Clinical features and independent predictors of Behçet's disease associated with myelodysplastic syndrome

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Abstract

Objective

To investigate the correlation of Behçet's disease (BD) with myelodysplastic syndrome (MDS) and identify the predictive risk factors in Chinese patients.

Methods

A retrospective study of BD associated with MDS (BD-MDS) patients from the First Affiliated Hospital of Zhengzhou University was conducted.

Results

Among 15 BD-MDS patients, 10 were female and 5 male. While 13 (86.7%) patients had abnormal karyotype, 11 patients with trisomy 8. 10 (66.7%) had gastrointestinal (GI) involvement. Compared with 60 general BD patients without MDS, the BD-MDS patients were significantly older. In addition, fever and GI involvement were more common in BD-MDS patients, whereas these patients had lower levels of leukocyte count, haemoglobin, and platelet count ($p<0.05$). Logistic regression analysis showed that GI involvement, low haemoglobin, and high ESR level were independently associated with the development of MDS in BD patients. BD-MDS patients with GI involvement (IBD-MDS) were usually much older and have more fever than IBD patients without MDS, as well as lower leukocyte count, haemoglobin level, platelet count, and higher erythrocyte sedimentation rate (ESR) and C-reactive protein levels ($p<0.05$). By comparison with 60 primary MDS patients without BD, the BD-MDS patients had more abnormal karyotypes and more trisomy 8 ($p<0.05$), while the distribution of 2016 WHO subtypes of MDS and IPSS-R categories were similar.

Conclusion

Our findings suggest that cytogenetic abnormalities, especially trisomy 8, may play a role in the association of GI involvement, BD, and MDS. GI involvement, low haemoglobin, and high ESR level were independent predictors for MDS development in BD patients.

Key words

Behçet's disease, myelodysplastic syndrome, gastrointestinal involvement, trisomy 8, predictors

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Introduction

Behçet's disease (BD) is a multisystemic inflammatory disease characterised by recurrent oral and genital ulcers, ocular inflammation, cutaneous lesions, as well as articular, vascular, neurological, and gastrointestinal (GI) manifestations. While BD is rarely complicated with leukaemia or other blood diseases, there does exist a correlation with myelodysplastic syndrome (MDS). MDS is an acquired clonal haematologic disorder characterised by impaired generation and maturation of haematopoietic cells in bone marrow, resulting in peripheral cytopenia and a high risk of transformation to acute leukaemia (1). Previous studies have demonstrated a correlation between BD and MDS (2-4). In addition, the majority of BD patients associated with MDS (BD-MDS) had GI manifestations, and the aetiology remains elusive. Genetic aberrations, especially trisomy 8, may play a role in the GI involvement in BD and MDS patients. However, most studies were case reports from Korea and Japan. As the prevalence of BD is also high in China (5), it is imperative to elucidate the clinical presentation and characteristic features in Chinese patients. Furthermore, comparison between BD-MDS patients and general BD patients without MDS, especially, BD with GI involvement (IBD) without MDS was lacking. Similarly, there is a scarcity of data about the comparison of BD-MDS patients and primary MDS patients without BD. In this study, we reported 15 new cases of BD-MDS patients and compared them with general BD/IBD patients without MDS and primary MDS patients without BD, in order to reveal different characteristics and predictive risk factors of BD-MDS patients.

Materials and methods

Patients

We conducted a retrospective study of patients who visited the First Affiliated Hospital of Zhengzhou University between January 1, 2010, and January 1, 2022, and these patients were diagnosed with BD-MDS for the first time. All patients fulfilled the 1990 International Study Group (ISG) BD criteria or the 2013 International Criteria for BD (ICBD). MDS was diagnosed and classified according to the 2016 World Health Organisation (WHO) classification, which included morphologic, immunophenotypic, cytogenetic, fluorescence in situ hybridisation (FISH), and molecular data. The exclusion criteria included: 1) age <18 years old, 2) complicated with other connective tissue diseases, 3) MDS secondary to infectious-, drug- or neoplasm-related disorders, and 4) incomplete clinical or laboratory data necessary for this study. Finally, there were 15 patients enrolled in our study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committee of the First Affiliated Hospital of Zhengzhou University (2021-KY-0649-002).

Control groups

The control groups included patients with general BD without MDS (n=60), IBD without MDS (n=40), and primary MDS without BD (n=60). They were randomly selected from the medical record library and stratified by the visit time consisting with the BD-MDS patients when they first diagnosed in a ratio of 1:4. BD or MDS patients younger than 18 years old were excluded and all patients with general BD were active. For patients hospitalised many times, the data of the first visit were collected from those with BD or MDS.

Clinical and laboratory examinations

A standard form was used to collect demographic, clinical, and laboratory data from medical records. Clinical features were collected at baseline and during follow-up: fever, skin and mucosal manifestations, arthritis, uveitis, GI involvement, neuropathy, vascular lesions, and pathergy reaction. The laboratory examinations included peripheral blood count and morphological analysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hepatitis virus and human immunodeficiency virus (HIV) serologies and immunological data (antineutrophil cytoplasmic and the titer of antinuclear antibodies). The MDS-related laboratory data such as bone marrow biopsy and examinations, chromosome karyotype analysis,

Table I. Clinical characteristics of 15 patients with BD-MDS patients.

Case No.	Age/Sex	MDS type	Karyotype	BD onset	BD symptoms	Endoscopic findings	IPSS-R
1	41/F	MDS-RS-MLD	+8	Simultaneously	Fe, O, G, A	-	Intermediate
2	22/F	MDS-MLD	+8	6m before MDS	O, G	-	Intermediate
3	56/F	MDS-U	+8	3m after MDS	O, S, A, P	-	Intermediate
4	39/F	MDS-EB-I	Normal	2m after MDS	O, G, S	-	High
5	44/F	MDS-MLD	Normal	120m before MDS	O, G, S	-	Intermediate
6	38/F	MDS-MLD	+8	35m before MDS	Fe, O, G, A, GI	Terminal ileum and colonic ulcer	Intermediate
7	75/M	MDS-EB-II	20q-, +8	53m before MDS	Fe, O, G, GI	Ileocecal ulcer	Very high
8	43/M	MDS-MLD	+8, +9, +16	Simultaneously	O, G, GI	Oesophageal and stomach ulcer	Intermediate
9	48/F	MDS-MLD	+8	216m before MDS	Fe, O, G, GI	Terminal ileum ulcer	High
10	37/F	MDS-SLD	+8, +9	2m before MDS	O, G, A, GI	colonic ulcer	Low
11	58/F	MDS-EB-I	5q-, +8	5m after MDS	Fe, O, GI	Ileocecal, small intestine and rectum ulcer	High
12	64/M	MDS-EB-I	+8	9m before MDS	Fe, O, G, GI	Terminal ileum, ileocecal valve and rectum ulcer	High
13	66/M	MDS-EB-I	+2, +5, +9, +9, +10, +10, +11, +14, +16, -19, +mar1, +mar2	Simultaneously	Fe, O, G, S, U, P, GI	entire colon and rectum ulcer	Very high
14	36/F	MDS-MLD	+8	24m before MDS	Fe, O, S, GI	Terminal ileum, ileocecal valve and colonic ulcer	Intermediate
15	52/M	MDS-MLD	20q-	24m before MDS	O, S, GI	Oesophageal, ileocecal valve and colonic ulcer	Low

Case No.	BD-specific treatment	MDS-specific treatment	Treatment targeting both diseases	Outcomes (BD/MDS)
1	GC	Stanozolol, Testosterone undecanoate	-	Improved/Stable
2	GC	Refuse	Thalidomide	Improved/Death
3	GC	Supportive care	Thalidomide	Improved/Stable
4	GC	CGA, HA, DA, AA	-	Improved/Death
5	GC	Supportive care	Thalidomide	Improved/Stable
6	GC	Decitabine	Thalidomide	Improved/Death
7	GC, Methotrexate	Decitabine	Thalidomide	Deteriorated /Death
8	GC	Refuse	Thalidomide	Deteriorated /Death
9	GC, Sulfasalazine	Refuse	Thalidomide	Unchanged/Death
10	GC	Supportive care	Tacrolimus, Thalidomide	Improved/Stable
11	GC, Mesalazine	Decitabine, Cytarabine	-	Deteriorated/Death
12	GC, Mesalazine	Refuse	-	Unchanged/Death
13	GC, Mesalazine	Azacitidine, Decitabine combined with CAG	Cyclosporin, Thalidomide	Improved/Death
14	GC, Adalimumab, IVIG	Stanozolol	Tacrolimus, Thalidomide	Improved/Stable
15	GC	Danazol	Cyclosporin, Thalidomide	Improved/Stable

A: arthritis; AA: Doxorubicin + Cytarabine; BD: Behçet's disease; CAG: Cytarabine + Aclarubicin + Granulocyte colony-stimulating factor; DA: Daunorubicin + Cytarabine; F: female; Fe: fever; G: genital ulcer; GC: glucocoticoids; GI: gastrointestinal involvement; HA: Homoharringtonine + Cytarabine; IPSS-R: revised international prognosis scoring system; IVIG: intravenous immunoglobulin; M: male; MDS: myelodysplastic syndrome; MDS-EB: myelodysplastic syndrome with excess blasts; MDS-MLD: myelodysplastic syndrome with multilineage dysplasia; MDS-RS-MLD: myelodysplastic syndrome with ring sideroblasts with multilineage dysplasia; MDS-RS-SLD: myelodysplastic syndrome with ring sideroblasts with single lineage dysplasia; MDS-SLD: myelodysplastic syndrome with single lineage dysplasia; MDS-U: myelodysplastic syndrome unclassifiable; O: oral ulcer; P: pathergy; S: skin lesion; U: uveitis.

and fluorescence FISH analyses were collected for risk stratification. The determination of chromosome abnormalities and naming was based on the International Naming System of Human Cytogenetics (ISCN) 2005. The revised international prognosis scoring system (IPSS-R), the gold standard for prognosis assessment of MDS, was utilised in this study. Endoscopic abnormalities were collected which contained anatomical evaluation and histopathological examination.

Statistical analysis

Continuous data were described as mean ± standard deviation (SD) or median (interquartile range) (IQR), while categorical variables were presented as numbers and percentages. Student's t-test or Mann-Whitney U-test was used to compare continuous data and Chi-square or Fisher's exact test for categorical variables. The factors that showed significant differences among the groups were subjected to a logistic regression model to identify the independently associated factors for the development of BD-MDS. SPSS 20.0 was used for statistical analyses. *p*-values less than 0.05 were considered statistically significant.

Results

Characteristics of the 15 BD-MDS patients

Among 15 patients diagnosed with BD-MDS, 10 were female and 5 were male (Table I). The mean age when first diagnosed with BD-MDS was 48.3±13.9

years. Compared with female patients, the mean age of the onset was older in male patients [(42.4±10.4) years *vs.* (60.0±13.2) years; $p<0.001$)]. The mean age was 45.6 ± 14.6 years when diagnosed with BD, and 48.2±13.9 years when diagnosed with MDS. BD was diagnosed prior to MDS in 9 patients, after MDS in 3 patients, while 3 patients were diagnosed at the same time.

All 15 patients fulfilled the 1990 ISG or 2013 ICBD criteria. Among them, oral ulceration was present in 15 cases, genital ulceration in 12, GI involvement in 10, fever in 9, skin lesions in 7, arthritis in 4, uveitis in 1, and pathergy reaction in 2. Vascular lesions and neuropathy were not seen in all patients. Among the 10 patients with IBD, ulcers occurred throughout the digestive tract. The most commonly involved location was ileocecal (70%), followed by the colon (50%), rectum (30%), oesophagus (20%), small intestine (10%), and stomach (10%).

The main subtype of MDS according to 2016 WHO classifications included 7 patients with myelodysplastic syndrome with multilineage dysplasia (MDS-MLD), 1 with myelodysplastic syndrome with single lineage dysplasia (MDS-SLD), 1 with myelodysplastic syndrome with ring sideroblasts with multilineage dysplasia (MDS-RS-MLD), 4 with myelodysplastic syndrome with excess blasts (MDS-EB)-I, 1 with MDS-EB-II, and 1 with myelodysplastic syndrome unclassifiable (MDS-U). Among the 15 patients, 13 (86.7%) had abnormal karyotype, while trisomy 8 was detected in 11 (73.3%) out of these 13 patients. These included single aberration (8 cases), double aberrations (3 cases), and complex aberrations (2 cases). Among the 11 patients with trisomy 8, 8 (72.7%) had GI involvement, and these GI-involved patients (n = 10) had trisomy 8 in 8 (80%). Based on the IPSS-R, there were 2 patients (13.3%) in the low-risk group, 7 (46.7%) in the intermediate-risk group, 4 (26.7%) in the high-risk group, and 2 (13.3%) in the very high-risk group.

All 15 patients were treated with glucocorticoids to alleviate the BD symptoms. Regarding MDS-specific treatment, 2 patients received demethylation drugs such as decitabine or azacitidine, 1 received chemotherapy consisting of cytarabine, 2 received demethylation drugs combined with chemotherapy. Four patients refused MDS-specific treatment, while the other 6 were treated with supportive care or androgen drugs according to the risk stratification. Altogether 11 patients were subjected to treatment targeting both diseases including thalidomide and calcineurin inhibitors such as tacrolimus or cyclosporin.

BD symptoms were improved in 10 patients after BD or MDS-specific treatment. Altogether 9 patients died with a median survival of 7 (1-24) months, 8 due to MDS, 1 due to severe infection. Other 6 patients were alive at the last follow-up. Mortality varied significantly by risk stratification ($p<0.05$). The mortality of patients with high or very high, intermediate, and low-risk stratification was 100%, 42.9%, and 0, respectively. Among the 6 patients with high or very high-risk stratification, 4 received methylation drugs or chemotherapy and died with a median survival of 7.5 (1-18) months, while 2 refused MDS-specific treatment and died with a mean survival of 4 months.

Table II. Characteristics of patients with BD-MDS patients and general BD without MDS.

	BD-MDS (n=15)	General BD without MDS (n=60)	*p*-value
Age at BD diagnosis, years, mean (SD)	45.6 (14.6)	37.8 (12.7)	0.042*
Male, n (%)	5 (33.3)	31 (51.7)	0.204
Duration, years, median (IQR)	6.0 (1.0-10.0)	5.0 (1.0-10.0)	0.921
Fever, n (%)	9 (60.0)	18 (30.0)	0.030*
Oral ulcer, n (%)	15 (100)	60 (100)	/
Genital ulcer, n (%)	12 (80.0)	44 (73.3)	0.595
Skin lesions, n (%)	7 (46.7)	42 (70.0)	0.089
Arthritis, n (%)	4 (26.7)	20 (33.3)	0.853
Vascular lesions, n (%)	0	9 (15.0)	0.112
Uveitis, n (%)	1 (6.7)	19 (31.7)	0.103
Neuropathy, n (%)	0	8 (13.8)	0.130
GI involvement, n (%)	10 (66.6)	10 (16.6)	<0.001*
Laboratory findings			
Leukocyte, 10^9/litre, mean (SD)	2.4 (0.9)	8.1 (2.8)	<0.001*
Haemoglobin, g/litre, mean (SD)	84.9 (22.6)	123.3 (19.5)	<0.001*
Platelets, 10^9/litre, median (IQR)	56.0 (29.0-87.0)	239.0 (200.5-397.6)	<0.001*
MCV, fL, mean (SD)	105.7 (12.1)	90.0 (5.3)	<0.001*
MCH, pg, mean (SD)	34.3 (3.2)	29.6 (2.1)	<0.001*
MCHC, g/L, mean (SD)	325.1 (14.2)	329.2 (9.9)	0.205
Anaemia, n (%)	12 (80)	15 (25)	<0.001
Macrocytic anaemia, n (%)	6 (40)	2 (3.3)	<0.001
ESR, mm/hour, median (IQR)	66.0 (32.0-103.0)	20.0 (8.8-39.5)	<0.001*
CRP, mg/liter, median (IQR)	80.0 (37.4-100.0)	12.0 (3.3-33.3)	0.001*

BD: Behçet's disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; MDS: myelodysplastic syndrome; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration.
*$p<0.05$.

Comparison of BD-MDS patients and general BD patients without MDS

By comparison with 60 patients of general BD patients without MDS, the BD-MDS patients were significantly older [(45.6±14.6) years *vs.* (37.8±12.7) years; $p=0.042$)], and had more fever (60.0% *vs.* 30.0%; $p=0.030$), GI involvement (66.6% *vs.* 20.0%; $p=0.001$), but the lower level of leukocyte count [(2.4±0.9) × 10^9/litre *vs.* (8.1±2.8) ×10^9/litre; $p<0.001$], haemoglobin [(84.9±22.6) g/litre *vs.* (123.3±19.5) g/litre; $p<0.001$], and platelet count [56.0 (29.0-87.0) × 10^9/litre *vs.* 239.0 (200.5-397.6) × 10^9/litre; $p<0.001$] (Table II). In addition, the level of mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) were higher in BD-MDS patients than in general BD patients. Anaemia, especially macrocytic anaemia, was more common in BD-MDS patients. Approximately 80% of MDS-BD patients had anaemia and half were macrocytic anaemia. Among the 6 patients with macrocytic anaemia,

Table III. Characteristics of patients with IBD-MDS patients and IBD without BD patients.

	IBD with MDS (n=10)	IBD without MDS (n=40)	*p*-value
Age at BD diagnosis, years, median (IQR)	49.0 (38.5-63.8)	30.0 (23.3-44.8)	0.002*
Male, n (%)	5 (50)	23 (57.5)	0.943
BD Duration, months, median (IQR)	54.0 (12.0-93.0)	94.5 (25.0-147.3)	0.070
IBD Duration, months, median (IQR)	11.0 (1.8-36.0)	12.0 (1.0-34.5)	0.952
Clinical manifestations, n (%)			
Fever	8 (80.0)	11 (27.5)	0.007*
Oral ulcer	10 (100)	40 (100)	/
Genital ulcer	8 (80)	27 (67.5)	0.700
Skin lesions	4 (40)	17 (42.5)	>0.999
Arthritis	2 (20)	9 (22.5)	>0.999
Vascular lesions	0	2 (5.0)	0.475
Uveitis	1 (10)	2 (5.0)	0.556
Neuropathy	0	0	/
Symptoms of GI involvement, n (%)			
Abdominal pain	9 (90)	32 (80)	0.782
Melena/haematochezia	4 (40)	17 (42.5)	>0.99
Nausea/vomiting	4 (40)	19 (47.5)	0.943
Diarrhoea	3 (30)	9 (22.5)	0.934
Location of GI ulcers, n (%)			
Oesophagus	2 (20)	10 (25)	>0.999
Stomach	1 (10)	3 (7.5)	>0.999
Ileocecal	7 (70)	29 (72.5)	>0.999
Small intestine	1 (10)	6 (15)	>0.999
Colon	5 (50)	8 (20)	0.126
Rectum	3 (30)	3 (7.5)	0.157
Multiple-site lesions, n (%)	7 (70)	15 (37.5)	0.135
Lesions confined to the ileocecal region, n (%)	2 (20)	17 (42.5)	0.344
Number of GI ulcers, n (%)			0.616
Single (1)	3 (30)	18 (45)	
Multiple (≥2)	7 (70)	22 (55)	
Ulcertation diameter, n (%)			0.635
<5mm	1 (10)	2 (5.0)	
5-20mm	5 (50)	18 (45)	
>20mm	4 (40)	20 (50)	
Laboratory findings at BD diagnosis			
Leukocyte, 10^9/litre, mean (SD)	2.64 (0.94)	7.90 (2.97)	<0.001*
Haemoglobin, g/litre, mean (SD)	82.90 (22.18)	117.69 (25.09)	<0.001*
Platelet,10^9/litre, median (IQR)	55.0 (40.3-98.5)	242.5 (199.0-363.6)	<0.001*
CRP, mg/litre, median (IQR)	87.1 (50.1-113.7)	14.7 (3.7-35.5)	0.001*
ESR, mm/hour, median (IQR)	53.0 (26.0-87.3)	18.5 (9.3-23.7)	0.006*

BD: Behçet's disease; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; IBD: Behçet's disease with gastrointestinal involvement; MDS: myelodysplastic syndrome. *p<0.05.

1 was diagnosed with MDS due to cytopenia before BD onset, 5 were presented with macrocytic anaemia years before MDS was diagnosed, with a median time of 35 (22-84) months. With regards to inflammatory biomarkers, ESR and CRP were significantly higher in BD-MDS patients (p<0.05). Logistic regression analysis showed that GI involvement (OR=8.617, 95% CI: 1.063-69.868, p=0.044), low haemoglobin (OR=0.923, 95% CI: 0.870–0.979, p=0.016), and high ESR (OR=1.046, 95% CI: 1.008–1.086, p<0.001) level were independently associated with the development of MDS in BD patients.

Comparison of IBD patients with MDS (IBD-MDS) and IBD patients without MDS

Among the 15 BD-MDS patients, 10 had GI involvement. We compared them with 40 IBD patients without MDS and analysed the demographic and clinical features of these two groups (Table III). There was no significant difference with regards to oral and genital ulcers, skin lesions, and arthritis. Vascular lesions, uveitis and neuropathy, the common manifestations in general BD, were not recorded or very rare in both groups. Patients with IBD-MDS were significantly older [49.0 (38.5–63.8) years *vs*. 30.0 (23.3-44.8) years; p=0.002] and fever was more common (80.0% *vs*. 27.5%; p=0.032) than IBD patients without MDS. In addition, the IBD-MDS patients were likely to have lower leukocyte count, haemoglobin level, and platelet count, as well as higher ESR and CRP levels (p<0.05). There was no statistically significant difference in the clinical symptoms of GI involvement between the two groups. Furthermore, no difference was found in the two groups with respect to the location, size and number of GI ulcers.

Comparison of BD-MDS patients and primary MDS patients without BD

The age, gender, and duration of the BD-MDS patients were comparable to primary MDS patients without BD (Table IV). The distribution of subtypes according to 2016 WHO classifications of MDS was similar between the two groups. By comparison with 60 primary MDS patients without BD, abnormal karyotypes were more common in the BD-MDS patients (86.7% *vs*. 41.7%; p<0.001), and more had trisomy 8 (73.3% *vs*. 13.3%; p<0.001). In terms of laboratory tests, BD-MDS patients had a higher level of haemoglobin [85.0 (58.0-108.0) g/litre *vs*. 66.2 (54.1-87.2) g/litre; p=0.048]. Regarding the classification of chromosome aberration, IPSS-R categories and IPSS-R score, there were no significant differences. Logistic regression analysis showed that older age (OR=1.117, 95% CI: 1.017–1.227, p=0.020) and low haemoglobin (OR=0.937, 95% CI: 0.879–0.999, p=0.046) were independently associated with the development of the co-occurrence of BD in MDS patients.

Discussion

After reviewing a series of 15 Chinese patients of BD-MDS, we demonstrate a particular clinical pattern of these patients compared with general BD/IBD patients or primary MDS patients. The association of BD-MDS was more

Table IV. Characteristics of patients with BD-MDS patients and primary MDS without BD.

	BD-MDS patients (n=15)	Primary MDS without BD (n=60)	*p*-value
Age at MDS diagnosis, years, mean (SD)	48.2 (13.9)	55.0 (16.1)	0.137
Male, n (%)	5 (33.3)	30 (50)	0.247
Duration, months, median (IQR)	12.0 (3.0-60.0)	4.0 (1.0-12.0)	0.070
Distribution of MDS subtypes, n (%)			0.406
MDS-SLD	1 (6.7)	7 (11.7)	
MDS-MLD	7 (46.7)	17 (28.3)	
MDS-RS-SLD	0	1 (1.7)	
MDS-RS-MLD	1 (6.7)	1 (1.7)	
MDS-EB-I	4 (26.7)	15 (25.0)	
MDS-EB-II	1 (6.7)	16 (26.7)	
MDS-U	1 (6.7)	3 (5.0)	
Abnormal karyotype, n (%)	13 (86.7)	25 (41.7)	0.002*
Distribution of chromosome aberrations, n (%)			
+8 only	7 (46.7)	4 (6.7)	<0.001*
+8 included	11 (73.3)	8 (13.3)	<0.001*
Classification of chromosome aberration, n (%)			0.439
Single aberration	8 (61.5)	12 (48.0)	
Double aberrations	3 (23.1)	4 (16.0)	
Complex aberrations	2 (15.4)	9 (36.0)	
IPSS-R risk categories, n (%)			0.642
Very low	0	1 (1.7)	
Low	2 (13.3)	14 (23.3)	
Intermediate	7 (46.7)	16 (26.7)	
High	4 (26.7)	18 (30.0)	
Very high	2 (13.3)	11 (18.3)	
IPSS-R score, mean (SD)	4.7 (1.4)	4.7 (1.8)	0.892
Leukocyte, 10^9/litre, median (IQR)	2.39 (1.82-3.10)	2.64 (2.00-4.30)	0.280
Haemoglobin, g/litre, median (IQR)	85.0 (58.0-108.0)	66.2 (54.1-87.2)	0.048*
Platelets,10^9/litre, median (IQR)	56.0 (29.0-87.0)	37.0 (16.0-90.3)	0.458

BD: Behçet's disease; IPSS-R: revised international prognosis scoring system; MDS: myelodysplastic syndrome; MDS-EB: myelodysplastic syndrome with excess blasts; MDS-MLD: myelodysplastic syndrome with multilineage dysplasia; MDS-RS-MLD: myelodysplastic syndrome with ring sideroblasts with multilineage dysplasia; MDS-RS-SLD: myelodysplastic syndrome with ring sideroblasts with single lineage dysplasia; MDS-SLD: myelodysplastic syndrome with single lineage dysplasia; MDS-U: myelodysplastic syndrome unclassifiable. *p<0.05.

common in females. The onset age of the disease in females was younger than males, consistent with a previous study. While MDS-MLD was the most common subtype, any subtypes may present in BD-MDS patients. The onset of BD and MDS was not always simultaneous. BD may occur before, after, or at the same time as MDS. Of the total 15 patients in our study, 60% were diagnosed with BD prior to MDS and 20% were diagnosed at the same time. Tada *et al*. reviewed 54 Japanese cases of BD-MDS from the literature as well as their own clinical experience, and the results showed that BD and MDS developed nearly simultaneously in 49.0% of cases, BD preceded MDS in 31.4% of the cases (6). It seems not very common that MDS developed before BD, indicating that BD-MDS may be a different clinical entity and such patients should not be treated simply as the BD-like symptoms of MDS.

Compared with general BD patients without MDS, BD-MDS patients were older. They often have a fever, a lower leukocyte count, haemoglobin level, and platelet count, as well as higher ESR and CRP. We also found a higher frequency of GI involvement in BD-MDS patients compared with general BD. No significant differences were found between BD-MDS and general BD patients regarding the occurrence of uveitis, vascular lesions, and neuropathy. Logistic regression analysis showed that GI involvement, low haemoglobin, and high ESR were independently associated with the development of MDS in BD patients.

Patients with IBD-MDS were more likely to be older and more frequently suffered from fever. They had lower leukocyte count, haemoglobin level, and platelet count. There was no statistical difference in clinical manifestation and symptoms of GI involvement between IBD-MDS patients and IBD patients without MDS. The distribution, number, and size of GI ulcers seemed similar. Ulcers could occur throughout the digestive tract, while ileocecal involvement was the most common site in both groups. The laboratory examinations such as ESR and CRP in IBD-MDS patients were higher than in IBD patients without MDS, indicating that inflammation and fever are common in IBD-MDS patients.

Compared with primary MDS patients without BD, the rate of chromosomal abnormalities was higher in BD-MDS patients. There was no obvious difference in the distribution of subtypes. Neither the IPSS-R categories nor IPSS-R score made any difference between two groups. Cytogenetic examination showed 86.7% cases with chromosomal abnormalities, and the prevalence rate of trisomy 8 was as high as 73.3%, which was consistent with previous reports (4, 7). Nevertheless, trisomy 8 can be detected only in 6.5% to 16.3% of primary MDS patients (8). It is plausible to postulate that trisomy 8 may play an important role in the association of BD with MDS patients.

A previous study has shown that among patients with MDS, trisomy 8 positive patients have more intestinal ulcers (9). The mechanisms by which trisomy 8 causes intestinal ulcers is not completely understood (10). Kimura et al. speculated that c-Myc oncogene located in chromosome 8 may play an important role in cell proliferation and epithelial regeneration (11). In addition, trisomy 8 is associated with low copy numbers of the human β-defensin 2 gene, which affects innate immunity (12). Chen *et al*. analysed the gene expression pattern in purified CD34-positive hematopoietic progenitor cells obtained from MDS patients with trisomy 8 and the results showed that upregulated genes in patients with trisomy 8 are primarily involved in immune and inflammatory responses, including TGF-β, TGF-βR, IL-6, IL-7β, VCAM-1 and ICAM-1 (13). The elevated pro-inflammatory

cytokines such as TNF-α, IL-1 and IL-6 may contribute to the development of intestinal ulcers (14). Moreover, a previous report demonstrated that the IL-7/IL-7R-dependent signalling pathway is involved in both immune response in intestinal mucosa and the development of colitis (15). Collectively, these findings suggest that trisomy 8 may be involved in the pathogenesis of GI lesions.

No recommendations are currently available for the optimal treatment of BD-MDS patients. Treatment regimens vary depending on the risk stratification and individual condition. Previous studies suggest that conventional medical therapies may be inefficiency to treat patients with BD-MDS (16). Immunosuppressive agents can improve BD-associated symptoms but not that associated with MDS. Treatment should focus on MDS because underlying immune abnormalities may be derived from MDS per se (17,18). In our study, BD-MDS patients with high or very high-risk stratification who received methylation drugs or chemotherapy survived longer time compared with those who refused MDS-specific treatment, although there was no significant difference. The results indicate that the mortality of BD-MDS patients is associated with risk stratification, and they are refractory to methylation drugs or chemotherapy. A series of case reports have shown that HSCT may be an effective alternative in BD patients with severe organ involvement, especially those with GI involvement, and are refractory to immunosuppressants (19, 20).

Pancytopenia is not common in BD patients. Particular attention should be paid and additional examinations such as bone marrow biopsy should be performed if pancytopenia occurs in BD patients. Our study showed anaemia, particularly, macrocytic anaemia, was more common in BD-MDS patients than in general BD patients. In addition, macrocytic anaemia may already exist long before BD-MDS is diagnosed. The diagnosis and treatment of such patients may be complicated, and in-depth understanding of the disease course may help achieve improved outcomes. Furthermore, the multidisciplinary collaboration of haematologists, rheumatologists, and gastroenterologists may improve the prognosis.

The limitations of this study included its retrospective nature and the relatively small number of patients. The cases were all recruited from a single centre of a tertiary hospital, which may lead to a negative result as well as the bias of a more severe form of this disease. Moreover, we did not analyse the prognosis of BD-MDS patients and primary MDS patients since the follow-up information of the control group was incomplete.

In conclusion, BD-MDS patients were usually older than general BD, whereas the onset age was relatively younger in females. In addition, fever, more frequent GI involvement, lower blood count, and higher ESR/CRP level may occur in such patients. GI involvement, lower haemoglobin, and higher ESR level were independent predictors for BD-MDS development. As BD-MDS may be a different clinical entity, the patients should not be treated simply as the BD-like symptoms of MDS. Cytogenetic abnormalities, especially trisomy 8, might have an important role in the association of GI involvement, BD and MDS. Once BD patients present with pancytopenia, further examinations are warranted.

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