cyclophosphamide pulse therapy (IVCY, 500 mg/day) and anti-coagulant therapy dramatically improved the dysarthria and ataxia, and the cerebellar and brain stem lesions disappeared rapidly after two weeks. However, new high intensity signals on DWI that indicated cerebral infarction were observed in the right thalamus and caudate nucleus at one month after her admission (Fig. 3). Magnetic resonance angiography (MRA) revealed no vascular stenosis, embolism or aneurysm. A repeated course of intravenous steroid pulse therapy led to improvement after two weeks. The complete clinical course is shown in Fig. 4. A right heart catheterization (RHC) was performed two months after admission, and revealed a mean

pulmonary arterial pressure (mPAP) of 36 mmHg, a pulmonary capillary wedge pressure (PCWP) of 3 mmHg, a cardiac index (CI) of 3.52 L/min and a pulmonary vascular resistance (PVR) of 526 dyne-sec/cm<sup>5</sup>, thus leading to a diagnosis of PAH and the administration of beraprost. Since then, no new cerebral lesions have been observed even though the patient suffered from bacterial pneumonia during her hospital stay. She was discharged four months after admission. RHC performed prior to discharge showed that her mPAP and PVR had decreased remarkably (Table 2). Ten rounds of IVCY were sufficient to maintain both the NPSLE and PAH in remission for 3 years with maintenance low dose PSL therapy (10 mg/day) and no required additional vasodilative therapy. Her current SLEDAI score is 2.

## Discussion

Neuropsychiatric manifestations are well known to be a serious complication associated with SLE. Previous reports have suggested that pathogenic autoantibodies such as the anti-phospholipid antibody, the anti-ribosomal P antibody and the anti-N-methyl-D-aspartate (NMDA) antibody, as well as inflammatory cytokines such as interleukin (IL)-2,



IVCY: intravenous cyclophosphamide, PSL: prednisolone, RHC: right heart catheterization

**Figure 4.** The clinical course of the patient.

IL-6, IL-8, IL-10, tumor necrosis factor (TNF)- $\alpha$  and interferon (IFN)- $\alpha$  are key players in the pathogenesis of NPSLE (9). Intensive immunosuppressive therapy such as high dose PSL and cyclophosphamide is required for the treatment of NPSLE (10).

MRI is one of the most common methods used in clinical practice to evaluate CNS involvement in lupus patients. It allows for a very sensitive detection of infarctions, hemorrhages and acute myelitis, and it can be used to monitor the response to therapy (11). DWI measures the diffusivity of water protons and has been increasingly used to distinguish cytotoxic edema in acute infarction from vasogenic edema and chronic infarction (2, 12). In our patient, MRI of the brain revealed two different cerebral lesions. First, high intensity signals on T2WI and FLAIR, which showed iso-intensity signals on T1WI and DWI, were observed in the brain stem and the bilateral cerebellum indicating vasogenic edema (Fig. 2a-d). This is commonly seen in the bilateral parieto-occipital subcortical white matter, and the condition is known as reversible posterior encephalopathy syndrome (RPLS) (12). However, these lesions can also occur in the frontal lobe, basal ganglia, thalamus, cerebellum, and brain stem (12). Most of the cases of RPLS that are observed in lupus patients are associated with triggers such as hypertension, preeclampsia, or with the administration of immunosuppressive agents. However, RPLS can also occur as a neurological manifestation of active lupus and sometimes requires intensive immunosuppressive therapy (13). Recently, RPLS has been increasingly considered to be one of the neuropsychiatric syndromes of active lupus (14). In this patient, an anti-hypertensive agent was not administered immediately following her admission because of the significantly decreased cerebral blood flow that was observed in the bilateral cerebellum and the right frontal and temporal lobes. The rapid response to the administered immunosuppressive

**Table 2.** Hemodynamics of the Patient

Duration after admission (months)	2	4	6
PAP (mmHg)	56/22 (36)	42/15 (25)	32/14 (18)
CO (CI) (L/min)	4.26 (3.52)	5.5 (4.23)	3.47 (2.67)
PVR (dyne $\cdot$ sec $\cdot$ cm $^{-5}$ )	526	291	346
BNP (pg/mL)	293.5	74.5	52.5

PAP: pulmonary arterial pressure, CO (CI): cardiac output (index), PVR: pulmonary vascular resistance, BNP: brain natriuretic peptide

therapy without irreversible changes suggested that these lesions were a vasogenic edema that associated with active lupus. Second, high intensity signals on DWI observed in the right thalamus and caudate nucleus indicated cerebral infarction (Fig. 3). These lesions were probably caused by a decreased cerebral blood flow. As expected, they rapidly improved after treatment. Therefore, the two cerebral lesions in this patient were both radiographically and mechanistically different.

PAH is defined by an mPAP of greater than 25 mmHg at rest and a PCWP of less than 15 mmHg. It has been increasingly recognized that inflammatory mechanisms could play an important role in the PAH pathogenesis and progression, particularly in patients with CTD (15). PAH associated with CTD, but not systemic sclerosis, responds well to intensive immunosuppressive therapy (16-18). In this patient, immunosuppressive therapy dramatically improved her pulmonary hemodynamics. A follow-up RHC that was performed six months after the start of her admission revealed that her mPAP had completely normalized (Table 2). No recurrence of PAH was observed for 3 years. These findings showed that PAH associated with active lupus could respond

to intensive immunosuppressive therapy.

NPSLE and PAH are sometimes observed in lupus patients; however, the simultaneous occurrence of both manifestations is very rare. Hardie et al. reported a 28-year-old woman who was diagnosed with SLE and then tetraplegia developed PAH 6 years after her original diagnosis (19). Funachi et al. reported that 6 out of 306 lupus patients (1.9%) had both NPSLE and PAH (20). Cefle et al. also reported that 4 out of 107 patients (3.7%) with SLE had both conditions (21). These reports suggested that the complication of these manifestations does occur in lupus patients; however, there are currently no case reports detailing the simultaneous development of NPSLE and PAH. Therefore, to the best of our knowledge, this is the first case report of a lupus patient who was concurrently diagnosed with both conditions.

The mechanism that caused both manifestations has not yet been elucidated. This patient may have several different pathogenic autoantibodies or an atypical autoantibody that caused both conditions. Vascular endothelial cell injuries may have been involved in the pathogenesis. Anti-endothelial cell antibodies (AECAs) are often detected in lupus patients and are considered to play important roles in the development of nephritis and atherosclerotic lesions related to vascular endothelial injuries (22). AECA was detected in the sera of this patient when we measured the binding activity of IgG to human umbilical vein endothelial cells (HUVECs) using flow cytometry (data not shown) (22). This AECA activity may have the potential to cause both manifestations.

In conclusion, we herein presented a case of SLE in which CNS involvement and PAH developed concurrently. Intensive immunosuppressive therapy was very effective for treating both conditions, thus indicating that both of these manifestations were mediated by autoimmune mechanisms. This case report may provide some useful insights concerning the pathogenesis of NPSLE and PAH.

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

## References

1. Liu Z, Davidson A. Taming lupus-a new understanding of pathogenesis is leading to clinical advances. *Nat Med* **18**: 871-882, 2012.
2. Castellino G, Govoni M, Giacuzzo S, Trotta F. Optimizing clinical monitoring of central nervous system involvement in SLE. *Autoimmun Rev* **7**: 297-304, 2008.
3. ACR Ad Hoc Committee on Neuropsychiatric lupus nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* **42**: 599-608, 1999.
4. Borchers AT, Aoki CA, Naguwa SM, Keen CL, Shoenfeld Y, Gershwin ME. Neuropsychiatric features of systemic lupus erythematosus. *Autoimmun Rev* **4**: 329-344, 2005.
5. Dhala A. Pulmonary arterial hypertension in systemic lupus erythematosus: current status and future direction. *Clin Dev Immunol* **2012**: 854941, 2012.
6. Johnson SR, Granton JT. Pulmonary hypertension in systemic sclerosis and systemic lupus erythematosus. *Eur Respir Rev* **20**: 277-286, 2011.
7. Condliffe R, Kiely DG, Peacock AJ, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* **179**: 151-157, 2009.
8. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* **35**: 630-640, 1992.
9. Efthimiou P, Blanco M. Pathogenesis of neuropsychiatric systemic lupus erythematosus and potential biomarkers. *Mod Rheumatol* **19**: 457-468, 2009.
10. Bertias GK, Ioannidis JPA, Aringer M, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. *Ann Rheum Dis* **69**: 2074-2082, 2010.
11. Appenzeller S, Pike GB, Clarke AE. Magnetic resonance imaging in the evaluation of central nervous system manifestations in systemic lupus erythematosus. *Clin Rev Allergy Immunol* **34**: 361-366, 2008.
12. Moritani T, Hiwatashi A, Shrier DA, Wang HZ, Numaguchi Y, Westesson PL. CNS vasculitis and vasculopathy. Efficacy and usefulness of diffusion-weighted echoplanar MR imaging. *Clin Imaging* **28**: 261-270, 2004.
13. Fujieda Y, Kataoka H, Odani T, et al. Clinical features of reversible posterior leukoencephalopathy syndrome in patients with systemic lupus erythematosus. *Mod Rheumatol* **21**: 276-281, 2011.
14. Barber CE, Leclerc R, Gladman DD, Urowitz MB, Fortin PR. Posterior reversible encephalopathy syndrome: an emerging disease manifestation in systemic lupus erythematosus. *Semin Arthritis Rheum* **41**: 353-363, 2011.
15. Price LC, Wort SJ, Perros F, et al. Inflammation in pulmonary arterial hypertension. *Chest* **141**: 210-221, 2012.
16. Sanchez O, Sitbon O, Jais X, Simonneau G, Humbert M. Immunosuppressive therapy in connective tissue disease-associated pulmonary arterial hypertension. *Chest* **130**: 182-189, 2006.
17. Jais X, Launay D, Yaici A, et al. Immunosuppressive therapy in lupus- and mixed connective tissue disease-associated pulmonary arterial hypertension. *Arthritis Rheum* **58**: 521-531, 2008.
18. Miyamichi-Yamamoto S, Fukumoto Y, Sugimura K, et al. Intensive immunosuppressive therapy improves pulmonary hemodynamics and long-term prognosis in patients with pulmonary arterial hypertension associated with connective tissue disease. *Circ J* **75**: 2668-2674, 2011.
19. Hardie RJ, Isenberg DA. Tetraplegia as a presenting feature of systemic lupus erythematosus complicated by pulmonary hypertension. *Ann Rheum Dis* **44**: 491-493, 1985.
20. Funachi M, Shimadzu H, Tamaki C, et al. Survival study by organ disorders in 306 Japanese patients with systemic lupus erythematosus. *Rheumatol Int* **27**: 243-249, 2007.
21. Cefle A, Inanc M, Sayarlioglu M, et al. Pulmonary hypertension in systemic lupus erythematosus: relationship with antiphospholipid antibodies and severe disease outcome. *Rheumatol Int* **31**: 183-189, 2011.
22. Shirai T, Fujii H, Ono M, et al. A novel autoantibody against fibronectin leucine-rich transmembrane protein 2 expressed on the endothelial cell surface identified by retroviral vector system in systemic lupus erythematosus. *Arthritis Res Ther* **14**: R157, 2012.