Review

The association of Behçet's disease with myelodysplastic syndrome in Japan: A review of the literature

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ABSTRACT

Objective. *To determine the clinical characteristics of patients with myelodysplastic syndrome (MDS)-associated Behçet's disease (BD) in Japan.*

Methods. *54 Japanese cases of MDS-associated BD obtained from the literature and from our own clinical experience were reviewed. The clinical features of MDS-associated BD were compared with those of the 1991 nationwide BD survey in Japan.*

Results. *In MDS-associated BD, the average age at onset was 42.6 years, which was 6.9 years later than for all BD patients; females developed disease more frequently than males (male: female ratio = 0.80). In MDS-associated BD cases, the occurrence of eye lesions was significantly lower, the frequency of intestinal lesions was markedly higher, and the rate of HLA-B51 positivity was lower than that in all BD. BD and MDS developed nearly simultaneously in 49.0% of cases; BD preceded MDS in 31.4% of the cases. The distribution of the age at BD onset showed two peaks, one in the 3rd decade and the other in the 6th decade. Females were more likely to develop younger-onset disease, while men were more likely to develop older-onset MDS-associated BD. Furthermore, in the older-onset group, BD was diagnosed together with or after the diagnosis of MDS, while half of the younger-onset group developed BD earlier than MDS.*

Conclusion. *MDS-associated BD patients form a distinct subset of patients. There may, in fact, be two major groups of MDS-associated BD patients based on age, gender, and temporal relationship of the two diseases.*

Introduction

Behçet's disease (BD) is a multisystemic inflammatory disease that affects various organs and causes mucocutaneous lesions (1, 2). Its incidence is high in Mediterranean countries and East Asia; Japan has one of the highest incidences of BD. Recently, cases of BD associated with myelodysplastic syndrome (MDS) have been reported. Many of these have occurred in Japan (3-20), but a few cases have been reported in other countries, including Italy, Germany, United States, Korea, Turkey, and Israel (21-26). These reports have reviewed small numbers of patients who developed BD and MDS and suggest that there is a low frequency of eye lesions and a high frequency of intestinal involvement (3, 4, 7-10, 12, 26).

In order to identify the clinical characteristics of MDS-associated BD, we collected and summarized the findings of reported Japanese cases and our own cases. We analyzed the clinical features of patients who had both BD and MDS and compared them to those of patients with either BD or MDS whose data were collected in nationwide Japanese surveys (27-29).

Methods

We collected case reports, including proceedings and abstracts, of BD associated with MDS in Japan that were described in English or Japanese. A total of 62 cases were obtained from 53 reports published between 1988 and 2004. Eleven reports in which the clinical features and symptoms of BD were not described, or the diagnosis of BD was very dubious were excluded. We based our diagnosis of BD on the Japanese criteria (30) or the International criteria for classification of BD (1). We reviewed a total of 51 reported Japanese cases of BD associated with MDS. Eleven cases were in English and 40 in Japanese. Twenty-four cases

Table I. Symptoms and HLA-B51 in patients with MDS-associated Behçet's disease.

Symptoms	No. of patients*	%	BD survey (%)
Oral	51 / 51	100.0	98.2
Genital	43 / 52	82.7	73.2
Eye	5 / 45	11.1	69.1
Skin	37 / 49	75.5	87.1
Gastrointestinal	36 / 53	67.9	15.5
Positive pathergy test	10 / 13	76.9	43.8
HLA-B51	11 / 30	36.7	54.9

*Number of evaluated patients varies due to limited information.

appeared in full papers (3-20) and 27 in abstracts or proceedings. Three additional cases from our hospital were added, bringing to 54 the total number of cases analyzed. From each report, the age of onset, gender, positive features of BD, HLA typing, periods from onset of BD to MDS, types of MDS, karyotype, therapy, and prognosis were recorded when provided. Onset of BD was defined by the emergence on history of at least two symptoms attributable to BD. Onset of MDS was defined as the emergence of cytopenia of any type attributable to MDS. We compared the clinical data of MDS-associated BD cases with those of BD cases reported in a 1991 nationwide survey in Japan (27), and with those of MDS as reported in a multicenter study in Japan (28, 29). Statistical analysis was carried out using χ^2 analysis; statistical significance was set at $p < 0.05$.

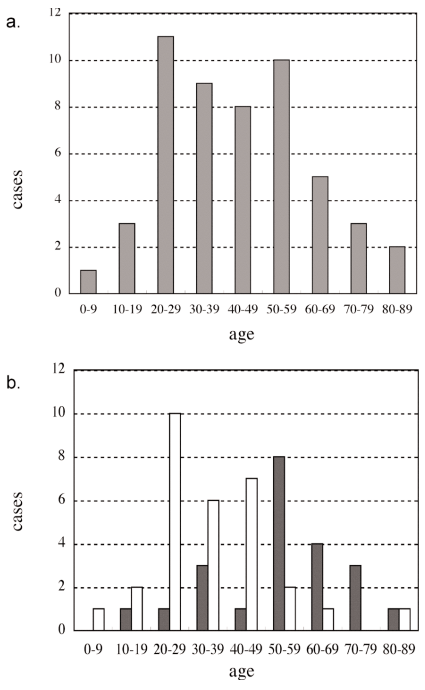

Fig. 1. Distribution of age of onset of Behçet's disease in patients with associated MDS. **(a)** Total patients and **(b)** male (closed box) and female patients (open box) shown separately.

Results

Gender, age of onset, and mode of presentation

The gender ratio (male: female) of Japanese patients with MDS-associated BD was 0.80 (24:30), which is slightly lower than of all BD patients (0.98) (27) and much lower than that of MDS patients (1.6) (28). The age group involved most frequently was the 6th decade (22.2%), followed by the 4th and 5th decades (16.7%). The age of onset of BD in MDS-associated cases was ascertained in 52 cases (22 males and 30 females). The mean age of onset was 42.6 years in MDS-associated BD cases, which is 6.9 years later than that in all BD cases (27). The distribution of onset of BD associated with MDS formed a bimodal distribution, with the highest frequency in the third decade (21.2%), followed by the 6th decade (19.2%) (Fig. 1a). Compared to the Japanese BD survey where 85% of patients developed BD between the ages of 20 and 49 years (27), only 53.8 % of MDS-associated cases developed during this period. When male and female patients were analyzed separately, 72.7% of male patients developed BD after the age of 50, in contrast to 13.3% of female patients (Figure 1b, $p < 0.0001$). These data suggest that there are two major groups of MDS-associated BD patients, younger-onset females and older-onset males.

The onset of both BD and MDS were identified in 51 cases (22 males and 29 females). In 25 of these cases (49.0%) the diseases developed almost simultaneously (± 1 year) (Fig. 2a). BD preceded MDS (up to 28 years) in 16 cases (31.4%), and MDS preceded BD (up to 5 years) in 10 cases (19.6%). There were 4 cases in which BD preceded MDS by more than 15 years.

Symptoms and HLA-B51

The rates of symptoms in MDS-associated BD compared to the Japanese BD survey (27) are summarized in Table I. All patients had recurrent oral ulcers. In MDS-associated BD, genital lesions were present in 82.7% of patients, which is 9.5% higher than in the BD survey, and skin lesions were found in 75.5% of cases, which is 11.6% lower than in the BD survey. Most strikingly, eye lesions were much less common in MDS-associated BD cases (11.1% vs. 69.1%), whereas the frequency of intestinal lesions was markedly higher (67.9% vs. 15.5 %) in MDS-associated BD cases. Furthermore, in MDS-associated cases, gastrointestinal lesions were mostly simple or multiple punched-out ulcers in the ileocecal region; addi-

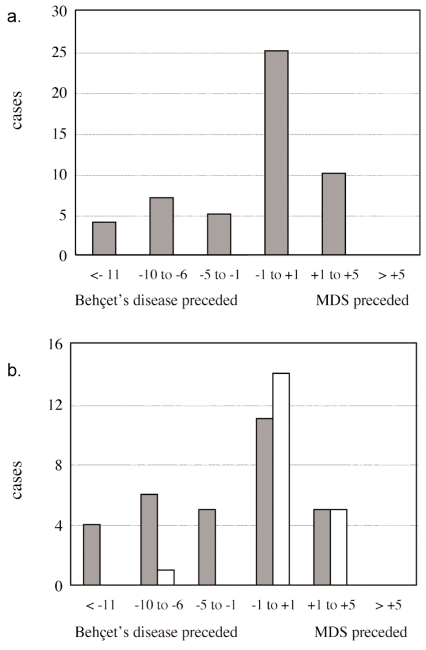

Fig. 2. Interval between onset of Behçet's disease and onset of MDS. **(a)** Total patients and **(b)** patients with younger-onset Behçet's disease (< 50 years, closed box) and patients with older-onset Behçet's disease (≥ 50 years, open box) shown separately.

tional ulcerative lesions were found in the colon and/or the ileum, which are typical findings in intestinal BD, and two cases had esophageal lesions and one case had stomach lesions. Arthritis was documented in 13 cases of MDS-associated BD, and epididymitis in one; two cases had central nervous system involvement, and three cases had vasculitis (an aortic lesion in one, and venous thrombosis in two). The pathergy test was reported in only 13 MDS-associated BD cases and was positive in 10, while HLA-B51 was reported to be positive in 11 cases and negative in 19 (positive rate 36.7%), which is lower than in the BD survey (54.9%)(27).

Features of MDS

MDS subtypes were available in 43 cases. Twenty-eight (65.1%) cases had refractory anemia (RA), six (14.0%) refractory anemia with an excess of blasts (RAEB), five (11.6%) refractory anemia with ringed sideroblasts, three (7.0%) RAEB in transformation (RAEB-t), and one (2.3%) chronic myelomonocytic leukemia. Compared to the estimated prevalence rate of each MDS subtype in Japan (29), RA was slightly more frequent (65.1% vs. 50%) and RAEB-t was less frequent (7.0% vs. 15%) in BD-associated cases. Progression to overt leukemia was reported in three cases. Among the abnormalities of karyotypes documented in 45 BD-associated cases, trisomy 8 was most frequent (86.7%), followed by trisomy 9 (13.3%) and trisomy 15 (8.8%). In 15 cases (33.3%), trisomy 8 was the only abnormality, and 17 cases (37.8%) showed more than two chromosomal changes.

In some cases, other hematological diseases have been reported to overlap with MDS and BD. Three such cases developed aplastic anemia before MDS; the intervals from the diagnosis of aplastic anemia to MDS ranged from 14 to 26 years and to BD ranged from 0 to 14 years. Two cases developed hemolytic anemia: in one case, the hemolytic anemia developed 3 years before BD and 18 years before MDS; the other case developed hemolytic anemia simultaneously with MDS, five years before BD. One case developed idiopathic thrombocytopenic purpura (ITP) 12 years before BD and 16 years before MDS. One case developed aplastic anemia and ITP independently more than 10 years before onset of BD and MDS.

Treatment and prognosis

In MDS-associated BD patients, the BD was treated with prednisolone in most cases with favorable effects. Some cases were treated with colchicine in addition to steroids. Cyclosporin A was given in four cases. Resection of the intestine, including emergency operation due to perforation, was reported in seven cases with intestinal BD. Bone marrow transplantation was reported for the treatment of MDS. Two cases (one with RAEB and the other with AML that had progressed from RAEB) were treated with cord blood transplantation that resulted in the remission of MDS as well as BD (8, 9). Ten MDS-associated BD patients died; eight of them were older than 50 years of age at the onset of BD. Seven MDS-associated BD cases died within one year after the diagnosis of MDS, and three other cases died two to five years after the diagnosis of MDS; six MDS-associated BD cases died within one year after the diagnosis of BD, three died from one to two years after the diagnosis of BD, and one died six years after the diagnosis of BD.

The comparison between younger-onset patients and older-onset patients

We compared the clinical pictures of MDS-associated BD patients in the younger-onset group (age of onset of BD < 50 years, n = 32) and in the older-onset group (age of onset of BD ≥ 50 years, n = 20). As shown in Figure 2b, 70.0% of the older-onset patients developed BD and MDS simultaneously, and 25.0% developed MDS earlier than BD. In contrast, 48.4% of the younger-onset patients developed BD earlier than MDS. The clinical manifestations of BD and MDS are summarized in Table II. The gender ratio of the younger-onset patients was 0.23 (6:26) and of the older-onset patients it was 4.0 (16:4) ($p < 0.0001$). The rates of ocular lesions and gastrointestinal lesions were not different between the groups. In older-onset patients, genital ulcers were less frequent (93.3% vs. 68.4%, $p < 0.05$) and the HLA-B51 positive rate was higher (23.8% vs. 66.7%, $p < 0.05$). All of the cases with overlapping hematological disease,

Table II. Clinical manifestations by age of BD onset.

	Younger-onset (< 50 years)		Older-onset (≥ 50 years)	
	No. of patients	%	No. of patients	%
Male	6 / 32	18.8	16 / 20*	80.0
Symptoms				
Oral	29 / 29	100.0	20 / 20	100.0
Genital	28 / 30	93.3	13 / 19†	68.4
Eye	4 / 25	16.0	1 / 18	5.6
Skin	18 / 27	66.7	17 / 20	85.0
Gastrointestinal	22 / 31	71.0	13 / 20	65.0
HLA-B51	5 / 21	23.8	6 / 9†	66.7
MDS				
RA	20 / 27	74.1	8 / 16	50.0
RAEB / RAEB-t	4 / 27	14.8	5 / 16	31.3
Trisomy 8	23 / 28	82.1	14 / 15	93.3
Hematological diseases				
Aplastic anemia	4 / 32	12.5	0 / 20	0.0
ITP	2 / 32	6.3	0 / 20	0.0
Hemolytic anemia	1 / 32	3.1	1 / 20	3.1
Mortality	2 / 32	6.3	8 / 20¶	40.0

*$p < 0.001$; †$p < 0.05$; ¶$p < 0.01$.

except one case with hemolytic anemia, were observed in the younger-onset patients. The mortality was higher in the older-onset patients than in the younger-onset patients (40.0% vs. 6.3%, $p < 0.01$).

Discussion

MDS is a clonal hematologic disease characterized by blood cell dysplasia. Various autoimmune diseases, including vasculitis of the skin, polyarthritis, relapsing polychondritis, peripheral neuropathy, and Sjögren's syndrome have been reported to be associated with MDS (31, 32). Recently, a number of case reports dealing with the association of MDS with BD have been published, mainly in Japan (3-26). To further characterize MDS-associated BD, we reviewed the cases reported in the Japanese literature, as well as our own cases, and analyzed their clinical features and the mode of BD presentation. We found that male patients and female patients with MDS-associated BD had a different age of BD onset. The majority of male patients were older-onset, while female patients were mostly younger-onset. This is a characteristic of MDS-associated BD patients, since, overall, both male and female Japanese BD patients have an onset in the 4th decade most commonly (27). On the other hand, in Japan, the prevalence of MDS is high in patients in their 7th to 9th decade (28). In most cases with older-onset MDS-associated BD, BD and MDS developed simultaneously, or MDS preceded BD. In these cases, it is possible that BD developed as a paraneoplastic syndrome of MDS. In fact, it has been reported that the successful treatment of MDS with cord blood transplantation induced remission of BD (8, 9). The pathogenesis of the development of BD in patients with MDS is unclear. It has been hypothesized that an abnormal antigen presentation, T cell responses to antigen, or T cell-B cell interaction in MDS might cause immune dysregulation that results in the development of autoimmune diseases (31).

In younger-onset patients, BD preceded MDS in some cases; this suggests that MDS could be associated with the course of BD. Several mechanisms may be involved in the development of MDS. The first possible mechanism could be the long-term effect that BD has on bone marrow cells. BD is a chronic inflammatory disease with recurrent acute phases or flares. Several inflammatory cytokines including IL-1β, IL-6, IL-8, IL-10, IL-17, IL-18, TNF-α, interferon-γ, and granulocyte colony-stimulating factor have been shown to be elevated in patients' sera, especially during the active phases of the disease (33-36). These frequent high-cytokine stimuli may play a role in the development of MDS. In fact, we have often observed that increased BD disease activity augmented cytopenia, and that anti-inflammatory therapy against BD led to improvement in the peripheral blood count in MDS-associated BD patients. The second possible mechanism could be that cytotoxic therapy for BD, such as colchicine and cyclophosphamide, may promote MDS; in three cases cytotoxic drugs were given as treatment for BD before the onset of MDS. In addition, two cases that developed MDS after treatment with chlorambucil, which is not used in Japan, have been reported outside Japan (22, 26). A third mechanism could have present in the six cases who had antecedent hematological diseases either before or with BD onset, and then later developed MDS. In such cases, it may be difficult to determine the exact time of MDS onset. However, the antecedent hematological diseases developed early (3 to 24 years of age), and the interval from the diagnosis of these diseases to the diagnosis of MDS was quite long (14 to 26 years). This would suggest that MDS develops either in the course of or after the recovery from a preceding hematological disease. We would speculate that in BD patients, the association of hematological diseases might be an important factor for the future development of MDS.

With respect to chromosomal abnormalities associated with MDS, trisomy 8 was the most frequently reported. In fact, one-third of patients had trisomy 8 as a single chromosomal change, which is much higher than the rate reported for MDS patients in Japan (7.5%) (29). Similar high frequencies of trisomy 8 were observed in the younger-onset and the older-onset patients. Kimura *et al.* reported that, among eight cases of MDS with trisomy 8, three had intestinal ulcers and five had thrombotic diseases, including acute myocardial infarction (37). These data indicate that trisomy 8 is related to the development of intestinal ulcer in MDS patients. It is also noteworthy that MDS is markedly more common than leukemia in Japanese BD patients. In fact, we only identified eight cases of chronic myelogenous leukemia and four cases of acute leukemia associated with BD in the literature during the same time period.

In conclusion, we have described the clinical characteristics of BD in cases associated with MDS; MDS-associated BD patients had a high frequency of intestinal lesions, a low frequency of eye lesions, a low HLA-B51positive rate, and two peaks in the age distribution for the onset of BD. In addition, we found that there are two types of MDS-associated BD: a younger-onset BD group that is primarily female, develops BD prior to or concomitantly with MDS, and has a good prognosis; and an older-onset BD group that is predominantly male, in whom the diagnosis of MDS is made before or at the same time as BD, and has a poor prognosis.

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