Review

A reappraisal of the association between Behçet's disease, myelodysplastic syndrome and the presence of trisomy 8: a systematic literature review

S.N. Esatoglu[1], G. Hatemi[2], A. Salihoglu[3], I. Hatemi[4], T. Soysal[3], A.F. Celik[4]

[1]Department of Internal Medicine;
[2]Division of Rheumatology;
[3]Division of Haematology;
[4]Division of Gastroenterology,
Department of Internal Medicine,
Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey.

Sinem Nihal Esatoglu, MD
Gulen Hatemi, MD, Assoc. Professor
Ayse Salihoglu, MD
Ibrahim Hatemi, MD, Assoc. Professor
Teoman Soysal, MD, Professor
Aykut Ferhat Celik, MD, Professor

Please address correspondence to:
Dr Gulen Hatemi,
Division of Rheumatology,
Department of Internal Medicine,
Cerrahpasa Medical School,
Istanbul University,
34098 Istanbul, Turkey.
E-mail: gulenhatemi@yahoo.com

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ABSTRACT

Objective. *A number of patients with Behçet's disease (BD) associated with myelodysplastic syndrome (MDS) with or without trisomy 8 have been reported. A high frequency of gastrointestinal (GI) involvement was reported in such patients. The aim of this systematic literature review was to delineate whether GI involvement is an inherent feature of BD associated with MDS, whether these patients do actually have BD rather than GI symptoms related to MDS, and whether the presence of trisomy 8 plays a role in the disease expression of BD associated with MDS.*

Methods. *A systematic literature review was performed in PubMed using the keywords (Behçet's disease OR Behçet's syndrome) AND (myelodysplastic syndrome OR trisomy 8) until December 2013.*

Results. *Data from 39 manuscripts that met the inclusion criteria, reporting on 52 patients were analysed. GI involvement was common in reports from both the Far East and non-Far East countries (75% vs. 50.0%, p=0.15). These patients had typical BD manifestations, except for 1 patient who had only oral ulcers and gastrointestinal involvement. The presence of trisomy 8 seems to be associated with an increased frequency of fever (79.5% vs. 33.3%, p=0.005).*

Conclusion. *GI involvement seems to be an inherent feature of BD associated with MDS regardless of geographic differences. Despite the increased frequency of GI involvement in these patients, MDS does not seem to modify the clinical expression of gastrointestinal involvement. Presence of trisomy 8 seems to modify the disease expression with an increased frequency of fever.*

Introduction

Behçet's disease (BD) is a chronic inflammatory condition of unknown aetiology and is characterised by mucocutaneous manifestations such as oral ulcers, genital ulcers, papulopustular lesions, nodular lesions, and pathergy phenomenon, vascular involvement, uveitis, central nervous system and gastrointestinal involvement (1). There are certain differences in clinical manifestations according to geographies. The most prominent example for this is GI involvement which is reported in up to 30% of BD patients from the Far East, in contrast to around 3–8% in Europe and the Middle East. On the other hand, there is also discussion whether the higher frequency of GI involvement reported from the Far East may be related to less stringent criteria for defining GI involvement (2, 3). Autoimmune diseases concomitant with haematologic disorders such as myelodysplastic syndrome (MDS), lymphoproliferative diseases and plasma cell dyscrasias have been reported. It is not clear whether the association between two disorders results from the immunsupressive agents that are used or from the altered immune function itself (4). In addition to autoimmune disorders, BD associated with MDS is also a well-recognised entity. Several patients have been reported, especially from Asian countries during the last 2 decades. Previous reviews of these patients have shown that GI involvement is a common feature of this association (5, 6) and may be severe and refractory to treatment (7, 8). However, certain issues regarding this association had not been sufficiently delineated. The high frequency of GI involvement may be interpreted as related to the high frequency of GI involvement among BD

patients in the Far East. However, interestingly, the presence of GI findings such as intestinal ulcers was reported in MDS patients without BD (5). Thus, it is not yet clear whether the high frequency of GI involvement in BD patients with associated MDS, is related to the geographies that these patients originate from, or it is an inherent feature of the association of BD and MDS. Moreover, we had the impression that some of the BD associated with MDS patients had few manifestations that could be pertained to BD, other than GI lesions. The presence of arthritis, various skin manifestations and gastrointestinal lesions have been reported in MDS patients (5, 9-11). Thus, we wondered whether the presence of GI lesions may have prompted a diagnosis of BD in these patients, and whether some of these patients may be mimicking BD.

Another interesting observation was that trisomy 8 is also present in several of these patients. In a previous study, the frequency of trisomy 8 in BD associated with MDS patients was reported as 86.7% (6), whereas it is present in only 7–9% of patients with primary MDS (12, 13). Patients with BD and constitutional trisomy 8, but without MDS have also been reported (14, 15). We wondered whether trisomy 8 is a modifying factor in the disease expression of BD associated with MDS.

We aimed to assess the association of BD, MDS and trisomy 8 by performing a systematic literature review and trying to answer the following questions:

i. whether GI involvement is an inherent feature of BD associated with MDS

ii. whether all of the reported BD-associated MDS patients fulfill different BD criteria

iii. whether trisomy 8 plays a role in the disease expression of BD associated with MDS.

Materials and methods

A systematic literature search including patients with Behçet's disease associated with MDS was performed. We searched PubMed with the keyword combination (Behçet's disease OR Behçet's syndrome) AND (myelodysplastic syndrome OR trisomy 8) up to December 2013 without any restrictions.

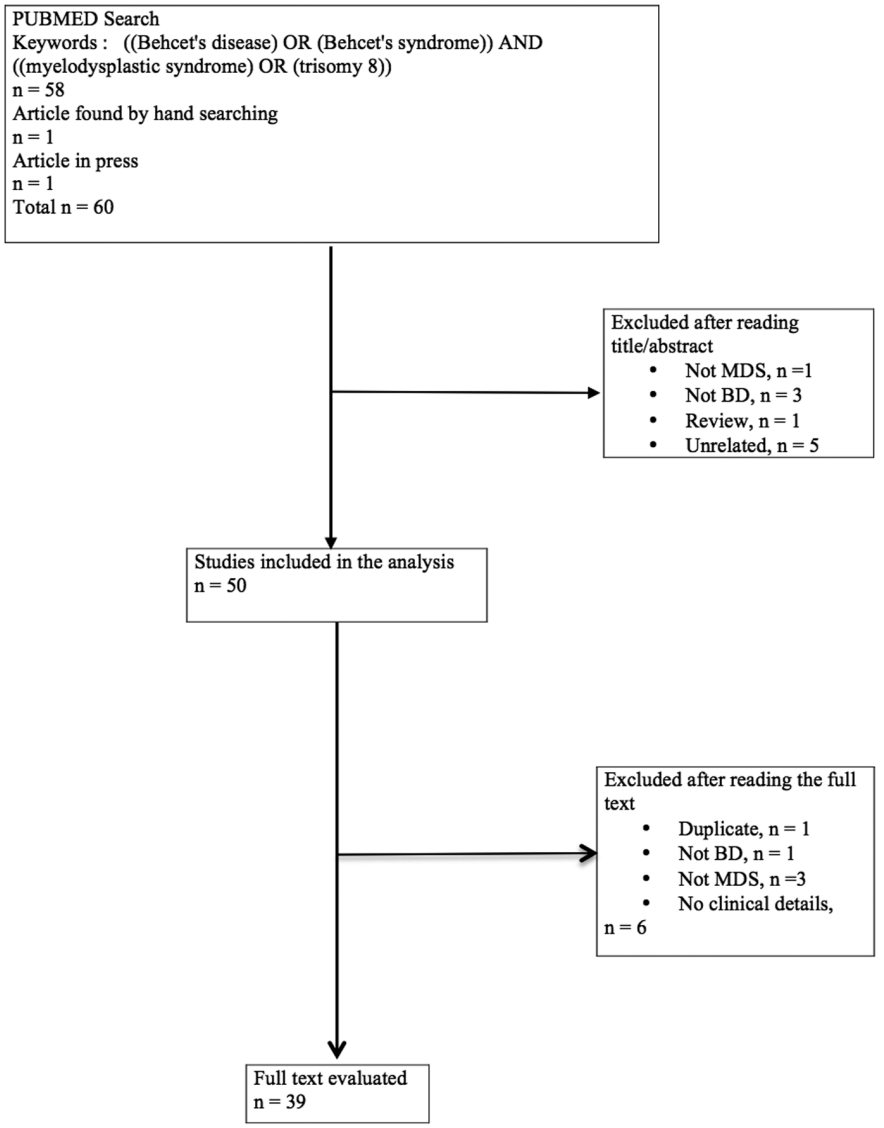

Fig. 1. Flow chart for selection of articles.

Studies that were about BD associated with MDS were included. The studies with insufficient clinical data were excluded. We collected data regarding patients' gender, BD manifestations, age at diagnosis of BD and MDS, GI involvement diagnosis time in relation to MDS, fulfillment of International Study Group (ISG) criteria for Behçet's Disease (16) and revised 1987 criteria of the Japanese group and features and type of GI involvement (17).

In order to delineate whether GI involvement is an inherent feature of BD associated with MDS and keeping in mind the geographic differences, we compared the frequency of GI involvement reported from Far East with those of patients reported from non-Far East countries. We also scrutinised the features and type of gastrointestinal involvement in these patients. In order to determine whether all of the BD associated with MDS patients actually have BD, we retrieved data on the other BD manifestations of these patients and fulfillment of ISG and Japanese criteria. Finally in order to determine the role of trisomy 8 in the disease expression of BD associated with MDS, we compared the frequency of each BD manifestation in MDS-associated BD patients with and without trisomy 8.

Continuous variables were compared by the Student's *t*-test and categorical variables were compared by the Chi-square test. Statistical significance was considered at the two-tailed 0.05 level

Table I. Demographic data, clinical features and presence of trisomy 8 of 53 patients of BD associated with MDS.

Author	Country	Sex/Age	GI İnvolvement	Other BD symptoms	HLA-B51	Fever	Tri 8[a]
Soysal *et al*. (2014)	Turkey	F/30	(+)	OU, GU, Skin, Joint		(+)	(+)
Toyogana *et al*. (2013)	Japan	M/36	(+)	OU	(+)	(-)	(+)
Toyogana *et al*. (2013)	Japan	F/37	(+)	OU, GU, Skin		(+)	(+)
Koguchi-Yoshioka *et al*. (2013)	Japan	M/63	(+)	OU, GU	(-)	(+)	(+)
Tanaka e*et al*. (2013)	Japan	M/57	(+)	OU, GU		(+)	(+)
Chen *et al*. (2012)	China	F/24	(+)	OU, GU, Skin, DVT		(+)	(+)
Iwata *et al*. (2011)	Japan	F/52	(+)	OU, GU, Skin, Joint, CNS	(-)	(-)	(+)
Shigemura *et al*. (2011)	Japan	F/4	(+)	OU, GU, Skin, Joint	(-)	(+)	(+)
Fujimura *et al*. (2010)	Japan	M/71	(-)	OU, Skin		(+)	(+)
Fujimura *et al*. (2010)	Japan	M/74	(-)	OU, Skin		(+)	(+)
Kovacs *et al*. (2009)	Hungary	M/75	(-)	OU, GU		(-)	(-)
Mantzourani *et al*. (2009)	Greece	M/68	(+)	OU, GU, Pathergy, DVT	(-)	(+)	(+)
Ahn *et al*. (2008)	Korea	F/42	(+)	OU, GU, Skin, Joint		(+)	(+)
Ahn *et al*. (2008)	Korea	M/36	(-)	OU, GU, Skin, Joint		(-)	(-)
Ahn *et al*. (2008)	Korea	M/53	(+)	OU, GU, Skin		(+)	(+)
Ahn *et al*. (2008)	Korea	F/49	(+)	OU, GU, Eye		(+)	(+)
Ahn *et al*. (2008)	Korea	F/31	(+)	OU, GU, Skin, Joint, Pathergy		(-)	(-)
Ahn *et al*. (2008)	Korea	M/47	(-)	OU, GU, Skin		(-)	(+)
Ahn *et al*. (2008)	Korea	F/67	(+)	OU, Skin, Joint, Eye		(-)	(-)
Ahn *et al*. (2008)	Korea	F/46	(+)	OU, GU, Skin		(+)	(+)
Lin *et al*. (2008)	Taiwan	F/49	(+)	O, G, Joint, Pathergy, AMIb		(+)	(+)
Thachil *et al*. (2008)	U.K	F/14	(-)	OU, GU, Pathergy		(-)	(+)
Fine *et al*. (2007)	USA	F/28	(-)	OU, GU		(-)	(+)
Nonami *et al*. (2007)	Japan	F/28	(+)	OU	(-)	(+)	(+)
Kawabata *et al*.(2006)	Japan	F/76	(+)	OU, GU, Skin	(+)	(+)	(+)
Kawabata *et al*. (2006)	Japan	M/75	(+)	OU, GU, Skin, Joint, Pathergy		(+)	(+)
Kuttikat *et al*. (2005)	U.K	M/54	(-)	OU, GU, Skin, Joint, Eye	(-)	(-)	(+)
Eder *et al*. (2005)	Israel	F/45	(+)	OU, GU, Skin, Joint		(+)	(-)
Ando *et al*. (2005)	Japan	M/49	(+)	OU, GU, Pathergy, DVT	(-)	(-)	(+)
Tsubata *et al*. (2005)	Japan	M/69	(+)	OU, Skin, Pathergy	(-)	(+)	(+)
Handa *et al*. (2004)	Japan	M/55	(+)	OU, GU, Skin		(-)	(-)
Tomonari *et al*. (2004)	Japan	F/36	(-)	OU, GU, Skin	(+)	(+)	(+)
Yamato *et al*. (2003)	Japan	F/10	(+)	OU, Skin		(+)	(-)
Fujita *et al*. (2002)	Japan	M/64	(+)	OU, GU, Pathergy	(-)	(+)	(+)
Karuvannur *et al*. (2001)	USA	M/61	(+)	OU, GU, Skin, Joint		(+)	(-)
Sirianni *et al*. (2001)	Italy	M/35	(-)	CNS		(-)	(-)
Ogawa *et al*. (2001)	Japan	M/25	(+)	OU, GU, Skin	(-)	(-)	(+)
Ogawa *et al*. (2001)	Japan	F/40	(+)	OU, GU, Skin, DVT	(-)	(+)	(+)
Tanaka *et al*. (2000)	Japan	M/39	(+)	OU, GU, Joint, DVT	(-)	(+)	(+)
Oh *et al*. (1999)	Korea	F/51	(+)	OU, GU, Joint, Pathergy		(+)	(+)
Nawata *et al*. (1999)	Japan	M/59	(-)	OU, GU, Skin	(+)	(+)	(+)
Bangerter *et al*. (1999)	Germany	F/43	(-)	OU, GU, Skin, Eye		(-)	(-)
Della Rossa *et al*. (1998)	Italy	M/50	(+)	OU, GU, Skin, Pathergy		(+)	(+)
Ohno *et al*. (1997)	Japan	F/34	(+)	OU, GU, Joint, Eye	(-)	(+)	(+)
Yano *et al*. (1996)	Japan	F/54	(-)	OU, GU, Skin, Pathergy	(-)	(+)	(+)
Yano *et al*. (1999)	Japan	F/23	(+)	OU, GU, Skin	(-)	(+)	(+)
Chyuma *et al*. (1992)	Japan	F/41	(+)	OU, Skin	(+)	(+)	(+)
Molina *et al*. (1992)	Spain	M/56	(+)	OU, GU, Skin, Pathergy		(+)	NR
Nakayama *et al*. (1989)	Japan	M/35	(-)	OU, GU, Skin, Joint, Eye		(-)	(-)
Nakayama *et al*. (1989)	Japan	M/52	(-)	OU, Skin, Joint		(+)	(-)
Nakayama *et al*. (1989)	Japan	M/57	(+)	OU, GU, Skin		(+)	(+)
Nehashi *et al*. (1988)	Japan	M/72	(-)	OU, GU, Skin	(+)	(+)	(+)

BD: Behçet's disease; MDS: Myelodysplastic syndrome; F: female; M: male; OU: oral ulcers; GU: genital ulcers; CNS: central nervous system involvement; DVT: deep vein thrombosis; NR: not reported; AMI: acute myocardial infarction [a]Presence of trisomy 8; [b]AMI had been thought to be due to vasculitis.

Results

Systematic review

The literature search yielded 58 articles. Ten articles were excluded after evaluating the title and abstract, 11 were excluded after reading the full-text (Fig. 1). An additional article was found during the hand search of the references of the retrieved articles. One article that was in press at the time of literature search was also included. Fifty-two patients were reported in these 39 manuscripts. Table I summarises the included studies (7, 8, 18-54). Among the 52 patients, 27 (51.9%) were men. Their mean age ± SD at the time of diagnosis of BD was 45.7±18.6 (4–80) and at the time of diagnosis of MDS was 46.9±17.4 (4-76). Thirty-nine (76.5%) patients had trisomy 8. Oral ulcers were the most common finding (98.1%), followed by genital ulcers (78.8%), skin lesions (69.2%) and GI involvement (69.2%).

Uveitis, which is a common feature of BD, was only recorded in 6 (11.5%) patients.

Geographical difference in relation to gastrointestinal involvement

Among the 52 patients, 40 were reported from the Far East (Japan (n=29), Korea (n=9), China (n=1) and Taiwan (n=1)), while 12 were reported from non-Far East countries (Germany (n=1), Israel (n=1), Turkey (n=1), Hungary (n=1), Greece (n=1), Italy (n=2), Spain (n=1), USA (n=2) and United Kingdom (n=2)). GI involvement was more common among the patients reported from Far East (75% *vs*. 50%), but the difference was not significant (p=0.15).

Characteristics of BD associated with MDS patients involving gastrointestinal tract

Among the 52 reported patients of BD-associated MDS, 36 had GI involvement (21 women, 16 men). Mean age at MDS diagnosis was 46 (±17.2) years (4-76) and mean age at BD diagnosis was 44.3 (±18.7) years (4-80). BD preceded the diagnosis of MDS in 15 patients while MDS preceded the diagnosis of BD in 7 patients. In 14 patients, both diseases were diagnosed simultaneously. Considering the time of GI diagnosis in relation to MDS, we found that GI involvement preceded MDS in 7 patients, occurred simultaneously in 18 patients, MDS preceded in 3 patients and information was not available in 8 patients. Among the 7 patients in whom GI involvement preceded MDS, 3 patients experienced GI flares at the time of MDS diagnosis.

BD manifestations of patients, symptoms of GI involvement, location of intestinal ulcers and presence of granuloma/vasculitis in histopathological examination are shown in Table II.

Fulfillment of BD criteria

Forty of 52 patients with BD associated with MDS fulfilled the ISG criteria (76.9%). Thirty-four patients fulfilled incomplete (65.4%) and 3 fulfilled complete (5.8%) revised 1987 criteria of the Japanese group. All of these were among the 40 patients who fulfilled ISG criteria. Thus 12/52 (23.1%) of the reported BD-associated MDS patients did not fulfill either of the criteria sets. Among the 12 patients who did not fulfill criteria, 6 had GI involvement. These 6 patients had other BD manifestations in addition to oral ulcers such as genital ulcers, nodular lesions or HLA B51 positivity, except for 1 patient who had only oral ulcers and GI lesions.

Table II. Clinical manifestations of BD associated with MDS with and without gastrointestinal involvement and total patient population.

	BD-MDS with GI involvement (n=36)	BD-MDS without GI involvement (n=16)	Total Patient Population (n=52)
Age at BD diagnosis (years), mean (SD)	44.3 ± 18.7	49 ± 18.3	45.7 ± 18.6
Age at MDS diagnosis (years), mean (SD)	46 ± 17.2	49.1 ± 18.1	46.9 ± 17.4
Male (no of patients, (%))	16/36 (44.4)	11/16 (68.7)	27/53 (51.9)
Symptoms of BD			
Oral ulcers	36/36 (100)	15/16 (93.8)	51/52 (98.1)
Genital ulcers	29/36 (80.6)	12/16 (75)	41/52 (78.8)
Eye lesions	3/36 (8.3)	3/16 (18.8)	6/52 (11.5)
Skin lesions	24/36 (66.7)	12/16 (75)	36/53 (69.2)
CNS involvement	1/36 (2.8)	1/16 (6.3)	2/52 (3.8)
Positive pathergy test	11/15 (73.3)	2/4 (50)	13/19 (68.4)
Arthritis	13/36 (36.1)	4/16 (25)	17/52 (32.7)
Vascular lesions	6/36 (16.7)	0/16 (0)	6/52 (11.5)
HLA-B51	3/16 (18.8)	3/5 (60)	6/21 (28.6)
Presence of trisomy 8	29/35 (82.9)	10/16 (62.5)	39/51 (76.5)
Symptoms of GI involvement			
Abdominal pain	24/29 (82.7)	NA	NA
Melena/ haematochezia	5/23 (21.7)	NA	NA
Diarrhea	7/23 (30.4)	NA	NA
Weight loss	4/22 (18.2)	NA	NA
Fever	29/36 (80.6)	7/16 (43.8)	36/52 (69.2)
Perforation	5/24 (20.8)	NA	NA
Ileus	1/29 (3.4)	NA	NA
Location of intestinal ulcers		NA	
Ileal	4 /22 (18.2)	NA	NA
Ileocecal	7 /22 (31.8)	NA	NA
Ileocolonic	7 /22 (31.8)	NA	NA
Colonic	4 /22 (18.2)	NA	NA
Histology		NA	
Granuloma	1/17 (5.9)	NA	NA
Vasculitis	3/17 (17.6)	NA	NA
Fulfillment of Behçet's disease criteria set			
ISG criteria	30/36 (83.3)	10/16 (62.5)	40/52 (76.9)
Incomplete Japanese criteria	28/36 (77.8)	6/16 (37.5)	34/52 (65.4)
Complete Japanese criteria	0	3/16 (18.8)	3/52 (5.8)

BD: Behçet's disease; MDS: Myelodysplastic syndrome; NA: Not applicable.

Characteristics of BD-associated MDS patients with or without trisomy 8

The clinical features of BD-associated MDS patients (evaluated in 51 patients) with and without trisomy 8 are given in Table III. The only significant difference in the clinical characteristics and frequency of BD manifestations between the two groups, was the increased frequency of fever (79.5% *vs*. 33.3%, p=0.005) in those with trisomy 8. GI involvement was somewhat more frequent in patients with trisomy 8, but the difference was not significant (74.4% *vs*. 50%, p=0.15). Eye involvement was more frequent among those without trisomy 8, but the difference was not statistically significant (7.7% *vs*. 25%, p=0.13). HLA-B51 results were reported in only 21 patients and these were all among the patients with trisomy 8. HLA-B51 was positive in 6/21 (28.6%).

Discussion

Our review showed that BD-associated MDS patients have a high frequency of GI involvement compared to the gener-

Table III. Clinical presentations of BD associated with MDS involving and not involving trisomy 8.

	BD-MDS with trisomy 8 (n=39)	BD-MDS without trisomy 8 (n=12)	*p*-value
Age at BD diagnosis (years), mean (SD)	45.6 ± 18.9	45.1 ± 18.7	0.94
Age at MDS diagnosis (years), mean (SD)	47.2 ± 17.6	45.4 ± 17.8	0.76
Male (no of patients, (%))	19 (48.7)	7 (58.3)	0.56
Oral ulcers	39 (100)	11 (91.7)	0.23
Genital ulcers	32 (82.1)	8 (66.7)	0.26
Eye lesions	3 (7.7)	3 (25)	0.13
Skin lesions	25 (64.1)	9 (83.3)	0.29
Positive pathergy test	11/17 (64.7)	1/1 (100)	1.00
Arthritis	10 (25.6)	7 (58.3)	0.07
Vascular lesions	6 (15.4)	0 (0)	0.31
GI involvement	29 (74.4)	6 (50)	0.15
Fever	31 (79.5)	4 (33.3)	0.005
HLA-B51	6/21 (28.6)	0	
Fulfillment of Behçet's disease criteria set			
ISG criteria	31 (79.5)	8 (66.7)	0.44
Incomplete Japanese criteria	27 (69.2)	6 (50)	0.23
Complete Japanese criteria	1 (2.6)	2 (16.7)	0.13

BD: Behçet's disease; MDS: Myelodysplastic syndrome.

al BD populations both in reports from the Far East (75%) and from non-Far East (50%). The increase is somewhat parallel to the background frequency of GI involvement in the general BD population in these regions (between 10–30% in the Far East and 3–8% in others) (2). GI features of BD-associated MDS patients were also similar to what was previously reported in gastrointestinal BD series (55, 56). Thus we can propose that having associated MDS increases the risk of gastrointestinal involvement in BD patients, but does not modify the clinical expression of gastrointestinal involvement.

When we checked the other manifestations of BD among the 52 BD patients with MDS, we observed that the frequencies of these manifestations were similar to what is generally observed in BD patients, except that eye involvement was uncommon (6/52, 11.5%). Most of the patients fulfilled ISG (40/52, 76.9%) and Japanese criteria (34/52, 65.4% incomplete and 3/52, 5.8% complete). The somewhat low frequency of eye involvement among the BD patients associated with MDS may be the reason for the low frequency of fulfilling Japanese criteria, since uveitis is one of the major features of this criteria set. When we looked at the specific disease features of the 12 patients who did not fulfill criteria, in order to question the diagnosis of BD, we realised that except for 2 patients one could comfortably call these BD. In those two patients, BD related findings were oral ulcers and GI involvement in 1 and oral ulcers and CNS involvement in the other.

In some previous reports of patients with MDS associated with BD, it was discussed that trisomy 8 may be responsible for or involved in the pathogenesis of intestinal ulceration in these patients. This assumption was mainly based on 2 previous studies. In one of these, Kimura and colleagues had retrospectively analysed clinical and laboratory features of 46 MDS patients followed in a haematology clinic and observed that 8 of these patients had trisomy 8. Three of these 8 patients had multiple intestinal ulcers while none of the MDS patients without trisomy 8 had intestinal ulcers (5). Another study by Ahn and colleagues compared the features of their BD patients with and without MDS and found that 6 of their 8 BD patients with MDS had intestinal ulceration (75%), compared to 9/66 of their BD patients without MDS (14%). Of the 6 patients with intestinal ulcers, 4 had trisomy 8 (26). We tried to delineate the possibility of trisomy 8 being the cause of gastrointestinal involvement in these patients, by comparing the frequency of gastrointestinal involvement in BD patients associated with MDS, with or without trisomy 8. Although there was a trend for an increased frequency of gastrointestinal involvement in the trisomy 8 positive group (74.4% *vs*. 50%), the difference was not statistically significant (p=0.15). This may be related to the small number of patients in each group. However the fact that half of the BD-associated MDS patients without trisomy 8 had gastrointestinal involvement makes us think that not only trisomy 8, but also MDS itself may play a role in the high frequency intestinal involvement in these patients.

The comparison of clinical features of patients with and without trisomy 8, aiming to determine whether the presence of trisomy 8 modifies disease expression of BS, showed that fever is significantly more common in patients with trisomy 8 (p=0.005). Overexpression of immune and inflammatory responses in MDS has been shown previously and fever is a usual finding in these patients (9). Interestingly, in BD-associated MDS patients, fever seems to be associated mainly with trisomy 8, since fever is present in only 4/12 (33.3%) of BD-associated MDS patients without trisomy 8.

One limitation of our study was that there were few reports of BD-associated MDS from non-Far East countries. Although this probably simply reflects the fact that this association is more common in the Far East, the small number of patients from non-Far East may have hampered our comparison of gastrointestinal involvement between the two regions. A further limitation was that we were not able give information on the prognosis of these patients and compare trisomy 8 positive and negative patients, since long term prognosis and response to treatment of different disease manifestations was not provided in most of the reports.

In conclusion, the frequency of GI involvement is higher in BD-associated MDS patients compared to what is usually observed in general BD populations and this increase is somewhat parallel to the background frequency of GI involvement both in the Far East and in other geographies. Thus we may reason that the increased frequency of

gastrointestinal involvement is an inherent feature of this association. The diagnosis of BD seems to be definite in most of the patients and the presence of intestinal ulcers, which is the one of the differences between ISG and Japanese criteria, was not the reason for a BD diagnosis in most of these patients. Finally the presence of trisomy 8 seems to modify the disease expression with an increased frequency of fever and in contrast to what was previously proposed, does not seem to be related with an increase in the frequency of gastrointestinal involvement.

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