Refractoriness of Intestinal Behçet's Disease with Myelodysplastic Syndrome involving Trisomy 8 to Medical Therapies – Our Case Experience and Literature Review –

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Key words: Behçet's disease, myelodysplastic syndrome, trisomy 8, biologic agent

Abstract

Background/Aims: Gastrointestinal lesions of Behçet's disease (BD) are often refractory to medical therapy and sometimes result in serious comorbidities, such as gastrointestinal perforation and massive bleeding. There are several reports of patients with BD comorbid with myelodysplastic syndrome (MDS) involving trisomy 8 that frequently have intestinal lesions refractory to conventional medical therapy. Little is known about the efficacy of infliximab (IFX) for these intestinal lesions. ***Methods:*** We present two cases of intestinal BD with MDS involving trisomy 8 who did not respond to IFX, and review previous reports of BD with MDS involving trisomy 8 concerning their responsiveness to conventional medical therapy. ***Results:*** Among 33 previously reported cases that received medical treatment for BD, 20 cases (60.6 %) showed temporary improvement of the BD symptoms, 10 (30.3 %) deteriorated, and 3 (9.1 %) showed no change. Among the 10 showing deterioration, 9 cases had intestinal lesions. Our two cases failed to respond to IFX, resulting in a poor prognosis. ***Conclusions:*** IFX might not be effective for improving intestinal BD comorbid with MDS involving trisomy 8. Trisomy 8 is associated with the BD prognosis and refractoriness to conventional medical therapy.

Introduction

Behçet's disease (BD), an inflammatory disease of unknown etiology, is characterized by recurrent oral ulcerations, genital ulcerations, eye and skin lesions, and a positive pathergy test [1]. Gastrointestinal lesions are present in 3% to 26% of BD patients and typically form discrete ulcers in the ileocecal area [2]. These gastrointestinal lesions are often refractory to conventional medical therapy [3], and sometimes cause life-threatening comorbidities such as intestinal perforation and massive bleeding [4].

Generally, colchicine, 5-aminosalicylic acid (5-ASA), corticosteroids, and immunosuppressive agents are used to treat BD. The effect of infliximab (IFX), a chimeric monoclonal antibody against tumor necrosis factor (TNF)-α on eye lesions and intestinal lesions refractory to conventional medical therapy in BD patients has been reported [5-7].

Several recent reports described a relationship between trisomy 8 associated with MDS and intestinal BD [8-10]. Because trisomy 8 induces the activation of an abnormal inflammatory process and immune gene expression [11], trisomy 8 in MDS could contribute to the aggravation of intestinal ulcers in patients with BD. In fact, the intestinal lesions in BD patients with trisomy 8 are refractory to conventional medical

therapy. Little is known, however, about the efficacy of IFX for treatment of the intestinal lesions of BD patients with trisomy 8.

In this report, we present two cases of BD patients with trisomy 8 that received IFX for their intestinal lesions and review previous reports of BD patients with MDS involving trisomy 8 with regard to their medical treatment.

Case report

Case 1

In February 2011, a 36-year-old Japanese man visited our hospital with a 2-month history of oral aphthoid ulcers and intermittent right lower quadrant abdominal pain. Laboratory data showed mild leukopenia (white blood cells 2500/μL [normal, 3500-8500/μL]), normocytic normochromic anemia (red blood cells 344×10^4/μL [normal, $400\text{-}570\times10^4$/μL], hemoglobin 11.2 g/dL [normal, 12.9-17.2 g/dL], mean corpuscular volume 92.3 fl [normal, 82-100 fl], mean corpuscular hemoglobin 32.6 pg [normal, 27.5-34.5 pg], mean corpuscular hemoglobin concentration 31.8% [normal, 32-35.5%]), and an elevated C reactive protein level (10.3 mg/dL [normal 0-0.3 mg/dL]). An abdominal computed tomography scan showed remarkably increased wall thickness of the ileocecum. Total colonoscopy revealed a large punched-out ulcer at the

ileocecal valve and scattered ulcer scars in the terminal ileum. Histologic findings of biopsy specimens indicated non-specific inflammation and no granuloma. The patient was in an afebrile state and had no eye symptoms, skin lesions, or genital ulcers. A serologic test was positive for HLA-B51 allele. Intestinal BD was suspected. A bone marrow biopsy performed to further evaluate the continuous leukopenia revealed hypocellularity of the bone marrow without an increase of blast cells. Although his bone marrow biopsy showed no cellular morphologic changes, cytogenetic analysis demonstrated the presence of an abnormal cell line: 47, XY, +8. Abnormal chromosomes were found in all 20 cells examined. These findings led to the diagnosis of MDS (refractory anemia).

Treatment with colchicine and 5-ASA was initiated for BD, but his symptoms deteriorated. In addition, despite intravenous corticosteroid administration at 50 mg/day, his symptoms did not subside. We started 3 mg/kg of IFX combined with methotrexate. This combination therapy was also not effective and the patient required ileocecal resection 1 month after starting the combination therapy.

Case 2

A 29-year-old Japanese woman was referred to our hospital in 1997 because of

recurrent oral ulcers and intermittent fever. Physical examination revealed genital ulcers, folliculitis-like eruptions, and erythema nodosum. Total colonoscopy showed multiple punched-out ulcers located from the terminal ileum to the ascending colon. Based on all of these findings, she was diagnosed with intestinal BD.

Her symptoms subsided after starting corticosteroid treatment at 60 mg/day. She complained of massive melena while reducing the dose of corticosteroid. Increasing the corticosteroid dose to 60 mg/day improved her symptoms, and she was maintained in a stable condition with less than 10 mg/day of corticosteroids thereafter.

In 2005, her laboratory data showed pancytopenia. A bone marrow biopsy performed to further evaluate her pancytopenia revealed normoplastic bone marrow with dysplasia in all three lineages of bone marrow cells. The rate of blastic cells remained at 2.0%. Cytogenetic analysis demonstrated the presence of two cell lines: 47, XX, +8 and 46, XX. Of the 20 cells examined, 12 showed an abnormal female karyotype with extra 8 chromosomes, and the remaining 8 cells had normal sets of chromosomes. These findings led to the diagnosis of MDS (refractory anemia).

The patient was treated with 300 mg of oral cyclosporine for MDS, but she required repeated transfusions of red blood cells and platelets. In 2006, her BD symptoms relapsed with recurrent intestinal ulcers. Her BD symptoms subsided with

2250 mg/day of 5-ASA and increased corticosteroid (30 mg/day). Despite the additional use of immunomodulators, her abdominal pain recurred while tapering the dose of corticosteroid. Therefore, we started 5 mg/kg of IFX in August 2007. Administration of IFX, however, did not ameliorate her abdominal pain. She had repeated febrile neutropenia and then developed septic shock, and died in November 2008.

Characteristics and outcomes of medical treatment in BD patients with MDS involving trisomy 8

Table 1 summarizes the previous reports of BD patients with MDS involving trisomy 8, which was searched using PubMed (date searched: June 1, 2013). We collected 41 cases from 29 reports. Of the 41 cases, intestinal ulcers were found in 29 cases (70.7%). On the other hand, eye lesions were found in only 3 cases (7.3%). Oral ulcers, genital ulcers, and skin lesions were found in 36 cases (87.8%), 30 cases (73.2%), and 28 cases (68.3%), respectively. Thirty-three cases received medication for their BD, two received hematopoietic stem cell transplantation for their MDS prior to the treatment for BD, and two received no medical treatment. In four cases, treatment outcome for the BD was not described.

As a result, 20 cases (60.6%) showed temporary improvement of the BD

symptoms, 10 (30.3%) deteriorated, and 3 (9.1%) showed no change. Among the 10 cases that showed deterioration, 9 (90%) had intestinal lesions.

Discussion

In the present case series, IFX was not effective for improving intestinal BD comorbid with MDS involving trisomy 8, suggesting the possibility that some factors other than TNF-α are involved in the pathogenesis of intestinal BD with MDS involving trisomy 8. Intestinal lesions of BD are usually refractory to conventional therapy and result in life-threatening comorbidities, such as intestinal perforation and massive bleeding. Recent reports showed that IFX has beneficial effects on these intractable intestinal lesions of BD. Little is known, however, about the effect of IFX in intestinal BD comorbid with MDS involving trisomy 8.

Trisomy 8 is one of the most frequent abnormalities found in 6.5% to 16.3% of primary MDS patients [12]. Furthermore, the prevalence rate of trisomy 8 is as high as 73.7% in MDS patients with BD [13]. Previous reports revealed several clinical characteristics such as a low prevalence rate of eye lesions and a high prevalence rate of intestinal lesions in BD patients with MDS involving trisomy 8 [14]. As shown in Table 1, only 7.3% of BD patients with MDS involving trisomy 8 had eye lesions whereas

70.7% had intestinal lesions [2, 8-10, 15-34]. These data showed a similar tendency as previous reports. We further tried to compare the behaviors of BD between those with MDS involving trisomy 8 and those with MDS involving other types of chromosomal aberrations. However, in addition to the rarity of BD with MDS, more than 70% of these patients had trisomy 8 as described above. Therefore, we could not obtain enough information, which could characterize the behavior of BD with chromosomal aberrations other than trisomy 8.

Chen et al. [11] analyzed the gene expression patterns in hematopoietic progenitor cells obtained from MDS patients with monosomy 7 and trisomy 8, and detected distinctively higher gene expression of several cytokines, such as IL-6, MCP-1, VCAM-1, and ICAM-1, which are involved in immune and inflammation in trisomy 8 patients. Furthermore, Kimura et al. [9] reported three cases of intestinal BD with MDS involving trisomy 8 who developed thrombosis and suggested that trisomy 8 is a risk factor not only for intestinal ulceration but also for thrombosis. On the other hand, in addition to the local migration of neutrophils stimulated by several cytokines, an impaired microbicidal function of neutrophils in MDS [35] might augment dysregulated immune response in BD. Thus, increased gene expression of inflammatory cytokines and thrombus formation related to trisomy 8, and abnormal functions of neutrophil in

MDS might contribute to the pathogenesis of intestinal ulcers in BD. Despite the use of several therapeutic agents, such as colchicine, 5-ASA, corticosteroids, and immunomodulators in the majority of cases, about 30% of BD patients with MDS involving trisomy 8 failed to respond to these conventional medical therapies. In addition, 90% of those who failed to respond had intestinal lesions.

Considering that extensive intramedullary cell death in MDS patients is related to TNF-α [36] and that serum TNF-α concentrations are increased in BD patients [37], IFX treatment would theoretically be ideal for BD patients with MDS. In one report, an intestinal BD patient with MDS involving trisomy 8 was successfully treated with a combination of IFX and methotrexate for her intestinal lesion [7]. Both of our cases, however, failed to respond to IFX and had a poor prognosis. Thus, the pathogenesis of BD with MDS involving trisomy 8 seems to be complicated, and other cytokines and chemokines independent of TNF-α or some other factors might be involved. Trisomy 8 is clearly associated with BD prognosis and refractoriness to conventional medical therapy. Therefore, further accumulation of clinical cases is necessary to elucidate the pathogenesis of BD with MDS involving trisomy 8.

Acknowledgement

This work was supported by JSPS KAKENHI Grant Number 25130706, 24229005, 24659363, 24590941, 25860532, and 23590940 and by Health and Labour Sciences Reserch Grant for Research on Rare and Intractable Diseases from Ministry of Health, Labour and Welfare, Japan.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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Table1. Reported cases of BD patients with MDS involving trisomy 8

Table 1.

Author	Age	Sex	MDS type	BD symptoms					HLA-B51	Therapy	Outcome	
				Oral ulcer	Genital ulcer	Skin lesion	Eye lesion	intestinal ulcer			BD	MDS
Nehashi, 1988	72	M	RA	+	+	+	-	-	+	S	Improved	Unchanged
Nakayama, 1989	57	M	RA	+	+	-	-	+	ND	S	Improved	Unchanged
Takishita, 1991	59	M	RAEB	+	-	-	+	-	ND	S	Death	Unchanged
Yoshizawa, 1992	45	F	RARS	+	+	+	-	-	ND	S	Improved	Unchanged
Chyuma, 1992	41	F	RARS	+	+	+	-	+	+	M, S	Improved	Unchanged
Ito, 1993	45	F	RAEB	-	+	-	-	-	ND	S	Improved	Unchanged
Yano, 1995	23	F	RA	+	+	+	-	+	ND	S, SASP	Improved	Unchanged
Yano, 1996	54	F	RA	+	+	+	-	-	-	S	Improved	Death
Ohno, 1997	34	F	RA	+	+	-	+	+	-	-	Improved	Unchanged
Della Rossa, 1998	50	M	RARS	+	+	+	-	+	-	M, S, AZA, CsA	Improved	Death
Nawata, 1999	59	M	RA	+	+	+	-	-	+	S	Improved	Unchanged
Tanaka, 2000	39	M	RA	+	+	-	-	+	-	M	Improved	Unchanged
Ogawa, 2001	25	M	RA	+	+	+	-	+	-	S	Improved	Unchanged
	41	F	RA	+	+	+	-	+	-	S	Improved	Unchanged
Kimura, 2001	74	F	RA	+	-	-	-	+	ND	S	Death	Unchanged
	36	F	RA	-	-	+	-	+	ND	S	Improved	Unchanged
	31	F	RA	-	-	-	-	+	ND	SASP, S	Death	Unchanged
Fujita, 2002	64	M	RA	+	+	-	-	+	-	S	Operation	Unchanged
Adachi, 2003	28	F	RA	+	+	+	-	+	-	SASP, M, S	Operation	Unchanged
	39	F	RA	+	+	+	-	+	-	Col, SASP, M, S	Operation	Unchanged
Hasegawa, 2003	43	F	RA	+	+	+	-	-	-	Col, S, AZA, CsA	Improved	Unchanged
Tomonari, 2004	27	F	RAEB	+	+	+	-	-	+	Col, S, HSCT	Improved	Improved
Ando, 2005	49	M	RA	+	+	-	-	+	ND	CsA	Unchanged	Improved
Kuttikat, 2005	54	M	RA	-	+	+	-	-	-	S, AZA	Unchanged	Unchanged
Tsubata, 2005	69	M	RAEB-t	+	-	+	-	+	+	SASP, M, S	Deteriorated	Death
Kawabata, 2006	76	F	RA	+	+	+	-	+	+	SASP	Improved	Unchanged
	75	M	RAEB	+	+	+	-	+	ND	Col, SASP	Improved	Unchanged
	67	F	RAEB	+	-	-	-	+	ND	Col, SASP	Deteriorated	Death
Nonami, 2007	28	F	RAEB	+	-	-	-	+	-	HSCT	Improved	Improved
Ahn, 2008	46	F	MDS-U	+	+	+	-	+	ND	S, AZA	Operation	ND
	34	F	RA	+	+	+	-	+	ND	S, AZA	ND	ND
	53	M	RCMD	+	+	+	-	+	ND	S, AZA	ND	ND

	49	F	RCMD	+	+	-	+	+	ND	S	ND	ND
	47	M	RAEB	+	+	+	-	-	ND	S	ND	ND
Fujimura, 2010	71	M	RA	+	-	+	-	-	ND	Col, S	Improved	Unchanged
	74	M	RA	-	-	+	-	-	ND	Col, S	Improved	Unchanged
Tomonari, 2011	4	F	ND	+	-	+	-	+	-	HSCT	Improved	Improved
Iwata, 2011	52	F	RARS	+	+	+	-	+	-	S, MTX, IFX	Improved	ND
Chen, 2012	24	F	RA	+	+	+	-	+	ND	-	Operation	ND
Present cases	36	M	RA	+	-	-	-	+	+	Col, M, S, MTX, CsA, IFX	Operation	Unchanged
	29	F	RA	+	+	+	-	+	-	M, S, AZA, CsA, Tac, IFX	Unchanged	Unchanged

	oral ulcer	genital ulcer	skin lesion	eye lesion	intestinal ulcer
N	36	30	28	3	29
% (/41)	87.8	73.2	68.3	7.3	70.7

* RA: refractory anemia, RAEB: refractory anemia with excess blasts, RARS: refractory anemia with ringed sideroblasts, RAEB-t: refractory anemia with excess blasts in transformation, MDS-U: myelodysplastic syndrome-unclassified, RCMD: refractory cytopenia with multilineage dysplasia, ND: no description, Col: colchicine, SASP: salazosulfapyridine, M: mesalazine, S: corticosteroid, MTX: methotrexate, AZA: azathioprine, CsA: cyclosporine, Tac: tacrolimus, IFX: infliximab, HSCT: hematopoietic stem cell transplantation