

[Case report]

## A CASE OF BEHÇET'S DISEASE AND SYSTEMIC SCLEROSIS DEVELOPING AFTER AN EARTHQUAKE DISASTER

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**Abstract :** Stressful life situation can trigger the onset and flare-ups of Behçet's disease (BD). In addition, the association of systemic sclerosis (SSc) and BD is rare. In this study, we report a patient who had Sjögren's syndrome as a primary disease and subsequently developed SSc and BD after an earthquake disaster and the death of her father.

**Key words :** Behçet's Disease, Systemic sclerosis

### INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disorder characterized by increased fibroblast activity resulting in accelerated collagen deposition and widespread vascular abnormalities, eventually leading to systemic fibrosis. The mechanism of fibrogenesis in SSc is thought to involve various cytokines produced by cells infiltrating the tissues, affecting fibroblasts and inducing the overproduction of collagens. Activated T and B cells infiltrate the lesions of patients with SSc, and activated B cells appear in the peripheral blood, reflecting autoantibody production and hypergammaglobulinemia in patients with SSc<sup>1)</sup>.

Behçet's Disease (BD) is a disorder of unknown etiology causing various symptoms, typically oral aphtha, genital ulcer, and ocular inflammation. BD-specific autoantibody or autoantigen reactive T cells have not been found to date, and the pathogenesis of BD remains to be established. However, increased functions of neutrophils such as chemotaxis, phagocytosis, and the overproduction of superoxide may cause tissue damage in patients with BD. Furthermore, clinical evidence suggests that hormonal alterations and emotional stress affect the clinical course and disease activity of BD<sup>2,3)</sup>.

SSc is usually considered a Th2-dominant

disease because fibrogenesis can be induced when Th2 cytokines (IL-4, IL-13) predominate over Th1 cytokines. In contrast, BD is considered to be a Th1-type autoimmune disease because Th1-cell predominant cytokines, such as TNF- $\alpha$ , IL-2, IL-8, and IFN- $\gamma$ , are increased in patients with BD. Therefore, SSc and BD are considered to be different from each other in the terms of Th1-Th2 balance. In addition, the association between SSc and BD is rare<sup>1-3)</sup>.

In this study, we report a patient who had Sjögren's syndrome as a primary disease and subsequently developed SSc and BD after an earthquake disaster and the death of her father.

### CASE PRESENTATION

The patient was a 32-year-old woman who developed dry eyes and Raynaud's phenomenon in December 2009. The condition progressed and she first visited our clinic in March 2010. She had a rash on the fingers but no skin stiffening or fingertip ulceration. No abnormal data were observed with regard to peripheral blood and hepatic and renal function. Rheumatoid factor was positive, the anti-nuclear antibody (ANA) titer was 1 : 1280 (speckled and nucleolar patterns), and anti-ssA antibody was positive. The Schirmer's test revealed that the

Table 1. Laboratory data on the first visit

CBC		Blood Chemistry		Serological Findings	
WBC	8,200/mm <sup>3</sup>	TP	7.5 g/dL	ANA	1,280 × (Sp, Nu)
Neut.	76%	Alb	4.3 g/dL	anti-U1RNP	1.9 U/mL
Lym.	17%	AST	17 IU/L	anti-ssA	23.7 U/mL
Mono.	6%	ALT	12 IU/L	anti-ssB	4.0 U/mL
Eosino.	1%	LDH	193 IU/L	anti-Sc170	<0.5 U/mL
RBC	387 × 10 <sup>4</sup> /mm <sup>3</sup>	ALP	106 IU/L	<b>Saxon test</b>	
Hb	13 g/dL	TB	0.9 mg/dL	0.52 g/2 min	
Ht	38.3%	BUN	14 mg/dL	(positive)	
Plt	20.3 × 10 <sup>4</sup> /mm <sup>3</sup>	Crea	0.47 mg/dL	<b>Schirmer's test</b>	
<b>Blood Coagulation</b>		UA	2.5 mg/dL	rt. 6 mm	
PT	90%	CRP	<0.03 mg/dL	lt. 3 mm	
PTINR	1.03	IgG	1,636 mg/dL	(positive)	
APTT	29.3 s	IgA	319 mg/dL		
Fib	233 mg/dL	IgM	121 mg/dL		
		C3	68 mg/dL		
		C4	19 mg/dL		

Table 2. Laboratory data when the patient developed Behçet's Disease

CBC		Blood Chemistry		Cytokines (serum)	
WBC	6,700/mm <sup>3</sup>	AST	17 IU/L	IL-4	61.5 pg/ml
Neut.	78%	ALT	9 IU/L	IFN-γ	not detectable
Lym.	12%	LDH	195 IU/L	IL-17	not detectable
Mono.	9%	ALP	128 IU/L	<b>HLA</b>	
Eosino.	1%	T-Bil	0.9 mg/dL	A2, A24, B51, B61	
RBC	380 × 10 <sup>4</sup> /mm <sup>3</sup>	BUN	13 mg/dL		
Hb	12.3 g/dL	Cr	0.51 mg/dL		
Ht	35.6%	CRP	1.25 mg/dL		
Plt	20.9 × 10 <sup>4</sup> /mm <sup>3</sup>				

right and left eye were 6 and 3 mm, respectively. The result of the Saxon test was 0.52 g/2 min (Table 1), and the patient was diagnosed with Sjögren's syndrome.

The patient's residence was situated in the evacuation zone due to the Great East Japan Earthquake and the Fukushima Nuclear Accident in March 2011. Consequently, the patient was forced to evacuate and move three times. Subsequently, Raynaud's phenomenon progressed and skin stiffening of the fingers was observed in May 2012. An anticentromere antibody test was positive (EIA index ; 64.7), and swelling and hyperplasia in the dermal collagen fibers were confirmed by a skin biopsy. She was diagnosed with limited cutaneous systemic sclerosis and palliative therapy was initiated.

In August 2012, the patient's father died and she experienced severe mental stress. The patient

presented to our clinic again with fever, a painful oral ulcer, genital pain, and a painful rash in October 2012. Oral ulcer, genital ulcer, and subcutaneous nodules were observed. No ophthalmologic abnormalities were observed. There were no abnormal data on peripheral blood or hepatic and renal function. C-reactive protein and serum IL-4 levels were elevated, whereas serum IFN-γ and IL-17 levels were undetectable. HLA B51 was positive (Table 2). Consequently, the patient was diagnosed with incomplete BD. Prednisolone was administered at an initial dose of 15 mg and was gradually decreased as the symptoms improved. At present, the patient is being treated with colchicine for BD.

## DISCUSSION

To date, four cases of SSc complicated by BD have been reported and three of these cases were

Table 3. Characteristics of reported cases of Behçet's Disease complicated by systemic sclerosis

Cases	Age/Sex	Type of SSc	Autoantibodies	BD findings	HLA B51	Other diseases
Ishi <i>et al.</i> <sup>4)</sup> 1974	24/M	sine Scleroderma	n.d.	OU, GU, intestinal ulcer	n.d.	None
Choy <i>et al.</i> <sup>5)</sup> 1993	54/F	limited cutaneous	Antinuclear Ab (+) Anticentromere Ab (-) Anti-topo I Ab (-)	OU, GU, Superficial thrombophlebitis	Negative	SjS
Hosono <i>et al.</i> <sup>6)</sup> 1994	55/F	limited cutaneous	Antinuclear Ab (+) Anticentromere Ab n.d. Anti-topo I Ab (-)	OU, GU, EN Arthritis	Positive	None
Yokota <i>et al.</i> <sup>7)</sup> 2004	62/M	limited cutaneous	Antinuclear Ab (-) Anticentromere Ab (-) Anti-topo I Ab (-)	OU, GU, EN Esophageal ulcer	Negative	Hepatitis C
This case	32/F	limited cutaneous	Antinuclear Ab (+) Anticentromere Ab (+) Anti-topo I Ab (-)	OU, GU, EN	Positive	SjS

SSc : Systemic sclerosis, BD : Behçet' Disease, n.d. : not described, OU : Oral ulcer, GU : Genital ulcer, EN : Erythema nodosum, SjS : Sjögren's syndrome

identified in Japan<sup>4-7)</sup>. The clinical findings of previously reported cases and the present case are shown in Table 3.

In the present patient, only the serum IL-4 level was elevated, whereas serum IFN- $\gamma$  and IL-17 levels were undetectable. Helper-T cells are classified as Th1 or Th2, based on the cytokines produced, and the resulting pathologies are frequently explained by the Th1-Th2 balance. The major Th1 cytokine IFN- $\gamma$  suppresses fibrogenesis, whereas the Th2 cytokines IL-4 and IL-13 enhance fibrogenesis. Thus, it is considered that fibrogenesis can be induced when Th2 cytokines predominate over Th1 cytokines<sup>1)</sup>. Consequently, SSc has been considered to be a Th2 cell-dominant disease. In contrast, BD is considered to be a Th1-type autoimmune disease because Th1-cell predominant cytokines, such as TNF- $\alpha$ , IL-2, IL-8, and IFN- $\gamma$ , are increased in patients with BD<sup>2,3)</sup>.

Recently, Th17 cells, which produce the typical cytokine IL-17, have also been implicated in the pathologies of SSc and BD. Elevated levels of IL-17 and increased number of Th17 cells have been reported in the blood of patients with SSc. A study of bleomycin-evoked skin stiffening in IL-17A knockout mice showed skin stiffening attenuations. Furthermore, IL-17 has been confirmed to enhance the production of TGF- $\beta$  from fibroblasts *in vitro*, and Th17 may be involved in the pathology of SSc<sup>8-10)</sup>. On the other hand, serum levels of IL-23, which stimulate IL-17 production, also correlate with the progression of uveitis in patients with BD, and the IL-17 mRNA expression is enhanced in the lesions of erythema nodosum. Thus, IL-17 is in-

involved in neutrophilic migration and excessive IL-17 may be a cause of neutrophilic hyperfunction in patients with BD<sup>11,12)</sup>. Although we did not observe elevated serum IL-17 levels in this patient, it is interesting that IL-17 is implicated in the pathology of BD and SSc, which are considered to be etiologically different from each other in the terms of Th1-Th2 balance.

To date, no autoantibody or autoantigen-reactive T cells have been correlated to BD. Thus, it is difficult to definitively explain the pathogenetic mechanism of BD. However, the rate of HLA B51 positivity is high among Japanese BD patients. Major histocompatibility complex class I molecules present intracellular antibodies to T cells. Therefore, it is possible that antigens with a high affinity to HLA B51 play a role in the onset of BD. However, the correlation between the onset of BD and HLA B51 positivity is strong in prevalent regions, including Japan, but is weak in non-prevalent areas, including Europe and the United States. Approximately 10%-15% of healthy Japanese are HLA B51-positive<sup>13)</sup>. Therefore, it is unclear whether HLA B51 is directly correlated with the onset of BD, although it is considered a disease-susceptibility gene.

The patient was diagnosed with Raynaud's phenomenon before the earthquake disaster and the ANA pattern was nucleolar; therefore, the patient originally had a predisposition towards SSc. However, the mean annual air temperature at the relocation site was lower than that at the previous relatively moderate site. Furthermore, the living conditions were not good, leading to a marked deterioration of Raynaud's phenomenon. It is possible

that the changes in the environment, including air temperature, were also responsible for the development of the SS.

Nearly 4 years after the earthquake and tsunami that struck Japan in 2011, about 236,000 people who lost their homes in the tsunami or were forced to evacuate because of radiation remain displaced in Japan. Kukihara *et al.* reported that 53.5% of the evacuees experienced clinical symptoms of post-traumatic stress disorder and 66.8% showed symptoms of depression in a study of 241 people from the town of Hirono, Fukushima Prefecture<sup>14</sup>. Furthermore, according to the Reconstruction Agency data, over 1,700 residents of Fukushima died from complications related to stress and other problems following the accident. These data indicate that stress caused by the loss of homes led to a marked increase in medical problems among evacuees, especially mental illnesses, such as depression.

The patient developed BD after repeatedly moving three times and faced severe stress due to the death of her father. We have frequently observed patients in whom skin and eye symptoms of BD aggravate due to mental stress. Some case reports have supported the relationship between mental stress and the course and activity of BD. Karlıdag *et al.* confirmed the relationship between BD and mental stress in 79.2% patients with BD; Toronto Alexithymia Scale, Hamilton Depression Rating Scale, and Beck Anxiety Inventory scores were higher in the BD group compared with the control group<sup>15</sup>. Anxiety and depression have also been observed in many patients with BD<sup>15,16</sup>. Koptagel-Ilal *et al.* reported that all BD patients had experienced stressful life situations prior to the onset of the disease and their problems included socioeconomic and/or family stresses<sup>17</sup>. In the present case, it is possible that serious stress, related to the death of her father combined with anxiety caused by evacuation, climate, and living environmental changes lead to the onset of BD.

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#### CONFLICT OF INTEREST

The authors have no conflicting financial interests.

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