謝辞
最後に本研究で難治性潰瘍の自然暦に関して現在協力をいただいている各施設の先生方に深謝申し上げる。また、治験機器開発会社である STORTS MEDICAL 社 Marlinghaus 博士に潰瘍治療プロトコールに関する情報提供など多大なる協力をいただいた。改めて深謝申し上げる。

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E. 結論

難治性潰瘍を伴うSSC、SLE、MCTDは、治療困難かつ社会生活に多大な不利益をきたす難治性病態で、これまでの治療法の有効性は限定的なものであった。低出力衝撃波療法は、これまで対応に苦労したこれら病態に対する治療として、全く現存の加療と違った原理で働くものであり有効性と安全性に優れた治療法である。

平成26年度は、平成24年度から行われているPOC試験、自然歴レジストリーの結果を基礎にして、同治療法の保険収載を目指した検証試験の準備をおこない、実際に治験を開始、治験患者の登録を満了した。本治験の結果で低出力衝撃波療法の強皮症難治性潰瘍に対する有効性が確認されれば、保険収載され大きな社会貢献となる。

F．健康危険情報

なし

G．研究発表

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石井智徳

Meet the Expert22

難治性全身性エリテマトーデスに対する治療

日本リウマチ学会 2015

石井智徳

次世代の膠原病治療

膠原病に伴う難治性皮膚潰瘍に対する体外衝撃波療法

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膠原病における検査の目的と意義
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ＴＳＫ　希望　会報80号　平成25年

H．知的財産権の出願・登録状況
なし

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。6名の全身性強皮症患者に対して、治療を終了した。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、6例とも1回の治療後に改善が見られた。潰瘍の大きさは全例で縮小して再発は見られなかった。有害事象は起きていない。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。6例の症例で低周波衝撃波の治療を終了した。現在、7例目の症例に関して治療継続中である。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
6名の指尖部潰瘍を有する全身性強皮症患者をエントリーし、途中脱落なく、全例、治療を終了した。治療終了後のRCSは、6例全例で改善が認められた。潰瘍に関しては、全例で縮小が確認された。

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。それらの症例は既存の治療に抵抗性の症例が多い。今回の新規治療方法、低出力衝撃波治療は、著明に末梢循環不全を改善させる。低周波衝撃波により、指尖部潰瘍による疼痛の改善と、潰瘍部分の面積の縮小が確認された。東北大学の症例とあわせて、今後の解析をすすめる。

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開始した。有用性が確認された。

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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

【雑誌】欧文

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Watanabe R, **Fujii H**, Shirai T, Saito S, Hatakeyama A, Sugimura K, Fukumoto Y, **Ishii T**, **Harigae H**.	Successful use of intensive immunosuppressive therapy for treating simultaneously occurring cerebral lesions and pulmonary arterial hypertension in a patient with systemic lupus erythematosus.	Internal Medicine	53(6)	627-631	2014
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【雑誌】和文

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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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

Ryu Watanabe[1], Hiroshi Fujii[1], Tsuyoshi Shirai[1], Shinichiro Saito[1], Akira Hatakeyama[2], Koichiro Sugimura[3], Yoshihiro Fukumoto[3], Tomonori Ishii[1] and Hideo Harigae[1]

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 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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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

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

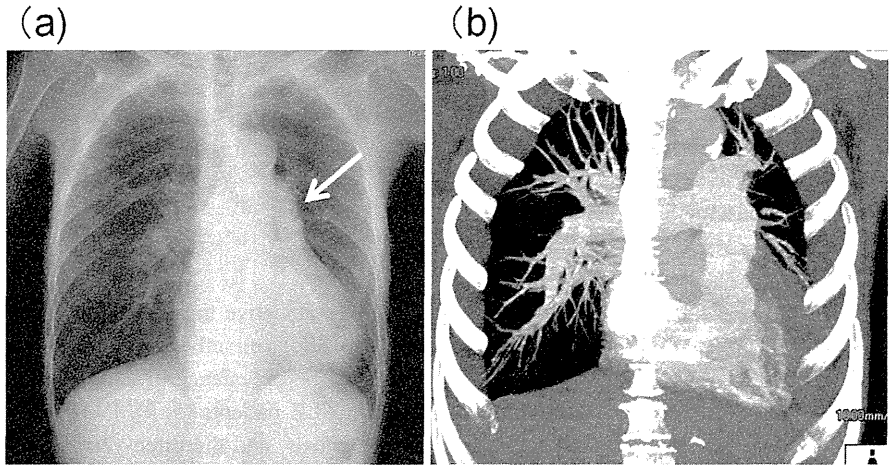


Figure 1. The chest X-ray and CT findings upon admission. (a) The chest X-ray showed a protrusion of the left second arch (arrow). (b) Enhanced CT showed no signs of pulmonary embolism.

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

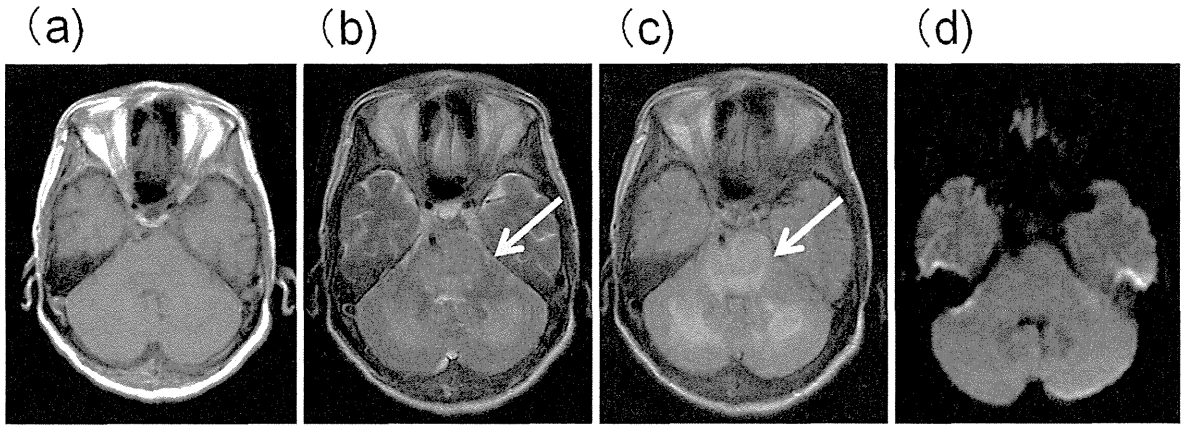


Figure 2. MRI findings of the brain stem and cerebellum opon admission. (a) T1WI. (b, c) T2WI and FLAIR. High intensity signals (arrow) were observed. (d) DWI.

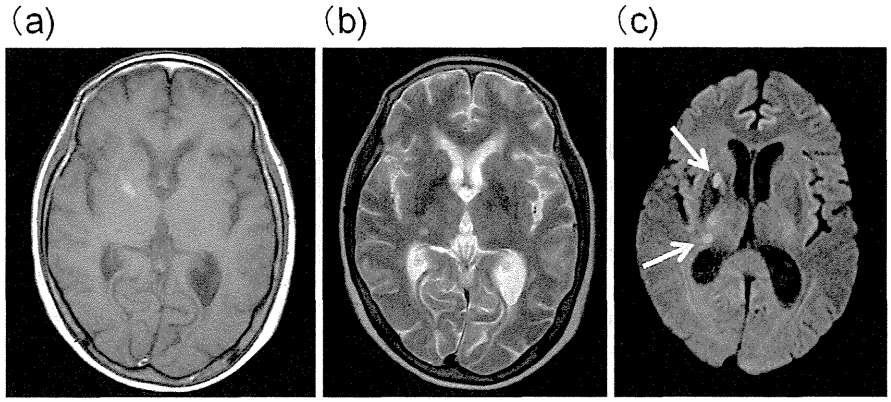


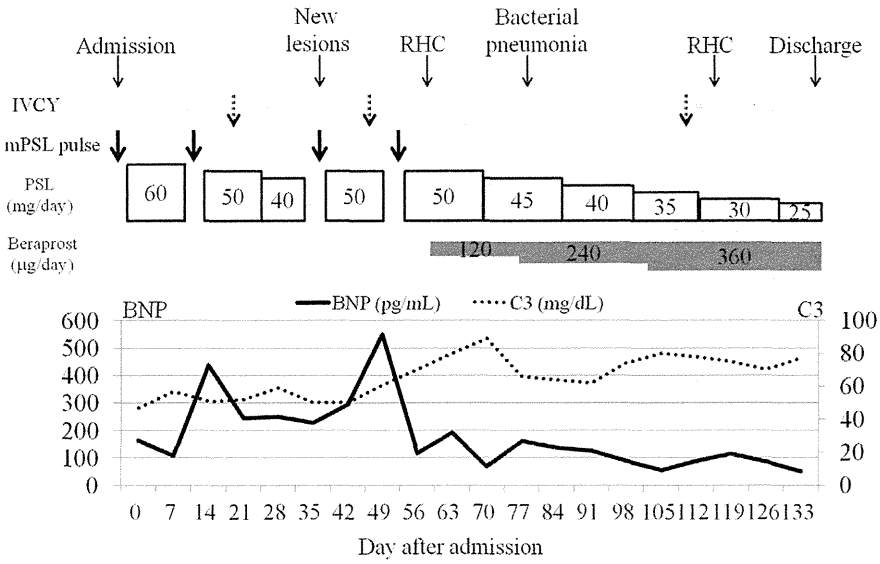
Figure 3. MRI findings of the right thalamus and caudate nucleus one month after admission. (a) T1WI. (b) T2WI. (c) DWI. High intensity signals (arrow) were observed.

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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Prevalence of Hepatitis B Virus Infection in Patients with Rheumatic Diseases in Tohoku Area: A Retrospective Multicenter Survey

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Hepatitis B virus (HBV) reactivation has been increasingly recognized in patients receiving chemotherapy and immunosuppressive therapy; however, the prevalence of HBV infection and rate of HBV screening in patients with rheumatic diseases remains unclear. In this study, we aimed to assess the prevalence of HBV infection and fulminant HBV hepatitis in patients with rheumatic diseases. We also investigated the rate of HBV screening before immunosuppressive therapy in patients with rheumatic diseases. A retrospective questionnaire survey was conducted in the North-east area (Tohoku) of Japan. Questionnaires, comprising 6 questions, were sent to 318 rheumatologists in May 2010, and responses were gathered until June 2011. In total, 71 rheumatologists (22.3%) responded to the survey. We enrolled 7,650 patients with rheumatoid arthritis (RA) and 1,031 patients with systemic lupus erythematosus (SLE). When limited to institutes at which almost all (≥ 90%) patients were tested for HBV serology, 1.1% (40/3,580) patients with RA and 0.3% (3/1,128) patients with SLE were positive for hepatitis B surface antigen (HBsAg), and 25.2% (177/703) patients with RA and 13.7% (34/248) patients with SLE were positive for hepatitis B core antibody (HBcAb).

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About one-third of rheumatologists did not check HBsAg and more than half did not check hepatitis B surface antibody (HBsAb) or HBcAb at all before therapy. Fulminant HBV hepatitis was observed in 1 RA patient who was current HBV carrier. In conclusion, the prevalence of HBV infection is high in patients with RA and SLE. HBV screening before immunosuppressive therapy should be strictly performed.

Keywords: hepatitis B virus; immunosuppressive therapy; rheumatoid arthritis; screening; systemic lupus erythematosus
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Introduction

After the widespread use of rituximab, an anti-CD20 monoclonal antibody, hepatitis B virus (HBV) reactivation has been increasingly recognized in patients receiving chemotherapy and immunosuppressive therapy (Oketani et al. 2012). Some studies have shown that HBV reactivation occurs not only in 'current HBV carriers', who are positive for hepatitis B surface antigen (HBsAg), but also in 'resolved HBV carriers', who are negative for HBsAg but positive for hepatitis B surface antibody (HBsAb) and/or hepatitis B core antibody (HBcAb) (Oketani et al. 2012). Particularly, HBV reactivation in resolved carriers may often cause a type of fulminant hepatitis, termed as *de novo* HBV hepatitis, with an extremely high mortality rate (Umemura et al. 2008).

Based on these results, Centers for Disease Control (CDC) recommended screening for HBV serology before chemotherapy and immunosuppressive therapy (Weinbaum et al. 2008). The American College of Rheumatology (ACR) also recommends HBV screening before immunosuppressive therapy (Singh et al. 2012), and recently, the Japanese College of Rheumatology (JCR) proposed an algorithm for HBV screening (Harigai et al. 2014). According to this algorithm, all patients should be screened for HBsAg before immunosuppressive therapy. In addition, those who are negative for HBsAg should be tested for HBsAb and HBcAb. HBV DNA quantification by real-time polymerase chain reaction (RT-PCR) should be performed in resolved HBV carriers. When HBV DNA becomes positive during and after therapy, prophylactic nucleoside analogs such as entecavir should be administered (Harigai et al. 2014). However, evidence to support validity of this algorithm to prevent severe hepatitis is not sufficient and especially needs to clarify cost-benefit relations.

HBV is endemic in Japan, and approximately 20% Japanese individuals are infected with HBV (Kiyosawa et al. 1994). Therefore, HBV screening before treatment should be more strictly performed in Japan than in other non-endemic countries. However, only few studies have reported the prevalence of HBV infection and rate of HBV screening in Japanese patients with rheumatic diseases (Urata et al. 2011; Mori 2011; Watanabe et al. 2013)

In this study, we assessed the prevalence of HBV infection and fulminant HBV hepatitis in patients with rheumatic diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). In addition, we investigated the rate of HBV screening before immunosuppressive therapy in patients with rheumatic diseases.

Methods

A retrospective questionnaire survey was conducted in the North-east area (Tohoku) of Japan. Questionnaires were sent to 318 rheumatologists in May 2010, and we waited for the response until June 2011. Following are the 6 questions listed in the questionnaire: (1) How many patients with RA have you treated? (2) How prevalent is HBV infection in patients with RA? (3) How many patients with SLE have you treated? (4) How prevalent is HBV infection in patients with SLE? (5) Do you examine serological HBV markers before treatment in patients with rheumatic diseases? (6) Have you ever experienced patients with fulminant HBV hepatitis? In this simplified questionnaire survey, we did not check a detail on sex, age, and hepatitis enzymes. We checked each HBV serological marker independently. Therefore, we did not check HBsAg positivity in HBcAb-positive patients.

Diagnoses of RA and SLE were based on RA classification criteria and SLE classification criteria (Arnett et al. 1988; Hochberg 1997; Aletaha et al. 2010). HBV serological tests were performed before starting immunosuppressive therapy at each institute. Immunosuppressive therapy was defined as the use of biologics, immunosuppressive disease-modifying antirheumatic drugs (DMARDs) including methotrexate (MTX), tacrolimus, leflunomide, mizoribine, corticosteroids, and other immunosuppressive agents (Harigai et al. 2014). The study protocol was approved by the ethics committees of Tohoku University Graduate School of Medicine.

Results

Overall response rate

Of the 318 rheumatologists, 71 (22.3%) responded to the questionnaire. Although we waited for the response until June 2011, all the answers obtained were before the Great East-Japan Earthquake (March 11, 2011).

Prevalence of HBV infection in patients with RA

In total, 7,650 patients with RA were enrolled. 0.7% (50/7,650) patients with RA were considered to be current HBV carriers, and 25.6% (214/837) were positive for HBcAb (Table 1). When the patient cohort was limited to institutes at which HBV serology was examined for almost all patients (≥ 90%), 1.1% (40/3,580) patients with RA were current HBV carriers, and 25.2% (177/703) were positive for HBcAb. Among patients receiving biologics, 0.3% (3/1,128) patients were positive for HBsAg, indicating that

Table 1. Positivity rate for each HBV serological marker in patients with RA.

		HBsAg	HBsAb	HBcAb
All patients	Total	50/7,650 (0.7%)	245/1,295 (18.9%)	214/837 (25.6%)
	at institutes ≥ 90% patients were examined	40/3,580 (1.1%)	169/1,011 (16.7%)	177/703 (25.2%)
Patients with biologics	Total	3/1,634 (0.2%)	68/512 (13.3%)	64/274 (23.4%)
	at institutes ≥ 90% patients were examined	3/1,128 (0.3%)	49/391 (12.5%)	57/199 (28.6%)

Table 2. Positivity rate for each HBV serological marker in patients with SLE.

	HBsAg	HBsAb	HBcAb
Total	3/1,031 (0.3%)	26/284 (9.2%)	38/267 (14.2%)
at institutes ≥ 90% patients were examined	3/704 (0.4%)	25/248 (10.1%)	34/248 (13.7%)

Table 3. Screening rate for each HBV marker before starting immunosuppressive therapy in 71 rheumatologists.

	HBsAg	HBsAb	HBcAb	HBV DNA
All patients	18 (25%)	2 (3%)	4 (6%)	0 (0%)
Not all patients	30 (42%)	24 (34%)	29 (41%)	21 (30%)
None	23 (32%)	45 (63%)	38 (54%)	50 (70%)
Total	71	71	71	71

biologics tended to be avoided in current HBV carriers. In contrast, biologics were prescribed for resolved HBV carriers at a similar rate to patients without HBV infection.

Prevalence of HBV infection in patients with SLE

Among 1,031 patients with SLE, 3 patients (0.3%) were positive for HBsAg (Table 2). When limited to institutes at which HBV serology was examined for almost all patients (≥ 90%), 0.4% (3/704) patients were positive for HBsAg and 13.7% (34/248) showed positive results for HBcAb, indicating that the prevalence of HBV infection in patients with SLE was lower than that in patients with RA ($p = 0.0002$, Chi-square test).

Rate of HBV screening before immunosuppressive therapy

The rate of screening for HBV serological markers before initiating treatment is summarized in Table 3. 71 rheumatologists answered it with respect to each HBV serological marker. HBsAg was examined for all patients by a relatively high number of clinicians (18/71, 25%); however, approximately one-third clinicians (23/71, 32%) did not check HBsAg at all and more than half of the clinicians did not check HBsAb or HBcAb at all.

Fulminant HBV hepatitis

Among all answers, fulminant HBV hepatitis was reported in 1 patient with RA. This patient was 70's female and current HBV carrier (HBsAg-positive, and hepatitis Be antigen-negative), but was treated by MTX 8 mg/week and prednisolone (PSL) 5 mg/day without nucleoside analogs in general physician's clinic. HBV DNA quantification was not performed in this clinic. The patient was admitted to a nearest university hospital and treated with plasma exchange and entecavir, but died of fulminant HBV hepatitis confirmed by HBV DNA quantification and autopsy.

Discussion

This retrospective multicenter questionnaire survey conducted in the North-east area of Japan demonstrated that approximately 1% patients with RA were current HBV carriers and more than 25% were considered to be resolved carriers. Previous reports in Japan showed similar results estimating that 25% (60/239) patients in Kumamoto and 31.5% (135/428) in Aomori were infected with HBV (Urata et al. 2011; Mori 2011), indicating that more than one-fourth patients with RA may be infected with HBV in Japan. However, the number of patients enrolled in this study is much larger than previous reports. To our knowledge, this is the largest study regarding prevalence of HBV infection in RA patients in Japan. Our data suggest that HBV screening and appropriate management of HBV should be strictly performed when initiating immunosuppressive therapy. Prevalence of HBV infection was significantly lower (16.5%; 41/248) in patients with SLE than that in patients with RA (Watanabe et al. 2013). It has been reported that older adults had a higher frequency of HBV