

[ CASE REPORT ]

## Behçet's Disease with Severe Autonomic Disorders Developing after Herpes Zoster

Serina Koto<sup>1,2</sup>, Masataka Umeda<sup>1,3</sup>, Hiroaki Kawano<sup>4</sup>, Yushiro Endo<sup>1</sup>, Toshimasa Shimizu<sup>1</sup>,  
Tomohiro Koga<sup>1</sup>, Kunihiro Ichinose<sup>1</sup>, Hideki Nakamura<sup>1</sup>, Akihiro Mukaino<sup>5</sup>,  
Osamu Higuchi<sup>6</sup>, Shunya Nakane<sup>5</sup> and Atsushi Kawakami<sup>1</sup>

### Abstract:

A 58-year-old Japanese woman with herpes zoster developed Behçet's disease (BD) with symptoms including orthostatic intolerance as an autonomic disorder. Multiple immune-suppressive therapies and a  $\beta$ -blocker successfully controlled both the disease activity of BD and the autonomic disorders. A cytokine multiplex analysis of her serum revealed the elevation of proinflammatory cytokines [interleukin (IL)-1, IL-6, IL-12, tumor necrosis factor alpha (TNF $\alpha$ ), and interferon gamma (IFN- $\gamma$ )] and a low IL-10 concentration. IL-10 production is reported to be important for defense against herpes zoster virus (VZV). Insufficient IL-10 production is reported in BD. The reactivation of VZV with this cytokine profile suggests that BD will develop with various symptoms, including severe autonomic disorders.

**Key words:** Behçet's disease, herpes zoster, autonomic disorder, IL-10

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### Introduction

Behçet's disease (BD) is an autoinflammatory disorder characterized by recurrent oral ulcers, skin symptoms, genital ulcers, and ocular inflammation. Autonomic disorders are also reported as common symptoms in BD (1). BD has been considered a multifactorial disease, the pathogenesis of which involves both genetic and environmental factors (2). Several viruses are considered as environmental factors that trigger the pathogenesis of BD (3). We herein describe the case of a patient with BD who had a gene associated with disease-susceptibility and who developed symptoms, including severe autonomic disorders, after contracting herpes zoster infection.

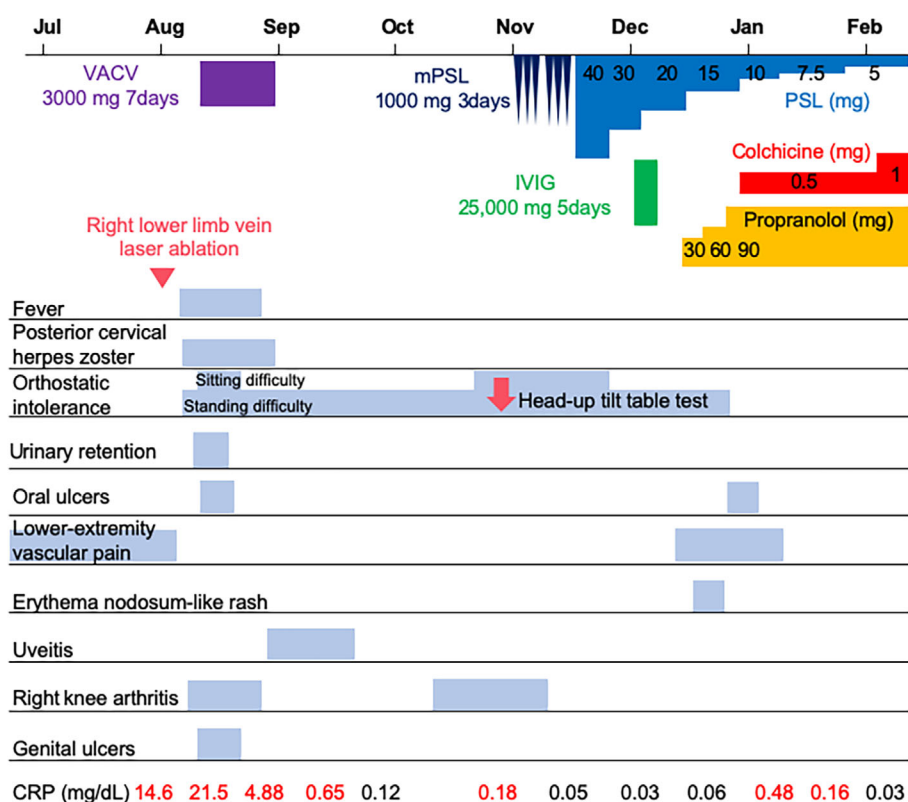
### Case Report

The patient was a 58-year-old Japanese woman who had been admitted to another hospital one week previously due to skin eruptions with pain at the back of her neck, fever, and right knee arthralgia. At the same time, she also developed symptoms, including dizziness, lightheadedness, and near-syncope that worsened upon maintaining upright posture and which was alleviated by recumbency. These symptoms were the same as the symptoms of orthostatic intolerance described in previous reports (4, 5). Herpes zoster was diagnosed based on the observation of skin eruptions that appeared as typical fluid-filled blisters. All blisters were completely crusted after treatment with valacyclovir; however, at 3 weeks after her admission to that hospital, BD was suspected and she was transferred to our hospital due to the development of genital ulcers, oral ulcers, and a positive Pa-

<sup>1</sup>Department of Immunology and Rheumatology, Nagasaki University Graduate School of Biomedical Sciences, Japan, <sup>2</sup>Department of Rheumatology, Sasebo City General Hospital, Japan, <sup>3</sup>Medical Education Development Center, Nagasaki University Hospital, Japan, <sup>4</sup>Department of Cardiovascular Medicine, Nagasaki University Graduate School of Biomedical Sciences, Japan, <sup>5</sup>Department of Molecular Neurology and Therapeutics, Kumamoto University Hospital, Japan and <sup>6</sup>Department of Clinical Research, Nagasaki Kawatana Medical Center, Japan

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Correspondence to Dr. Masataka Umeda, masatakau0807@gmail.com



**Figure 1.** The patient's clinical course. VACV: valacyclovir, mPSL: methyl prednisolone, PSL: prednisolone, IVIG: intravenous immunoglobulin

**Table.** Comparison of Our Patient's Data with Those of 57 Healthy Individuals.

	Present case	Healthy individuals (95%CI)
IL-10	undetectable	1.15-6.39
IFN- $\gamma$	98.96	14.7-32.9
IL-1 $\beta$	29.5	1.48-4.07
IL-6	48.6	1.22-6.24
IL-12 p70	55.37	6.29-36.0
TNF $\alpha$	19.2	8.78-11.8

The results of the cytokine multiplex array of the patient's serum at the time of admission to our hospital are shown. The 95% confidence interval (CI) of the serum cytokine levels from healthy individuals (n=57) are indicated as a control. Units: pg/mL.

IL: interleukin, IFN- $\gamma$ : interferon gamma, TNF $\alpha$ : tumor necrosis factor alpha

therapy test result. She had also suffered from urinary retention as bladder dysfunction for 1 week.

The patient's clinical course is illustrated in Fig. 1. On physical examination, her body temperature was 37.5°C and her other vital signs were normal. A physical examination revealed genital ulcers, tenderness and swelling of the right knee. A neurological examination revealed no abnormalities with the exception of an impaired left pupil direct light reflex.

The initial laboratory studies revealed the following: her blood and serum chemistry test results were normal, with the exception of the following findings: erythrocyte sedimentation rate (ESR), 78 mm/h; C-reactive protein (CRP),

4.88 mg/dL; fibrin degradation products (FDP), 10.7  $\mu$ g/mL; and D-dimer, 4.9  $\mu$ g/mL. Tests for rheumatoid factor, antinuclear antibodies (ANA), anti-CCP antibodies, and anti-ganglionic acetylcholine receptor antibodies were all negative. The viral markers for hepatitis B, cytomegalovirus, herpes simplex virus (HSV), and varicella zoster virus (VZV) all showed a prior infection pattern. An HLA-A, -B serotype analysis revealed that the patient had the disease-sensitive alleles for BD: A26 and B51.

A cytokine multiplex array using serum obtained at the time of admission to our hospital revealed increased levels of proinflammatory cytokines [interleukin (IL)-1 $\beta$ , IL-6, IL-12 p70, tumor necrosis factor alpha (TNF $\alpha$ ), and interferon gamma (IFN- $\gamma$ )], in comparison to serum from healthy controls, whereas IL-10 was undetectable in the patient's serum (Table).

The results of a cerebrospinal fluid analysis showed only a mildly increased number of white blood cells [18/ $\mu$ L (mononuclear cells 94%)], and the IL-6 level was 2.8 pg/mL (normal range, <16.55 pg/mL (6)). Magnetic resonance imaging of the brain showed no evidence of encephalitis. Ultrasonography revealed deep vein thrombosis (DVT) in the right soleus muscle vein. An ophthalmologic examination revealed iritis as anterior uveitis in both eyes.

At 2 weeks after the patient's admission to our hospital, these symptoms (with the exception of orthostatic intolerance) improved spontaneously without any immunosuppressive treatment. After the administration of warfarin for DVT, she was discharged from our hospital.

However, at 2 months after discharge, the patient was admitted to our hospital again due to an exacerbation of the orthostatic intolerance and relapse of the right knee arthritis. The recurrence of oral ulcers and the first development of erythema nodosum (EN)-like eruptions (red and tender nodules in both legs) (Fig. 2) were also observed at this point. We therefore diagnosed the patient with BD based on the current and previous findings. To examine her orthostatic intolerance objectively, autonomic function tests were conducted. The analysis of the coefficient of variation of R-R interval (CVR-R) during deep breathing showed a decline (2.12%) and the disappearance of respiratory-induced variations.

A heart rate variability (HRV) analysis using 24-hour Holter monitor revealed a high-frequency (HF) value of



**Figure 2.** Erythema nodosum (EN)-like eruptions. Multiple thumb-sized erythemas with tenderness were observed on both legs at the second admission to our hospital.

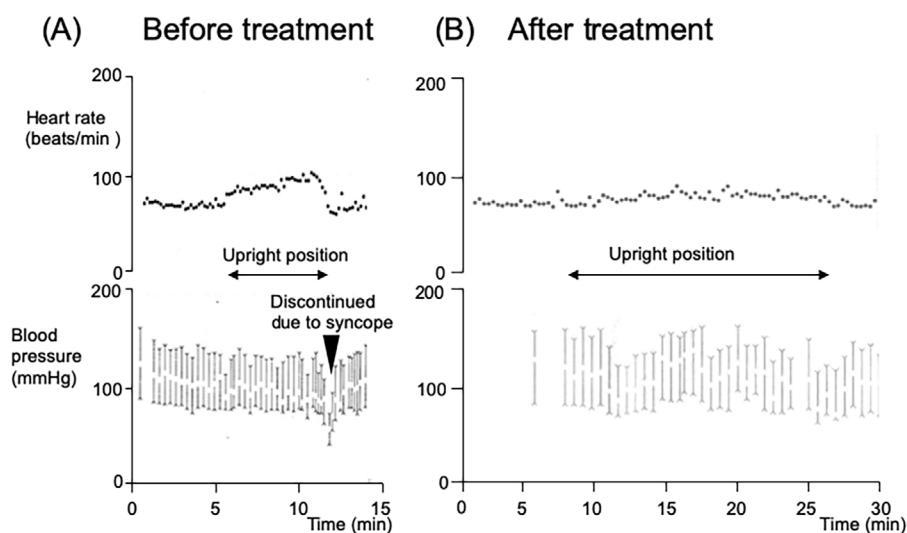
263.66 [age mean±standard deviation (SD): 514.5±99.7] and a low-frequency/high-frequency (LF/HF) ratio of 1.28 (age mean±SD: 1.39±0.14). A head-up tilt table test (HUT) showed neurally mediated syncope (mixed type) (Fig. 3A).

Based on these results, we hypothesized that the patient's orthostatic intolerance was caused by autonomic dysfunction associated with BD. We initiated treatment with methylprednisolone (mPSL) pulse therapy (1,000 mg/day for 3 days, twice) and then administered oral prednisolone (40 mg/day). These treatments effectively improved the patient's arthritis, but her orthostatic intolerance persisted. Additional therapy with intravenous immunoglobulin (IVIG) (25,000 mg/day for 5 days) and colchicine (starting at 0.5 mg/day, increasing to 1 mg/day) improved the orthostatic intolerance. The addition of propranolol as a  $\beta$ -blocker (starting at 30 mg/day, increasing to 90 mg/day) was also effective for the patient's remaining symptom of orthostatic intolerance.

At a 2-year follow-up examination, the patient's orthostatic intolerance had recovered to a level at which she could perform housekeeping, and a HUT was negative (Fig. 3B). The dosage of propranolol had been reduced, and colchicine alone had completely controlled the BD activity without relapse.

## Discussion

Our patient developed BD with various complications, including severe autonomic disorder, which might have been triggered by varicella zoster. Several reports have mentioned a relationship between BD and the Herpesviridae family. It has been reported that the rate of serological positivity for



**Figure 3.** The patient's autonomic disorder, which was detected by an abnormal head-up tilt table test (HUT) result, was reversible by treatment. A: Before treatment. An increase in the heart rate ( $\geq 30$  beats/min) and nausea developed within 10 min after tilting by 70°. At 20 min after the tilting, syncope with hypotension and bradycardia were observed. Due to syncope, the HUT was immediately discontinued, and the patient recovered from these symptoms. Based on these results, neurally-mediated syncope (mixed type) was diagnosed. B: After treatment. No changes in heart rate, hypotension, syncope or nausea were observed during tilting in a new HUT session.

VZV IgG and IgM antibodies does not differ between patients with BD and those with other skin diseases (7); however, another report showed that the VZV IgG titer in BD patients with neurological involvement was higher than that in those without neurological involvement (8). A nationwide population-based study in Taiwan revealed that the risk of anterior uveitis increased in the year following a diagnosis of herpes zoster (9).

HSV-1 reactivation was reported to cause BD-like symptoms (fever, arthritis, genital ulcers, uveitis) in a 13-year-old Japanese girl with the HLA-B51 haplotype (10). An HSV-1-infected mouse model develops oral, genital, and skin ulcers, eye involvement, arthritis, and intestinal involvement, and has been widely used as a model of BD (11). In light of these reports, it appears that members of the Herpesviridae family may contribute to the development of BD.

A cytokine multiplex array revealed that cytokines that are relevant to the pathogenesis of BD (12), i.e., IL-1 $\beta$ , IL-6, IL-12 p70, TNF $\alpha$ , and IFN- $\gamma$ , were increased, while IL-10 was undetectable in the patient's serum. IL-10 has an anti-inflammatory effect that suppresses proinflammatory cytokines such as IL-1, IL-6, IL-12, TNF $\alpha$ , and IFN- $\gamma$  (13, 14). Serum IL-10 levels from patients with BD have also been reported to be lower than those of healthy controls (15). According to a genome-wide association analysis of BD, the disease risk allele of *IL10* locus rs1518111 was associated with the reduced production of IL-10 (16).

In the context of VZV, the serum IL-10 level was reported to increase after immunization for VZV (17). It was reported that individuals with polymorphism of the *IL10* gene have susceptibility to herpes zoster (18). These reports suggest that IL-10 may have an important role in the defense against VZV.

All of the cytokines that were elevated in our patient (IL-1, IL-6, IL-12, TNF $\alpha$ , and IFN- $\gamma$ ) are also reported to be produced by VZV infection (17, 19, 20). The production of these proinflammatory cytokines induced by VZV infection may also trigger the occurrence of BD.

Remarkably, our patient developed severe autonomic disorders. Autonomic disorders have been reported as not only clinical but also subclinical complications of BD (1, 21-29). An analysis of 25 patients with BD revealed that 21 (84%) of the patients had symptoms such as bladder dysfunction, symptoms of orthostatic hypotension, and sweating abnormalities (1). VZV infection itself has been known to affect the autonomic ganglia and can cause autonomic disorders (30). Autonomic nerve dysfunction caused by vasculitis has been thought to be a mechanism of autonomic disorder in BD; however, the precise mechanisms remain to be elucidated (28). In our patient's case, both herpes zoster and the subsequent development of BD may have contributed to the exacerbation of her severe autonomic disorders.

The appropriate methods for the assessment of autonomic disorders in BD are controversial (28). Sympathetic skin response (SSR), R-R interval variation (RRIV) tests and pupilometry techniques are reported to be useful to detecting

autonomic abnormalities in patients with BD (1, 21, 22, 24, 25, 28). Autonomic abnormalities were also detected by RRIV tests and a pupil light reflex test in the present patient. The Valsalva maneuver was reported to objectively reveal orthostatic intolerance in a patient with BD (27). There seems to be only one previous case report of a patient with BD whose autonomic disorders were evaluated using the HUT (29). In that report, the patient with BD who had syncope episodes was examined with the HUT, and patient developed asystole lasting 20 seconds during the HUT. Based on this result, the patient was treated with dual-chamber (DDD-R) pacemaker implantation.

As described above, although autonomic symptoms are not uncommon in BD, there are few cases in which the clinical course of autonomic dysfunctions after treatment are evaluated objectively. To the best of our knowledge, the present report is the first to note that the HUT was useful for objectively revealing the reversibility (by treatment) of autonomic disorders in a patient with BD.

Some cardiovascular agonists, such as  $\beta$ -blockers, have been used to treat orthostatic intolerance (27). However, the necessity of immunotherapy for autonomic disorders associated with BD has not been established thus far. Patients with autoimmune diseases, such as Sjögren syndrome, systemic lupus erythematosus, systemic sclerosis, ankylosing spondylitis, and rheumatoid arthritis, also develop autonomic disorders, and some immunotherapies have been reported to be beneficial for these conditions (31-34). Intravenous cyclophosphamide was reported to be effective for the treatment of a steroid refractory patient with BD who developed a sympathetic storm (hyperthermia, tachycardia, and hyperhidrosis) that was considered to be autonomic dysfunction caused by neuro-BD (35). IVIG has been commonly used in the treatment of autoimmune autonomic ganglionopathy, which is characterized by immune-mediated disruption of fast synaptic transmission across the peripheral autonomic ganglia (35, 36). Additionally, several reports have shown that IVIG was beneficial for the treatment of various refractory symptoms of BD, including uveitis, oral ulcers, gastrointestinal ulcers, neuro-BD, and arthritis (37-39). Based on these reports, we administered IVIG to the present patient. IVIG can be a good treatment option for refractory BD with autonomic disorders.

Taking the past reports and the findings from our patient's case together, we hypothesize that the insufficient production of IL-10 associated with VZV infection is associated with the development of BD in patients carrying sensitive alleles. The accumulation of further cases and functional studies are required to clarify the mechanisms underlying the association between BD and VZV. Even though the autonomic disorders in BD are common and can significantly impair the patients' quality of life, the precise mechanisms underlying their development have not been determined and optimal therapeutic approaches remain to be established. The HUT can be a good method for diagnosing autonomic disorders in BD and for evaluating the longitudi-

nal effects of therapy.

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

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