図７　自然歴レジストリー登録患者背景

登録患者背景	
年齢	45～67（平均57）
性別	男：女　0：15
原病	強皮症12　SLE 3
Ca拮抗薬	3例
経口PG剤	10例
抗血小板薬	8例
抗凝固薬	2例
点滴PG剤	3例
エンドセリン受容体拮抗薬	1例
PDE5阻害薬	2例
喫煙歴	2例（BI　50、800）

図８　自然歴レジストリー患者　潰瘍数の変化

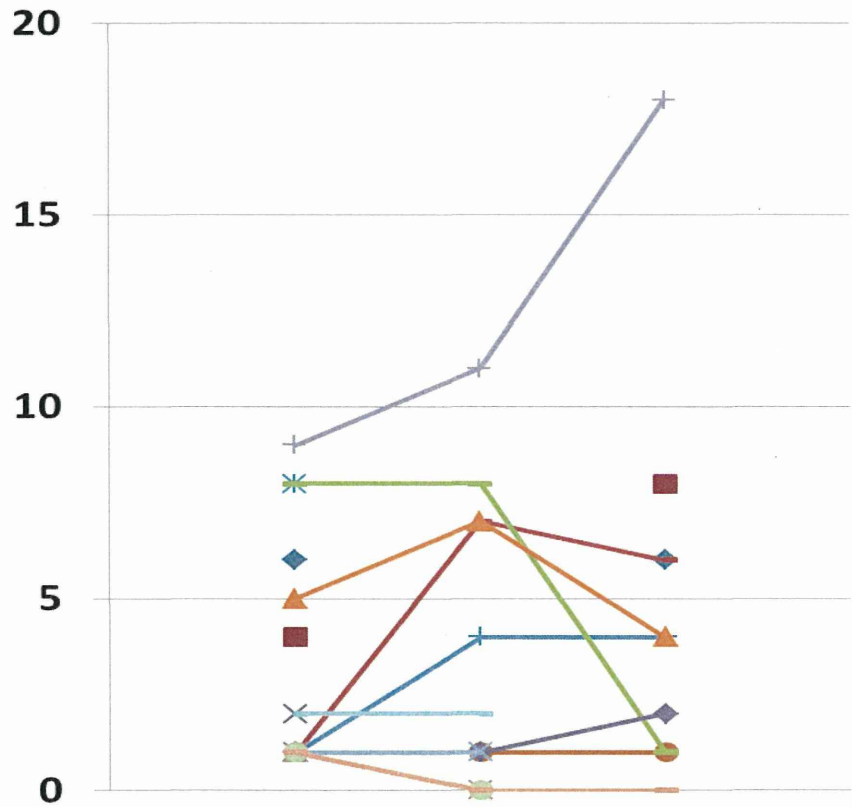


図９　自然歴レジストリー　痛みに関する VAS の変化

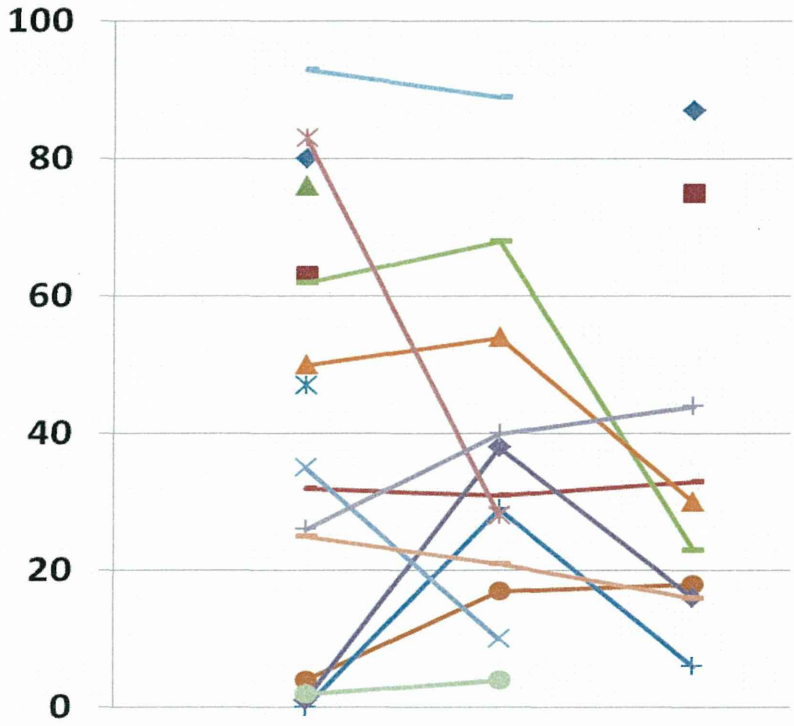
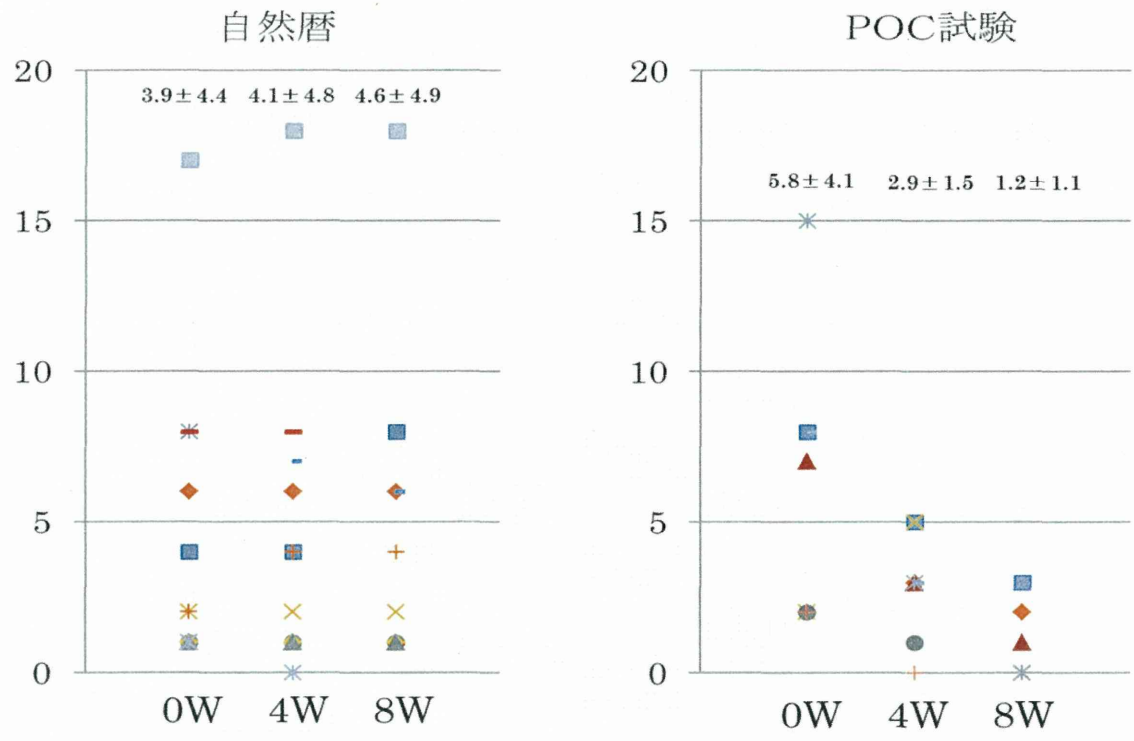


図１０　自然歴レジストリーと POC 試験における潰瘍改善速度の違い
（観察・治療開始後 8 週時における総潰瘍数の減少数の平均値）



Ⅱ. 分 担 研 究 報 告 書

厚生労働科学研究費補助金　難治性疾患等克服研究事業

（難治性疾患克服研究事業）

分担研究報告書

難治性潰瘍を伴う強皮症、混合性結合組織病、全身性エリテマトーデスに対する低出力体外衝撃波治療法

全身性強皮症患者の指尖部潰瘍に関する研究

研究分担者　川口鎮司　東京女子医科大学リウマチ科　臨床教授

研究要旨：全身性強皮症の指尖部潰瘍に対して低出力衝撃波治療の有用性を前向きに検討する。現在、7 名の全身性強皮症患者が登録終了し、６名がプロトコールに沿って衝撃波の治療を終えている。全例、衝撃波治療を週に１回行い、８週続けて行う。患者の全般的評価は、Raynaud Condition Score (RCS)と潰瘍の数で評価した。RCS は、３例とも１回の治療後に改善が見られた。潰瘍の数は今のところ変化はない。有害事象は起きていない。RCS の改善が１回目の治療にて見られたことより、低周波衝撃波治療の指尖部潰瘍に対する有効性はあると考える。

A. 研究目的

末梢循環不全に伴う皮膚潰瘍は、全身性強皮症の 5-10%に出現し、その半数程度は、難治性である。現在、我々が治療に用いているものは、薬物療法と保温に努めるという対症療法である。薬物療法では、もっとも有効と考えられるのは、プロスタグランジン E1 の静注療法である。この治療は、連日、行う必要があり、外来治療では患者の負担は大きい。内服治療では、プロスタサイクリン製剤であるベラプロストが最も有用性が高いと考えている。これらの治療を行いながらも、皮膚潰瘍が進行したり、手指あるいは足趾の壊疽に陥る症例が少なくない。低出力体外衝撃波治療により、末梢の循環改善が認められ、その結果、レイノー現象の改善、皮膚潰瘍の減少、壊疽の予防が可能になれば、全身性強皮症の治療として、患者への利益は大きいと考える。そこで、東京女子医科大学附属膠原病リウマチ痛風センターに通院中の全身性強皮症の患者を対象にして低周波衝撃波治療の有用性を検討した。

B. 研究方法

東京女子医科大学附属膠原病リウマチ痛風センターに通院中の指尖部潰瘍を合併した全身性強皮症の患者とした。全例で 15 例を行う予定であったが、7 例を登録したところで終了とした。低周波衝撃波の治療方法の詳細は、研究責任者の項を参照とする。レイノー現象の程度を Raynaud Condition Score (RCS)にて評価し、手指または足趾に生じている皮膚潰瘍の数または壊疽の数を測定した。

(倫理面への配慮)

研究計画は東京女子医科大学倫理委員会の承認を得ている。エントリーする患者には研究方法を十分に説明し、文書にて同意を得ている。

C. 研究結果

現在、6 名の指尖部潰瘍を有する全身性強皮症患者にプロトコール通りの衝撃波を行うことができ、途中脱落はなかった。7 例目の症例は平成 27 年 3 月末までに照射が終了して解析にうつる予定である。

皮膚潰瘍は、東京近郊では秋から冬期にかけて悪化するのが通常である。昨年の冬期に照射を行った 5 例に関しては、昨年と比較して今年は皮膚潰瘍の発現がみられなかった。

D. 考察

全身性強皮症では、末梢循環不全は 90%以上の症例で認められるが、皮膚潰瘍に至る症例は 10-15%である。冬期に症状が生じて、夏には消失する症例が多い。平成 25 年から平成 26 年の冬にかけて指尖部潰瘍が生じた 5 症例に関して、衝撃波を行っていた。これらの 5 症例全例において、昨年とは異なり、本年の冬期には指尖部潰瘍は発生しなかった。このころは、低出力衝撃波治療は、1 年間での観察では、有効性が確認されたことになる。

短期の指尖部潰瘍に対する効果も明らかであるが、1 年程度の長期での潰瘍予防の効果が認められる可能性が示唆された。

E. 結論

全身性強皮症の指尖部潰瘍に対して、低出力衝撃波治療の有用性の研究を行い、その有用性を確認した。

F. 研究発表

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2. 学会発表

なし

G. 知的財産権の出願・登録状況（予定を含む）

1. 特許取得

該当なし

2. 実用新案登録

該当なし

3. その他

該当なし

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

【書籍】

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発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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川口鎮司	混合性結合組織病	日本内科学会雑誌	103	2501-2506	2014
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浦田幸朋、石井智徳、張替秀郎、佐々木毅　その他 12 名	東北地方における B 型肝炎再活性化前向き研究について	最新医学	68(3)	395-402	2013

Ⅳ. 研究成果の刊行物、別冊

INTERNAL MEDICINE

□ CASE REPORT □

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

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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

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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 multidisciplinary 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 associated 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

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Table 1. Laboratory Findings of the Patient

Complete blood cell counts			Urinalysis					
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	454×10^4	/μL	Biochemistry			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	11.1×10^4	/μL	ALT	15	IU/L	ANA	80	fold
Coagulation			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

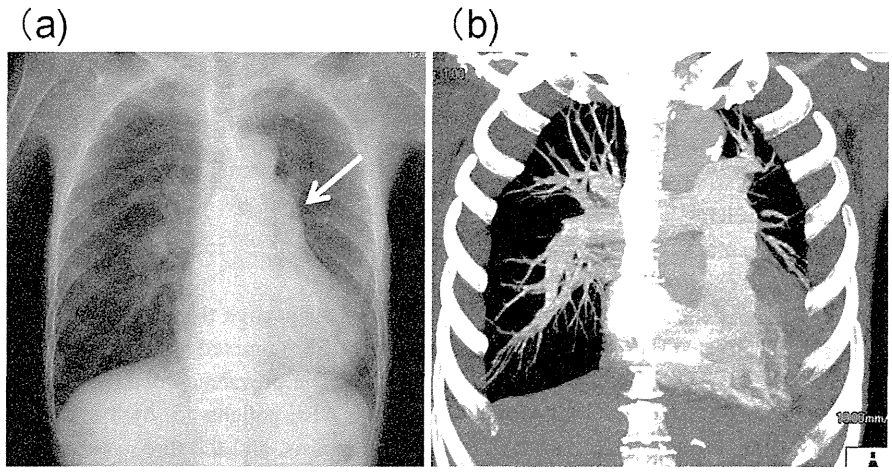


Figure 1. The chest X-ray and CT findings upon admission. (a) The chest X-ray showed a protrusion of the left second arch (arrow). (b) Enhanced CT showed no signs of pulmonary embolism.

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℃, her heart rate was 126 beats/min and her oxygen saturation level (SpO_2) 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

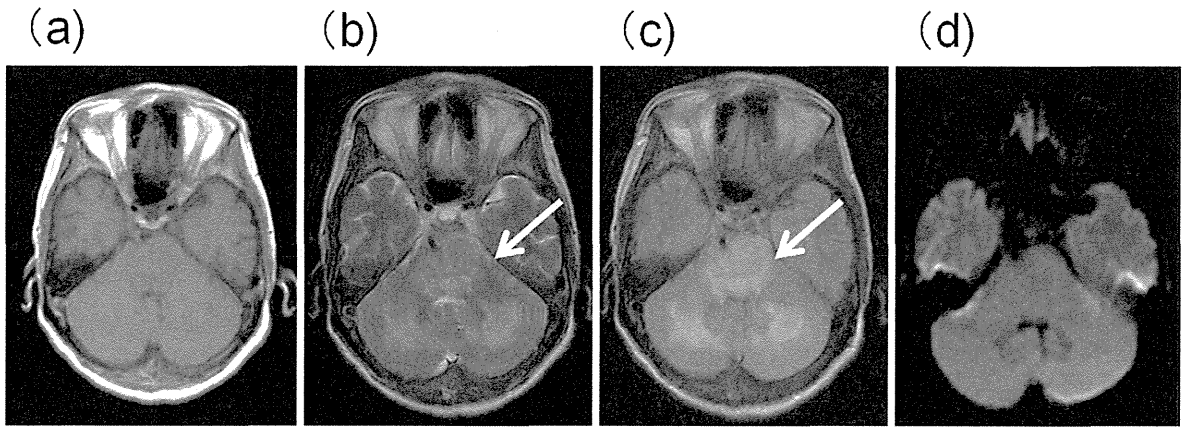


Figure 2. MRI findings of the brain stem and cerebellum opon admission. (a) T1WI. (b, c) T2WI and FLAIR. High intensity signals (arrow) were observed. (d) DWI.

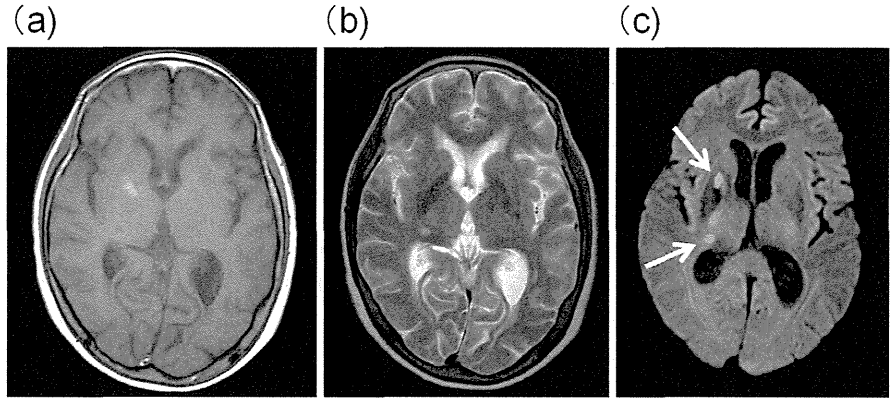


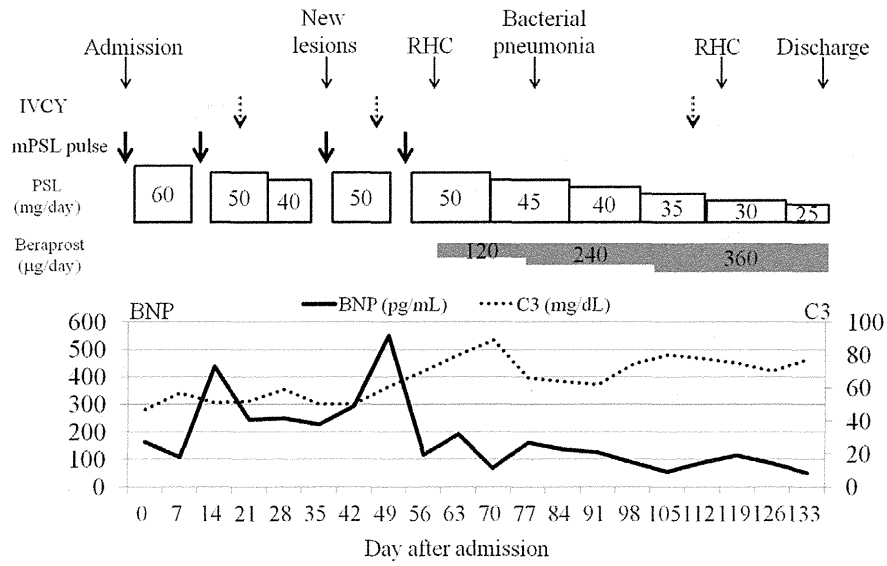
Figure 3. MRI findings of the right thalamus and caudate nucleus one month after admission. (a) T1WI. (b) T2WI. (c) DWI. High intensity signals (arrow) were observed.

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^5, 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)-α and interferon (IFN)-α 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 isointensity 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 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.

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 • sec • 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

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). Funauchi 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 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).

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