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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 SSc1).

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 BD2,3).

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-α, IL-2, IL-8, and IFN-γ, 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 rare1-3).

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
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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

| CBC | Blood Chemistry | Serological Findings |
|-----|-----------------|----------------------|
| WBC 8,200/mm³ | 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-Scl70 <0.5 U/mL |
| RBC 387 × 10⁶/mm³ | ALP 106 IU/L | |
| Hb 13 g/dL | TB 0.9 mg/dL | |
| Ht 38.3% | BUN 14 mg/dL | (positive) |
| Plt 20.3 × 10⁶/mm³ | Crea 0.47 mg/dL | |
| Blood Coagulation | UA 2.5 mg/dL | |
| PT 90% | CRP <0.03 mg/dL | |
| PTINR 1.03 | IgG 1,636 mg/dL | |
| APTT 29.3 s | IgA 319 mg/dL | |
| Fib 233 mg/dL | IgM 121 mg/dL | |
| C3 31 mg/dL | (positive) | |
| C4 37 mg/dL | |

| CBC | Blood Chemistry | Cytokines (serum) |
|-----|-----------------|-------------------|
| WBC 6,700/mm³ | 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 | |
| Eosino. 1% | T-Bil 0.9 mg/dL | |
| RBC 380 × 10⁶/mm³ | 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 × 10⁹/mm | |

**Table 1.** Laboratory data on the first visit

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

**DISCUSSION**

To date, four cases of SSC complicated by BD have been reported and three of these cases were
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-γ 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-γ 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. 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-α, IL-2, IL-8, and IFN-γ, are increased in patients with BD.

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-β from fibroblasts in vitro, and Th17 may be involved in the pathology of SSc.

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 et al.   | 24/M    | sine        | n.d.                            | OU, GU, intestinal ulcer | n.d.    | None          |
| 1974          |         | Scleroderma |                                 |                      |         |               |
| Choy et al.   | 54/F    | limited     | Antinuclear Ab (+)               | OU, GU, Superficial thrombophlebitis | Negative | SjS           |
| 1993          |         | cutaneous   | Anticentromere Ab (-)            |                     |         |               |
| Hosono et al. | 55/F    | limited     | Antinuclear Ab (+)               | OU, GU, EN Arthritis | Positive | None          |
| 1994          |         | cutaneous   | Anticentromere Ab n.d.           |                     |         |               |
| Yokota et al. | 62/M    | limited     | Antinuclear Ab (-)               | OU, GU, EN Esophageal ulcer | Negative | Hepatitis C   |
| 2004          |         | cutaneous   | Anticentromere Ab (-)            |                     |         |               |
|              |         |             | Anti-topo I Ab (-)               |                      |         |               |
| This case     | 32/F    | limited     | Antinuclear Ab (+)               | OU, GU, EN           | Positive | SjS           |
|              |         | cutaneous   | Anticentromere Ab (+)            |                     |         |               |
|              |         |             | Anti-topo I Ab (-)               |                      |         |               |

SSc: Systemic sclerosis, BD: Behçet’s Disease, n.d.: not described, OU: Oral ulcer, GU: Genital ulcer, EN: Erythema nodosum, SjS: Sjögren’s syndrome.
that the changes in the environment, including air temperature, were also responsible for the development of the SSc.

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 Prefecture14). 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. Karlidag 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 group15). Anxiety and depression have also been observed in many patients with BD15,16). Koptagel-llal et al. reported that all BD patients had experienced stressful life situations prior to the onset of the disease and their problems included socio-economic and/or family stresses17). 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.

REFERENCES

1. Varga J, Denton CP. Systemic Sclerosis and the Scleroderma-Spectrum Disorders. In : Firestein GS, Budd RC, Harris ED Jr., McInnes IB, Ruddy S, Sergent JS, eds. KELLEY’S Textbook of Rheumatology, 8th ed. SAUNDERS ELSEVIER, Philadelphia, 1311–1351, 2009.
2. Louden BA, Jorizzo L. Behcet’s Disease. In : Firestein GS, Budd RC, Harris ED Jr., McInnes IB, Ruddy S, Sergent JS, eds. KELLEY’S Textbook of Rheumatology, 8th ed. SAUNDERS ELSEVIER, Philadelphia, 1475–1480, 2009.
3. Türsen Ü. Pathophysiology of the Behcet’s disease. Patholg Res Int, 2012. doi : 10.1155/2012/493015.
4. Ishiii Y, Chisaka N, Muroya T. Behçet byo wo utagawareta shinkousei kyouhishou (PSS) no ichirei (in Japanese). Hokkaido igaku zasshi, 49: 567–568, 1974.
5. Choy E, Kingsley G, Panayi G. Systemic sclerosis occurring in a patient with adamantiades–Behcet’s disease. Brit J Rheumatol, 32 : 160–161, 1993.
6. Hosono T, Kondo H. Behcet’s disease associated with Systemic Sclerosis (Scleroderma) (in Japanese). Connect Tissue, 25 : 271–275, 1994.
7. Yokota K, Hirano H, Akiba H, et al. A case of Behcet’s disease with esophageal ulcers complicated with systemic sclerosis, chronic hepatitis C, and pancytopenia (in Japanese). Jpn J Clin Immunol, 27 : 164–170, 2004.
8. Murata M, Fujimoto M, Matsushita T, et al. Clinical association of serum interleukin-17 levels in systemic sclerosis : is systemic sclerosis a Th17 disease? J Dermatol Sci, 50 : 240–242, 2008.
9. Nakashima T, Jinnin M, Yamane K, et al. Impaired IL–17 signaling pathway contributes to the increased collagen expression in scleroderma fibroblasts. J Immunol, 188 : 3573–3583, 2012.
10. Okamato Y, Hasegawa M, Matsushita T, et al. Potential roles of interleukin-17A in the development of skin fibrosis in mice. Arthritis Rheum, 64 : 3726–3735, 2012.
11. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. N Engl J Med, 361 : 888–898, 2009.
12. Legn RX, Chen GM, Pan HF, Ye DQ. The role of IL-23/IL-17 axis in the etiopathogenesis of Behcet’s disease. Clin Rheumatol, 29 : 1209, 2010.
13. de Menthon M, Lavalley MP, Maldini C, Guillemin L, Mahr A. HLA-B51/B5 and the risk of Behcet’s disease : a systematic review and meta-analysis of case-control genetic association studies. Arthritis Rheum, 61 : 1287, 2009.
14. Kukihara H, Yamawaki N, Uchiyama K, Arai S, Horikawa E. Trauma, depression, and resilience of earthquake/tsunami/nuclear disaster survivors of Hirono, Fukushima, Japan. Psychiatry Clin Neurosci, 68: 524, 2014.

15. Karlidag R, Unal S, Evereklioglu C, Sipahi B, Er H, Yologlu S. Stressful life events, anxiety, depression and coping mechanisms in patients with Behcet’s disease. J Eur Acad Dermatol Venereol, 17: 670-675, 2003.

16. Evereklioglu C, Cokkeser Y, Doganay S, Er H, Kizilay A. Audio-vestibular evaluation in patients with Behcet’s syndrome. J Laryngol Otol, 115: 704-708, 2001.

17. Koptagel Ilal G, Tunçer Ö, Enbiyaoğlu G, Bayramoğlu Z. A psychosomatic investigation of Behcet’s disease. Psychother Psychosom, 40: 263-271, 1983.