Rheumatology 2008;47:1228–1230
Advance Access publication 11 June 2008
doi:10.1093/rheumatology/ken162

Concise Report

Behcet's disease associated with bone marrow failure in Korean patients: clinical characteristics and the association of intestinal ulceration and trisomy 8

J. K. Ahn[1], H.-S. Cha[1], E.-M. Koh[1], S.-H. Kim[2], Y. G. Kim[3], C.-K. Lee[3] and B. Yoo[3]

Objectives. The aim of this study was to determine the clinical characteristics of Behcet's disease (BD) associated with bone marrow failure (BMF), classified as conditions such as myelodysplastic syndrome (MDS) or aplastic anaemia (AA), in Korea.
Methods. A retrospective analysis was made of 13 patients with BD associated with BMF (MDS 8 cases, AA 5 cases) and 66 patients with BD not associated with BMF. These patients all fulfilled the diagnostic criteria of the international BD study group.
Results. BD patients with BMF showed significantly lower leucocyte count, haemoglobin level and platelet count when compared with patients without BMF ($P < 0.001$). BD patients with BMF had significantly higher serum CRP level at the time of BD diagnosis compared with patients without BMF ($P = 0.03$). Intestinal lesions were more frequent in BD patients with BMF than those without BMF (61.5% *vs* 13.6%, $P = 0.001$). Cytogenetic abnormality was observed in 90.9% of BD patients with BMF. Of the cytogenetic abnormalities, trisomy 8 was most common, occurring in 70% of the patients. In four patients with refractory BD associated with BMF, successful treatment of BMF by haematopoietic stem cell transplantation resulted in clinical remission of BD.
Conclusions. Our study indicates that intestinal ulceration is a characteristic finding in BD associated with BMF. It also suggests that cytogenetic aberration, especially trisomy 8, may play an important role in the pathogenesis of BD associated with BMF.

Key words: Behcet's disease, Myelodysplastic syndrome, Aplastic anaemia, Intestinal ulceration, Trisomy 8.

Introduction

Behcet's disease (BD) is a systemic vasculitis of unknown aetiology, characterized by orogenital ulcers, uveitis, arthritis and involvement of the gastrointestinal tract, central nervous system (CNS) and blood vessels. The prevalence of BD is considerably high in Korea, China, Japan and Turkey [1]. Recently, there have been sporadic case reports of BD associated with myelodysplastic syndrome (MDS), mainly in Japanese patients [2, 3]. It has recently become apparent that autoimmune mechanism plays an important role in the development of MDS and aplastic anaemia (AA) [4, 5].

In one study, ~10% of patients with MDS were accompanied by other autoimmune diseases such as SLE, SS and Hashimoto's thyroditis [5]. However, little is known about the association of BD with bone marrow failure (BMF), such as MDS or AA. Clinical characteristics of patients of BD associated with BMF are not well understood, either.

In this study, we investigated the clinical characteristics of BD patients with BMF in comparison with BD patients without BMF. In addition, we report four patients who achieved complete remission of both BMF and BD after haematopoietic stem cell transplantation (HSCT).

Patients and methods

Medical records at two tertiary hospitals spanning from August 1995 through January 2007 were reviewed to identify patients who were diagnosed with BD associated with BMF. Thirteen patients were included in this study, and they all fulfilled the diagnostic criteria of the international BD study group [6]. Of these 13 patients, 8 were diagnosed with MDS and 5 were diagnosed with AA. The diagnosis of BMF was based on peripheral blood laboratory test and bone marrow examination. The classification of MDS followed the World Health Organization classification [7]. We regarded 66 patients who were diagnosed of BD without BMF as the control group. These patients were identified between January 2006 and January 2007, and all fulfilled the diagnostic criteria of the international BD study group [6]. For all study patients enrolled, the following demographic and clinical data were obtained from the medical records and analysed: age at diagnosis of BD, MDS or AA, sex, duration of disease, clinical signs and symptoms, treatment modalities and laboratory data including bone marrow examination and chromosomal analysis.

Data are expressed as means and S.D. and frequency (percentage). The Student's *t*-test was used to compare two groups in terms of continuous variable distributions and the χ^2-test was used to compare categorical variables. Differences were considered statistically significant at the $P < 0.05$ level.

Results

Characteristics of the BD patients with or without BMF are presented in Table 1. All patients in this study had oral ulcers. In BD associated with BMF, genital ulcers were the second most common clinical finding (92.3%), followed by skin lesion (69.2%), intestinal ulceration (61.5%) and arthritis (38.5%). Patients with BD associated with BMF tended to be older than those without BMF. Leucocyte count, haemoglobin level and platelet count at diagnosis of BD were significantly lower in patients with BMF compared with patients without BMF ($P < 0.001$). CRP level at the time of BD diagnosis was significantly higher in patients with BMF compared with patients without BMF ($P = 0.03$). Intestinal lesions, which were located mainly in terminal ileum and ileocecal valve, were significantly more frequent in BD patients with BMF than those without BMF ($P = 0.001$). None of the 13 BD patients

[1]Department of Medicine, [2]Department of Laboratory Medicine and Genetics, Samsung Medical Center, Sungkyunkwan University School of Medicine and [3]Department of Internal Medicine, Division of Rheumatology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea.

Submitted 31 December 2007; revised version accepted 31 March 2008.

Correspondence to: H.-S. Cha, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Ilwon-Dong, Gangnam-Gu, Seoul 135-710, Republic of Korea. E-mail: hoonsuk.cha@samsung.com

with BMF had vascular lesions. Most cases were treated with colchicine, steroid and SSZ. Prednisolone and SSZ tended to be more frequently used in BD patients with BMF than in those without BMF ($P = 0.069$ and 0.081, respectively).

Thirteen patients diagnosed with BD associated with BMF are listed in Table 2. The age at the time of diagnosis of BD and BMF was 44.5 (±12.7) and 44.2 (±12.9) yrs, respectively. Disease duration of BD and BMF was 70.0 (±64.9) and 52.5 (±63.4) months, respectively. In 7 of the 13 subjects (53.8%), BMF was diagnosed before or concomitantly with BD. Of the MDS cases, refractory cytopenia with multilineage dysplasia (RCMD) was the most common type, being found in three cases (37.5%). In chromosomal analyses of 11 available patients, chromosomal aberration was observed in 10 patients (90.9%), with trisomy 8 observed in 7 patients (63.6%). Among seven cases of BMF with trisomy 8, intestinal BD was discovered in five cases (71.4%). All five of the patients with intestinal ulceration and trisomy 8 presented with sudden onset of a high-grade fever up to 39–40°C, severe abdominal pain and mucocutaneous symptoms at the time of BD diagnosis. These patients were treated with high-dose steroid and/or immunosuppressants. In particular, we observed a 46-yr-old female who received total colectomy for multiple intestinal perforations despite treatment of high-dose prednisolone (1 mg/kg/day) and AZA (150 mg/day) (Case 8). Among BD patients associated with BMF, only four cases have used AZA or ciclosporin for treatment of BD. All these cases had intestinal lesions. In Cases 1 and 3, the diagnosis of MDS preceded the use of AZA with 12 and 10 months, respectively. In Case 7, AZA has been stopped 4 months before the time of diagnosis of MDS.

HSCT was performed in four cases. Peripheral blood stem cell transplantation was performed in two BD patients with MDS (Case 2 with refractory anemia with excess blast-1 (RAEB-1) and Case 5 with RCMD-ringed sideroblasts) and allogeneic bone marrow transplantation was performed in two BD patients with AA (Case 9 and 10). These patients had active BD manifestations in spite of corticosteroid and/or immunosuppressive treatment, before undergoing HSCT. All cases achieved successful engraftment after HSCT, and the symptoms and signs related to BD disappeared. In Cases 5 and 9, with intestinal ulcers, endoscopic follow-up examination after HSCT showed that the ulcerative lesions in the terminal ileum and ileocecal valve were replaced by normal mucosa. Follow-up time after HSCT was 25, 4, 78 and 58 months in Case 2, 5, 9 and 10, respectively, and BD remained in clinical remission until the last follow-up visit.

TABLE 1. Comparison of symptoms, signs and laboratory findings in patients with BD with or without BMF

	BD with BMF ($n=13$)	BD without BMF ($n=66$)	P-value
Age at BD Dx	44.5 ± 12.7	37.7 ± 11.2	0.055
Male (%)	5 (38.5)	27 (40.9)	1.000
Laboratory findings at BD Dx			
WBC (cells/μl)	3027 ± 767.5	8124.1 ± 3114.2	<0.001
Hb (g/dl)	10.0 ± 2.3	13.1 ± 1.6	<0.001
Platelet ($\times 10^3/\mu$l)	80.3 ± 51.0	284.8 ± 89.4	<0.001
CRP (mg/dl)	4.6 ± 4.8	1.33 ± 2.2	0.030
ESR (mm/h)	45.7 ± 27.3	37.3 ± 28.1	0.345
Signs			
Oral ulcer	13 (100)	66 (100)	1.000
Genital ulcer	12 (92.3)	51 (77.3)	0.286
Positive pathergy test[a]	2 (50.0)	10 (35.7)	0.610
Vascular lesion	0 (0)	11 (16.7)	0.248
Ocular lesion	3 (23.1)	10 (15.2)	0.440
Arthritis	5 (38.5)	33 (50.0)	0.550
Skin lesion	9 (69.2)	58 (87.9)	0.103
EN-like lesion	5 (38.5)	38 (57.6)	0.236
Pseudofolliculitis	7 (53.8)	21 (31.8)	0.203
Acneiform eruptions	2 (15.4)	20 (30.3)	0.334
Intestinal lesion	8 (61.5)	9 (13.6)	0.001
Medication use			
Prednisolone	10 (76.9)	31 (47.0)	0.069
Colchicine	11 (84.6)	55 (83.3)	1.000
SSZ	6 (46.2)	14 (21.2)	0.081
NSAID	1 (7.7)	12 (18.2)	0.683
AZA	4 (30.8)	11 (16.7)	0.256
Ciclosporin	1 (7.7)	5 (7.6)	1.000

Unless otherwise indicated, values are frequency (percentage) or mean ± S.D.
[a]Number of evaluated patients is four cases (BD with BMF) and 28 cases (BD without BMF).
Dx: diagnosis; WBC: white blood cell count; Hb: haemoglobin; EN: erythema nodosum.

Discussion

Our study suggests that there may be an association between BD and BMF such as MDS or AA. The mechanism of the association of BD and BMF is not known. Inflammatory cytokines such as TNF-α, IFN-γ, IL-6 and IL-8 are thought to play a role in the pathophysiology of MDS and AA [5, 8]. Elevated levels of TNF-α have been reported in the bone marrow of MDS patients. The high TNF-α expression has been implicated in the increased reactive oxygen species (ROS) production observed in CD34+ marrow cells of MDS [5]. BD patients also have elevated levels of TNF-α, IL-1β, IL-6 and IL-8 in the serum, and neutrophils from patients with BD demonstrate increased production of ROS [1]. On the basis of these findings, BD and BMF might partially share a common pathogenesis that involves Th1-cytokines such as TNF-α and IFN-γ. It also suggests that TNF-α might be a potential therapeutic target in BD associated with BMF. Indeed, infliximab was effective in the treatment of refractory BD [9], and infliximab was reported to be marginally effective in the treatment of MDS [10].

We analysed 13 cases of BD associated with BMF and compared clinical data from these patients with clinical data

TABLE 2. Clinical features of patients with BD associated with BMF

Case	Sex	Age[a]	Classification[b]	Karyotype	Symptoms[c]	Interval[d] (months)	Remarks[e]
1	F	34	RA	47, XX, +8	O, G, S, A, I	91	
2	M	36	RAEB-1	46, XY, t(2;12)(q36;q24.1)	O, G, S, A	8	PBSCT
3	M	53	RCMD	47, XY, +8[6]/46, XY[2]	O, G, S, I	10	MDS preceded
4	F	49	RCMD	47, XX, +8[17]/46, XX[3]	O, G, U, I	3	MDS preceded
5	F	31	RCMD-RS	46, XX, del(5)(q13q33)del(20)(q11.2)	O, G, S, A, P, I	0	PBSCT
6	M	47	RAEB-2	47, XY, +8	O, G, S	0	
7	F	66	RCMD	46, XX, del (20)(q11,2)	O, S, A, U, I	14	
8	F	46	MDS-U	47, XY, +8	O, G, S, I	3	Total colectomy
9	F	35	AA	48, XX, +8, +9	O, G, S, P, I	72	Allogeneic BMT
10	M	43	AA	47, XY, +8	O, G, S	0	Allogeneic BMT
11	F	69	AA	46, XX	O, G, U	0	
12	M	43	AA	–	O, G, S, A, I	61	AA preceded
13	F	27	AA	–	O, G, S	121	

[a]Age at the time of diagnosis of BD. [b]The World Health Organization classification of the myeloid neoplasm (2002); RCMD: Refractory cytopenia with multilineage dysplasia; RA: Refractory anaemia; RS: ringed sideroblasts; MDS-U: myelodysplastic syndrome-unclassified; [c]O: oral ulcer; G: genital ulcer; S: skin lesion; A: articular symptoms; I: intestinal ulcer; U: uveitis; P: positive pathergy test. [d]Time interval between BD diagnosis and BMF diagnosis. [e]PBSCT and BMT denote peripheral blood stem cell transplantation and bone marrow transplantation. Karyotype was not available in Cases 12 and 13.

from patients without BMF. In BD patients with BMF, the frequency of intestinal BD was significantly higher than in those without BMF (61.5% *vs* 13.6%). Considering that the previously reported frequency of intestinal ulcers was ~2–25% in BD [11, 12], intestinal lesions seem to be a characteristic finding in BD associated with BMF. BD patients with BMF had significantly higher serum CRP level compared with the patients without BMF, at the time of BD diagnosis. Five patients with intestinal lesions and trisomy 8 presented with acute severe systemic inflammation and full-blown BD symptoms, including severe mucocutaneous manifestations. Patients with BMF tended to be more frequently prescribed with corticosteroids and immunosuppressants, and some of these patients were refractory to corticosteroids and immunosuppressive treatment. These findings reflect the high frequency of intestinal lesions in BD associated with BMF, but they also suggest that these patients have higher disease activity than patients without BMF. For one thing, immunosuppressive agents given previously for the treatment of BD may cause secondary MDS. It was reported that complex genetic alterations involving chromosomes 5 and 7 are characteristic in therapy-related MDS or AML following prolonged AZA treatment [13]. However, none of the four BD patients who were treated with immunosuppressants had cytogenetic abnormalities of chromosomes 5 and 7. Also, in three cases, AZA was not used at the time of diagnosis of MDS. Cytopenia has already been observed in the time of diagnosis of BD in Cases 7 and 8. Considering these findings, it is less likely that the use of immunosuppressive agents has been associated with the development of BMF in our study.

Cytogenetic abnormalities are found in about half of the MDS patients [4]. In our study, cytogenetic abnormalities were found in >90% of the BD patients with BMF. The incidence of trisomy 8 is reported to be ~10% for MDS patients with chromosomal abnormalities [14]. In patients with AA, chromosome 7 abnormalities accounted for 40% of observed aberrations, followed by trisomy 8 [15]. Most strikingly, in the current study and other cases reports, the proportion of trisomy 8 in patients with BD associated with BMF is reported to be ~64–86% [2, 3]. In the analysis of the gene expression pattern in CD34+ haematopoietic cells obtained from patients with BMF and trisomy 8, it was reported that genes involved in immune and inflammatory response (TGF-β, IL-6, MCP-1, adhesion molecules) were overexpressed [16, 17]. Recent work also shows that chromosome 8 may be related to immunity and inflammation [18]. Furthermore, trisomy 8 in MDS is reported to be a risk factor for intestinal ulceration [19]. It is inferred that trisomy 8 causes abnormalities of inflammatory cytokine profiles, leading to intestinal lesions. On the basis of these observations, cytogenetic abnormalities, especially trisomy 8, might have an important implication in BD associated with BMF and intestinal lesions.

For four patients with severe BD associated with BMF, we performed HSCT for the treatment of BMF and obtained remission of not only BMF, but also BD. This observation suggests that HSCT may become an alternative treatment option for refractory BD associated with BMF.

In conclusion, we should make efforts to establish the possibility of underlying BMF in patients with BD showing leucopenia or thrombocytopenia. Conversely, if a patient with BMF develops recurrent oral ulcers, a diagnosis of BD including intestinal involvement should be considered. BD associated with BMF is thought to be a new clinical disease entity, distinct from BD and autoimmune manifestations of BMF. Further studies will be required to ascertain the pathological link between BD associated with BMF and cytogenetic abnormalities, including trisomy 8.

Rheumatology key messages

- BD associated with BMF may be a new clinical disease entity, distinct from BD and autoimmune manifestations of BMF.
- Our study suggests the pathological link between BD associated with BMF and cytogenetic abnormalities, including trisomy 8.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Sakane T, Takeno M, Suzuki N, Inaba G. Behcet's disease. N Engl J Med 1999;341:1284–91.
2 Tada Y, Koarada S, Haruta Y, Mitamura M, Ohta A, Nagasawa K. The association of Behcet's disease with myelodysplastic syndrome in Japan: a review of the literature. Clin Exp Rheumatol 2006;24:S115–9.
3 Kawabata H, Sawaki T, Kawanami T *et al.* Myelodysplastic syndrome complicated with inflammatory intestinal ulcers: significance of trisomy 8. Intern Med 2006;45:1309–14.
4 Young NS. Harrison's internal medicine, 16th edition. New York: McGraw-Hill, 2005;617–26.
5 Voulgarelis M, Giannouli S, Ritis K, Tzioufas AG. Myelodysplasia-associated autoimmunity: clinical and pathophysiologic concepts. Eur J Clin Invest 2004;34:690–700.
6 Criteria for diagnosis of Behcet's disease. International study group for Behcet's disease. Lancet 1990;335:1078–80.
7 Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;100:2292–302.
8 Hsu HC, Lee YM, Tsai WH *et al.* Circulating levels of thrombopoietic and inflammatory cytokines in patients with acute myeloblastic leukemia and myelodysplastic syndrome. Oncology 2002;63:64–9.
9 Sfikakis PP, Markomichelakis N, Alpsoy E *et al.* Anti-TNF therapy in the management of Behcet's disease—review and basis for recommendations. Rheumatology 2007;46:736–41.
10 Raza A, Candoni A, Khan U *et al.* Remicade as TNF suppressor in patients with myelodysplastic syndromes. Leuk Lymphoma 2004;45:2099–104.
11 Barnes CG, Yazici H. Behcet's syndrome. Rheumatology 1999;38:1171–4.
12 Gurler A, Boyvat A, Tursen U. Clinical manifestations of Behcet's disease: an analysis of 2147 patients. Yonsei Med J 1997;38:423–7.
13 Arnold JA, Ranson SA, Abdalla SH. Azathioprine-associated acute myeloid leukaemia with trilineage dysplasia and complex karyotype: a case report and review of the literature. Clin Lab Haematol 1999;21:289–92.
14 Sole F, Prieto F, Badia L *et al.* Cytogenetic studies in 112 cases of untreated myelodysplastic syndromes. Cancer Genet Cytogenet 1992;64:12–20.
15 Maciejewski JP, Risitano A, Sloand EM, Nunez O, Young NS. Distinct clinical outcomes for cytogenetic abnormalities evolving from aplastic anemia. Blood 2002;99:3129–35.
16 Chen G, Zeng W, Miyazato A *et al.* Distinctive gene expression profiles of CD34 cells from patients with myelodysplastic syndrome characterized by specific chromosomal abnormalities. Blood 2004;104:4210–8.
17 Zeng W, Chen G, Kajigaya S *et al.* Gene expression profiling in CD34 cells to identify differences between aplastic anemia patients and healthy volunteers. Blood 2004;103:325–32.
18 Fellermann K, Stange DE, Schaeffeler E *et al.* A chromosome 8 gene-cluster polymorphism with low human beta-defensin 2 gene copy number predisposes to Crohn disease of the colon. Am J Hum Genet 2006;79:439–48.
19 Kimura S, Kuroda J, Akaogi T, Hayashi H, Kobayashi Y, Kondo M. Trisomy 8 involved in myelodysplastic syndromes as a risk factor for intestinal ulcers and thrombosis—Behcet's syndrome. Leuk Lymphoma 2001;42:115–21.