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CASE REPORT

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Behçet's disease associated with myelodysplastic syndrome with elevated levels of inflammatory cytokines

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Abstract We report the case of a 56-year-old Japanese woman with Behçet's disease and myelodysplastic syndrome (MDS), who had a history of episodic high-grade fever, recurrent oral and genital ulcers, and erythema nodosum, during a 13-year period from 1989 to 2002. Bone marrow aspirates obtained in January 1995 showed refractory anemia with trisomy 8, a subtype of MDS. Her serum levels of soluble interleukin-2 receptor (IL-2R), interferon-γ, IL-1β, IL-6, IL-8, and granulocyte–macrophage colony stimulating factor in the active state were higher than those in the inactive state, whereas those of tumor necrosis factor-α and IL-10 did not increase even in the active state. In this case, it was speculated that a T-cell immune response might have been involved in the disease pathogenesis, and that the repeated febrile episodes might have been a manifestation of neutrophil hyperfunction induced by increased serum levels of inflammatory cytokines.

Key words Behçet's disease · Cytokine · Fever · Myelodysplastic syndrome (MDS) · Trisomy 8

Introduction

Behçet's disease is a multisystem disorder producing recurrent oral ulcers, genital ulcers, eye lesions, and skin lesions.[1] In addition, Behçet's disease is characterized by the infiltration of many neutrophils into the inflamed area of the affected organs.[2] Although the pathogenesis of this disease is unknown, the tissue injury is thought to be due to excessive generation of reactive oxygen species (ROS) by activated neutrophils.[3] Myelodysplastic sydrome (MDS) is characterized by varying degrees of ineffective hematopoiesis.[4] Furthermore, immunological abnormalities are frequent in patients with MDS.[5–7] Here, we report a case of Behçet's disease and MDS with trisomy 8. The patient complained of repeated febrile episodes, and we suspected that these episodes might have been associated with the activation of neutrophils induced by increased serum levels of inflammatory cytokines.

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Case report

A 43-year-old Japanese woman had experienced episodic high-grade fever, recurrent oral and genital ulcers, polyarthralgia, and erythema nodosum since 1989 (Fig. 1). Behçet's disease had been diagnosed in December 1989 on the basis of the criteria of the International Study Group for Behçet's Disease.[1] Thereafter, the patient had been admitted to our hospital for approximately 1 month in January 1990, and again in January 1995, because of high-grade fever, oral aphtha, and fatigue.

At her first admission, in January 1990, the patient suffered from high fever (40.9°C), painful oral and genital ulcers, polyarthralgia, and erythema nodosum on the legs and ankles. As shown in Tables 1 and 2, hematological examinations showed only mild iron-deficiency anemia without myelodysplasia. The levels of complement components (C3 and C4) in serum were normal. Rheumatoid factor and antinuclear antibodies were negative during the 13 years from 1990 to 2002. The patient's HLA type was A24, −; B61, 62; and Cw3, w8. No abnormalities in the cardiovascular or respiratory organs were observed during those 13 years. At the first admission, the patient was treated with a daily dose of 30 mg prednisolone, which rapidly brought the symptoms under control, and was then discharged from hospital in February 1990. After the withdrawal of prednisolone, the symptoms gradually worsened. When high-grade fever and fatigue became intolerable, she was again

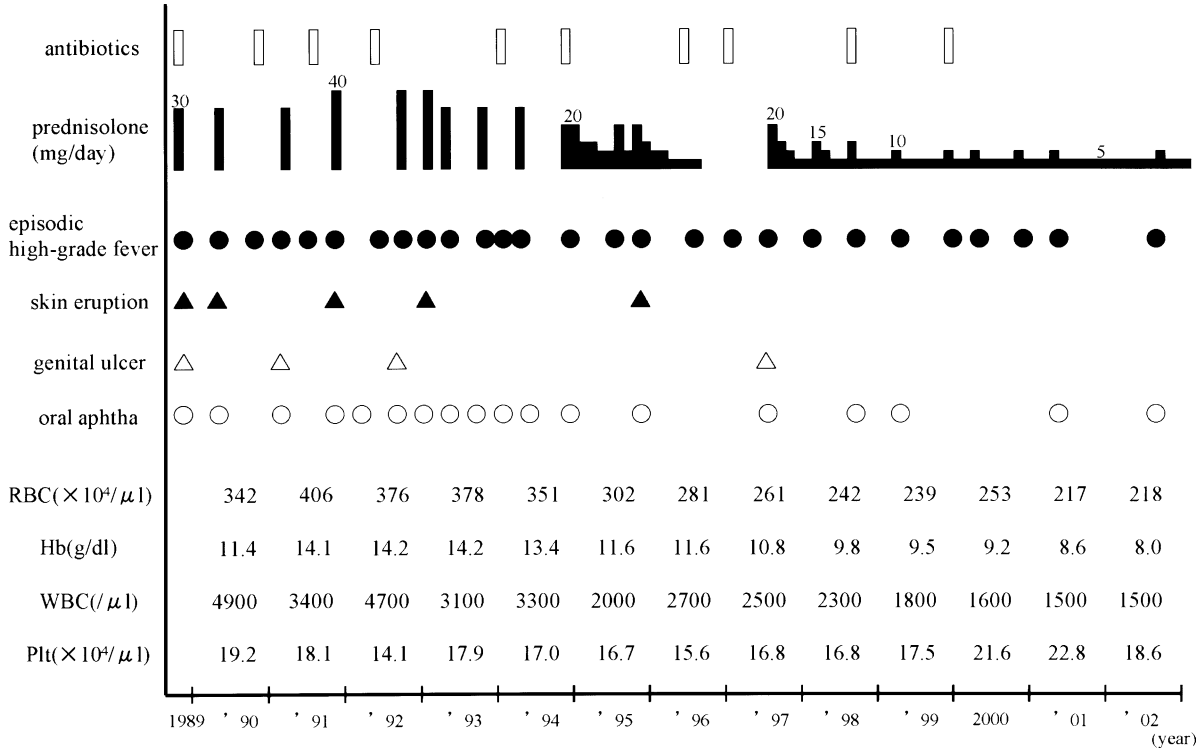

Fig. 1. Clinical course of the patient over the 13 years from 1989 to 2002

treated with a daily dose of 30 or 40 mg prednisolone. She was next admitted to our hospital in January 1995 because of high-grade fever, oral aphtha, and fatigue. At this time, a hemogram showed mild leukocytopenia and anemia, with a hemoglobin concentration of 11.6 g/dl, leukocyte count 2000/μl, with 60% neutrophils, 34% lymphocytes, 4% monocytes, 0% eosinophils, and 1% basophils, and a platelet count of 16.7×10^4/μl (Table 2). Bone marrow aspiration showed mild myeloid maturation arrest. A chromosomal study showed 47XX, +8. A diagnosis of refractory anemia (RA) in MDS was made based on the above findings. The patient was treated with a daily dose of 20 mg prednisolone plus antibiotics, and the symptoms were again brought under control within a month.

After the second discharge from hospital in February 1995, prednisolone was given continually at a varying daily dose of 5–20 mg. Although we tried administering other drugs, such as colchicine, azathioprine, and cyclosporin A, they had to be discontinued because of side-effects: colchicine caused abdominal pain and severe diarrhea, and azathioprine and cyclosporin A caused alopecia. During the 13 years from 1989 to 2002, the patient experienced approximately 27 episodes of high-grade fever lasting for 3–7 days (see Fig. 1). Five of these episodes were apparently due to infection, because bacterial cultures were positive and the fever was resolved after the administration of antibiotics. The other episodes responded to an increased dose of prednisolone and there were no apparent signs of infection. Other symptoms, such as skin eruptions, genital ulcers, and oral aphthae, diminished gradually. Her leukocyte count gradually decreased from 3000–5000/μl to 1000–2000/μl during the 13 years. Her hemoglobin concentration also decreased from 12 g/dl to 8 g/dl, but the platelet count did not change. Bone marrow aspiration revealed mild myeloid maturation arrest and erythroid dysplasia (Fig. 2). Chromosomal analysis and fluorescence in situ hybridization (FISH) of bone marrow cells in both January 1995 and September 1999 revealed trisomy 8 (Fig. 3). To examine whether inflammatory cytokines were associated with the pathogenesis of Behçet's disease, we compared the serum levels of soluble interleukin-2 receptor (IL-2R), interferon (IFN)-γ, IL-1β, IL-6, IL-8, IL-10, granulocyte–macrophage colony stimulating factor (GM-CSF), and tumor necrosis factor (TNF)-α between the active and inactive states. As shown in Table 3, the serum levels of IL-2R, IFN-γ, IL-1β, IL-6, IL-8, and GM-CSF in the active state were higher than those in the inactive state (1260 versus 142 U/ml, 32.4 versus <0.1 IU/ml, 579 versus <8 pg/ml, 69.3 versus 1.6 pg/ml, 107 versus <15 pg/ml, and 8.2 versus <2 pg/ml, respectively). However, the serum levels of TNF-α and IL-10 did not increase even in the active state.

Discussion

Behçet's disease is a clinically and pathologically distinct entity of unknown etiology. However, when the disease is in its active state, the production of ROS by neutrophils is known to increase, and is involved in the disease pathogen-

Table 1. Laboratory findings at the time of first admission in January 1990

Blood chemistry	
TP	6.9 g/dl
Alb.	48.2%
α-1-gl.	5.9%
α-2-gl.	11.8%
β-gl.	10.4%
γ-gl.	23.8%
T.bil.	0.8 mg/dl
GOT	33 IU/l
GPT	42 IU/l
LDH	169 IU/l
ALP	282 IU/l
γ-GTP	30 IU/l
BUN	14 mg
Uric-A	1.9 mg/dl
Creat.	0.5 mg/dl
CPK	18 IU/l
Aldolase	1.0 IU/l
Fe	20 mg/dl
Ferritin	21.7 ng/dl
Vit B12	631 pg/ml
folic acid	7.3 ng/ml
Urinalysis	np
ESR	69 mm/h
Serology	
CRP	15.62 mg/dl
ASO	27 U/ml
ASK	X 160
TPHA	(−)
HBS-Ag	(−)
HCV-Ab	(−)
RA	(−)
ANA	(−)
dsDNA	(−)
RNP	(−)
Sm	(−)
SS-A	9.5 index
Scl-70	(−)
Thyroid test	<X 10
Microsome test	<X 80
CH50	45 U/ml
C3	99 mg/dl
C4	41.0 mg/dl
IgG	1832 mg/dl
IgA	530 mg/dl
IgM	253 mg/dl
IgE	231 IU/ml
HLA; A24, −, B61, B62, CW3, CW8	

LDH, lactic dehydrogenase; ALP, alkaline leukocyte phosphatase; GTP, guanosine triphosphate; BUN, blood urea nitrogen; CPK, creatine phosphokinase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ASO, allele-specific digorucleotide; HBS-Ag, hepatitis B surface antigen; HCV, hepatitis C virus; RA, refractory anemia; ANA, antinuclear antibody; RNP, RNA polymerase

esis.[2,3] Neutrophils from patients with Behçet's disease show increased ROS production, enhanced chemotaxis, and excessive production of lysosomal enzymes, indicating that the neutrophils are overactive, leading to tissue injury. However, Sakane[8] has proposed that Behçet's disease may have an autoimmune nature: a novel multistep molecular mimicry mechanism may induce and/or exacerbate the disease through bacterial antigens that activate T cells previously educated by self-peptides of heat shock protein (HSP). This theory is supported by the fact that T cells in

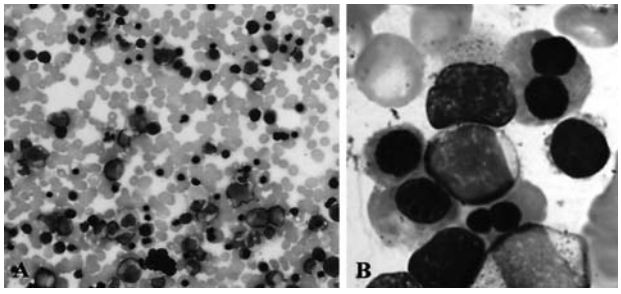

Fig. 2. Bone marrow aspiration showing mild myeloid maturation arrest and erythroid dysplasia (May–Giemsa stain, **A**: ×400, **B**: ×1000)

Behçet's disease proliferate vigorously in response to a specific peptide, HSP-60, and that T cells with specific TCR Vβ subfamilies proliferate and increase in number in response to this peptide in an antigen-specific manner. Recurrent exposure to the HSP may erode tolerance to self-HSP, and provoke T cell responses to self- and microbial-HSP. Such T cells produce Th1-like proinflammatory and/or inflammatory cytokines, leading to tissue injury, possibly via macrophage activation, and activation and/or recruitment of neutrophils. In our patient, the serum levels of soluble IL-2R, IFN-γ, IL-1β, IL-6, IL-8, and GM-CSF were high when the disease was active, but returned to normal during the inactive state. An increased concentration of soluble IL-2R indicates the activation of lymphocytes, especially T cells. IFN-γ is produced by Th1, $CD8^+$, NK, and monocytes/macrophages, and induces the production by macrophages of inflammatory mediators such as IL-1β, IL-6, IL-8, and GM-CSF, leading to ROS production by neutrophils.[9,10] Therefore, the repeated febrile episodes suffered by our patient may have been triggered by T cell responses to self- and microbial-HSP. Further investigation of this possibility will be necessary.

Cytokines are involved in the regulation of immune responses and inflammatory reactions. Various cytokines have been reported to play a role in the pathogenesis of Behçet's disease.[9–16] An increased serum level of IFN-γ has been shown in Behcet's disease.[11] Since then, the spontaneous production of IFN-γ from cultured T cells in affected patients has also been reported.[12] The concentration of soluble IL-2R has been found to be increased in sera of patients with Behçet's disease, and the level during the active phase of the disease is higher than that during the inactive phase.[13] These findings suggest that T-cell immune responses are involved in the pathogenesis of Behçet's disease. Furthermore, the spontaneous secretion of GM-CSF, TNF-α, IL-6, and IL-8 by monocytes is significantly increased in patients with active Behçet's disease, leading to increased ROS production by neutrophils.[9,10] Among these cytokines, IL-8, which is characterized as a neutrophil chemotactic factor and a neutrophil activating factor, has been reported to play an important role in the pathogenesis of Behçet's disease.[9,14–16] al-Dalaan et al.[14] reported that about half of 53 patients with Behçet's disease possessed high serum levels of IL-8, but not of other cytokines such as

Table 2. Hemogram and bone marrow cells

	January 11, 1990	January 30, 1995	October 14, 2002
Hemogram			
WBC (/μl)	4900	2000	1500
St (%)	7.0	6.0	3.0
Seg	72.2	54.0	38.0
Ly	11.0	34.0	38.0
Mo	9.2	4.0	18.0
Eo	0.6	0	0
Ba	0	1.0	0
Blast	0	0	1.0
Ebl	0	0	2.0
RBC (10^4/μl)	342	302	218
Hb (g/dl)	11.4	11.6	8.0
Ht (%)	34.1	32.6	27.6
Platelets (10^4/μl)	19.2	16.7	18.6
Reticulo (‰)	19	8	10
Bone marrow			
NCC (10^4/μl)	ND	13.9	10.9
MgK (/μl)		75	80
Blast (%)		1.4	1.3
Pro		4.8	4.5
My		10.0	8.0
Met		2.8	1.9
St		5.4	6.4
Set		8.6	2.2
Eo		1.4	0.2
Ba		0.2	0.1
Ly		13.2	6.6
Pl		1.8	1.2
Mo		2.6	1.3
Erythroblast			
Ba		7.2	6.4
Poly		35.2	50.5
Orth		5.4	8.7
M/E		0.7	0.38

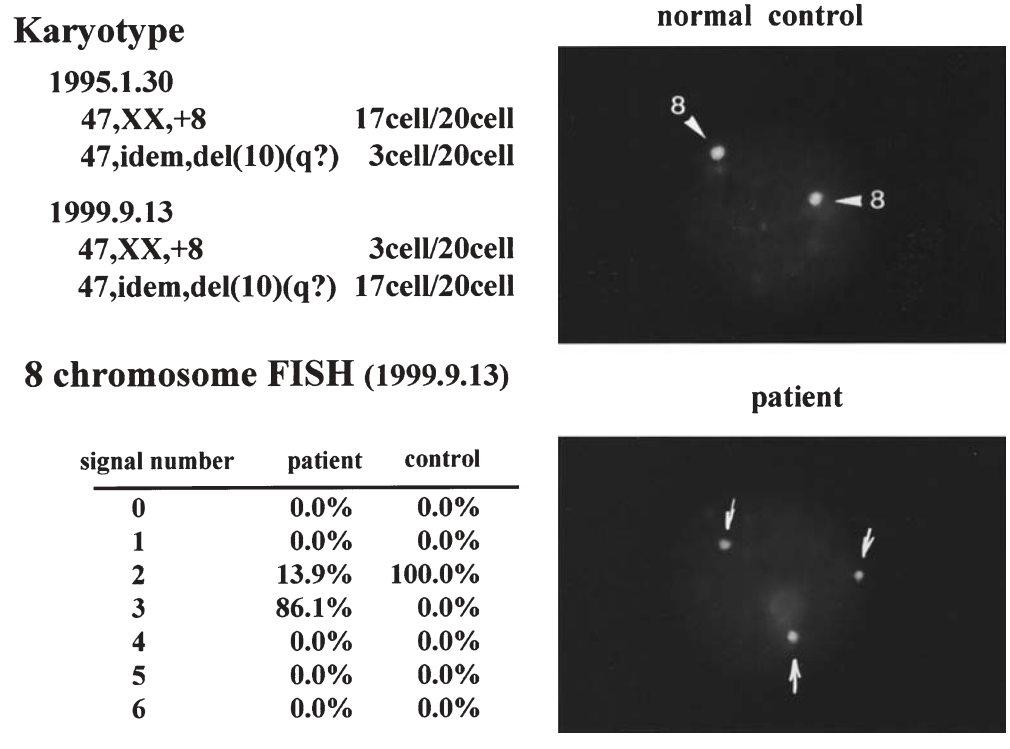

Fig. 3. Chromosomal analysis and fluorescence in situ hybridization indicating trisomy 8

Table 3. Serum levels of cytokines and inflammatory markers

	March 19, 2001 (active)	June 4, 2002 (inactive)	Normal serum level
sIL-2R (U/ml)	1260	142	145–519
IFN-γ (IU/ml)	32.4	<0.1	<0.1
IL-1β (pg/ml)	579	<8	<8
IL-6 (pg/ml)	69.3	1.6	<4.0
IL-8 (pg/ml)	107	<15	<15
IL-10 (pg/ml)	<2	ND	<160.0
GM-CSF (pg/ml)	8.2	<2	<2
TNF-α (pg/ml)	18	ND	<40.0
CRP (mg/dl)	7.00	0.09	<0.25

IL-6 and TNFα. Wang et al.[15] have reported that the serum levels of IL-8 in 43 Behçet's disease patients were significantly higher than those in 46 healthy volunteers. Nawata et al.[16] reported a case of Behçet's disease and MDS with trisomy 8 which was similar to the present one, and in which the patient complained of repeated febrile episodes and showed increased serum levels of IL-6 and IL-8, but not of TNF-α and IL-1β.

Behçet's disease is a rare complication of MDS, and to date 21 patients with Behçet's disease associated with MDS have been reported.[16–30] Their clinical characteristics are summarized in Table 4. The median age of the patients was 48 years (range 23–74 years). The majority (76.2%) were Japanese, reflecting the fact that the incidence of Behçet's disease is relatively high in central and eastern Asia.[31] Many patients had an incomplete form of Behçet's disease, and (rarely) some had eye lesions. Furthermore, 13 patients (61.9%) had gastrointestinal lesions. Kimura et al.[29] reported that MDS with trisomy 8 was a risk factor for intestinal ulcers and thrombosis. The 21 patients reported with both conditions included 15 with RA, three with RA with ring sideroblasts (RARS), and three with RA with excess blasts (RAEB). Surprisingly, among these patients, 15 (75%) had trisomy 8. Nine patients had trisomy 8 as the sole cytogenetic abnormality, and six had trisomy 8 associated with other clonal abnormalities. Since trisomy 8 is observed in 10%–20% of patients with MDS,[32,33] the high frequency of trisomy 8 in patients in Behçet's disease with MDS suggests that trisomy 8 may be associated with the disease pathogenesis. Immunological abnormalities are frequent in patients with MDS.[5–7,32,33] A number of functional and quantitative abnormalities of monocytes, and T-, B-, and NK-lymphocytes have been reported. The abnormal lymphocytes or monocytes in patients with MDS may act by releasing cytokines that perturb the endothelial cell lining of blood vessels in the skin, synovia, and peripheral nerves or other organs, thus producing the clinical features. However, trisomy 8 has not been reported to elicit characteristic immunological abnormalities. Therefore, we recommend further study of the association of trisomy 8 with the pathogenesis of Behçet's disease.

Table 4. Clinical characteristics of 21 patients with Behçet's disease associated with myelodysplastic syndrome (MDS)

Case	Age/sex	Karyotype	Type of MDS	Behçet's disease type	Uveitis	Intestinal involvement	Preceding disease	Outcome	Reference
1	72/M	47,XY,+8,del(280)(q11)	RA	I	−	−	MDS	Improvement	17
2	35/M	46,XY	RA	C	+	−	MDS	MDS, no change	18
3	57/M	47,XY,+8	RA	I	−	+	MDS	MDS, no change	18
4	52/M	47,XY,+22,t(9;22)	RA	I	−	−	MDS	Platelet count, no change	18
5	59/M	44,XY,−5,−7,−18,3q−, 17q−,20q+,+mar	RAEB →RAEB-T	I	+	−	MDS	Death	19
6	41/F	47,XX,+8	RARS	I	−	+	Behçet	RBC count, no change	20
7	45/F	48,XX,+8,+15	RARS	I	−	+	MDS	MDS, no change	21
8	56/M	ND	RAEB	I	−	+	Unknown	Unknown	22
9	23/F	47,XX,+8	RA	I	−	+	MDS	Improvement	23
10	54/F	47,XX,+8	RA	I	−	−	MDS	Death	23
11	34/F	47,XX,+8	RA	I	+	+	MDS	Improvement	24
12	50/M	47,XY,+8	RARS	I	−	+	Behçet	Death	25
13	39/F	47,XX,−7	RAEB-T	C	+	−	Behçet	Death	26
14	59/M	47,XY,+8,−7	RA	I	+	−	MDS	Improvement	16
15	50/F	46,XX,−8,−20+del	RA	I	−	−	Unknown	MDS, no change	27
16	39/M	47,XY,+8	RA	I	−	+	MDS	MDS, no change	28
17	74/F	45,X,−X,+8,+mar	RA	I	−	+	Unknown	Unknown	29
18	36/F	47,XX,+8,dup(1)(q12;q44)	RA	I	−	+	Unknown	Unknown	29
19	31/F	47,XX,+8	RA	I	−	+	Unknown	Unknown	29
20	67/M	47,XY,+8	RA	I	−	+	Unknown	Unknown	30
21	56/F	47,XX,+8	RA	I	−	−	Behçet	MDS, no change	Current case

RAEB, RA with excess blasts; RARS, RA with ring sideroblasts

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