□ CASE REPORT □

Myelodysplastic Syndrome Complicated with Inflammatory Intestinal Ulcers: Significance of Trisomy 8

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Abstract

Three cases of myelodysplastic syndrome (MDS) complicated with inflammatory intestinal ulcers all had cytogenetic abnormalities with trisomy 8. The first two patients were diagnosed with intestinal Behçet's disease and were successfully treated with salazosulphapyridine, and the third patient died after leukemic transformation. We review the reported cases of MDS complicated with Behçet's disease. Most of these cases are Japanese, having intestinal involvement as well as cytogenetic abnormalities with trisomy 8. We discuss the significance of trisomy 8 in intestinal involvement in MDS.

Key words: Behçet's disease, cytokines, leukemia

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Introduction

Myelodysplastic syndrome (MDS) is the term for a group of clonal hematologic disorders with impaired cell differentiation (1). In MDS, anemia, thrombocytopenia and/or neutropenia are common manifestations, which may cause heart failure, life-threatening hemorrhage and serious infection. Cytogenetic abnormalities of bone marrow cells such as monosomy 7 and trisomy 8 can frequently be found in patients with MDS. We recently encountered three cases of MDS complicated with inflammatory intestinal ulceration; all of these cases had fever, massive melena and multiple ulcerations in the ileocecal region, and on bone marrow examination, cytogenetic abnormalities with trisomy 8 were present. Two were diagnosed with intestinal Behçet's disease (BD).

BD is a chronic inflammatory disorder characterized mainly by recurrent oral aphthae, genital ulcers, uveitis and skin lesions. In some cases, vasculitis and inflammation of the gastrointestinal tract or central nervous system occurs.

We describe these three cases and discuss the significance of this chromosomal abnormality, trisomy 8, in the intestinal involvement in MDS, especially in association with BD.

Case Report

Case 1

A 76-year-old woman was referred to our hospital for severe anemia. Bone marrow examination revealed that her marrow was hypoplastic, and megakaryocytic dysplasia as well as emperipoiesis of neutrophils within megakaryocytes were observed (Fig. 1, panel a). The karyotype of her bone marrow cells was 47 XX, +8. She was diagnosed with MDS and refractory anemia (RA) in the French-American-British classification. She had been treated with melphalan, an anabolic steroid, and occasional red blood cell transfusion. Recurrent oral aphtha occurred when she was 79. She was admitted to our hospital for severe abdominal pain and high-grade fever when she was 80. A blood test showed severe anemia with a red blood cell count of $1.81 \times 10^6/\mu\text{l}$, hemoglo-

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Figure 1. Panel a: Megakaryocytic dysplasia with emperipolesis of neutrophils observed in the bone marrow in Case 1 (original magnification, $\times 400$). Panel b: Hyperplastic marrow with megakaryocytic dysplasia observed in Case 2. In panels a and b, the original magnification was $\times 400$. Panels c and d: Intestinal ulcers observed in the cecum in Cases 2 and 3, respectively.

bin (Hb) of 5.7 g/dl and hematocrit of 18.3 %. C-reactive protein (CRP) was elevated to 18.0 mg/dl. Endoscopic examination of her gastrointestinal tract revealed multiple ulcers in the ileocecal region. Histopathologic examination of these ulcers showed non-specific inflammation. She had HLA-B51. Taken together, she was diagnosed with intestinal BD. Her pathergy test was negative. Despite intensive treatment with antibiotics, recurrent attacks of abdominal pain, melena, and fever persisted during the following year. After the administration of salazosulphapyridine, her abdominal symptoms were gradually diminished.

Case 2

A 75-year-old man was admitted to our hospital for high-grade fever and abdominal pain. He had had a sore throat and recurrent oral aphthae for 5 months before admission. On admission, his body temperature was elevated to 39.5°C. His blood test showed that Hb was 12.2 g/dl, white blood cell count was 16,600/ μ l, platelet count was 199,000/ μ l and CRP was 16.7 mg/dl. He had aphthae on his tongue, folliculitis on his skin, and genital ulcers. His pathergy test was positive. He was diagnosed with BD, and antibiotics and

colchicine were administered. Despite this treatment, the high-grade fever accompanied with abdominal pain, oral aphthae and skin lesions recurred 3 times during the subsequent 7 months. Interestingly, each attack began with the sudden onset of a high-grade fever accompanied by slight thrombocytopenia and marked elevation of CRP and serum creatinine kinase (CK) levels. After treatment with antibiotics, CRP and CK levels decreased rapidly, the platelet count overshot, and erythema nodosum as well as oral aphthae appeared, followed by melena (Fig. 2). Seven months after his first admission, he had an attack of fever and abdominal pain with massive melena. Endoscopic examination of his gastrointestinal tract revealed multiple ulcers in the ileocecal region (Fig. 1, panel c). As his anemia (Hb 5.2 g/dl) at this point was slightly macrocytic, we performed a bone marrow examination, which revealed marked myeloid hyperplasia with increased blast cells and a karyotype of 47 XY +8 (Fig. 1, panel b). He was diagnosed with MDS and refractory anemia with excess blasts (RAEB). After treatment with intravenous hyper-alimentation and salazosulphapyridine, his BD symptoms disappeared.

Figure 2. Clinical course of Case 2. Each attack began with a high-grade fever, erythema nodosa, elevation of C-reactive protein (CRP) and creatinine kinase (CK) levels as well as a slight decrease in platelet (PLT) counts. In each attack, administration of antibiotics quickly normalized the levels of CRP and CK, and the PLT count overshot. Oral and genital aphthae as well as melena occurred subsequently. After the last episode of melena, salazosulphapiridine was started. Colchicine was continued throughout the course shown in this figure.

Case 3

A 67-year-old woman was admitted to our hospital for diarrhea, nausea and vomiting. As she had anemia, thrombocytopenia and leukocytosis, we performed a bone marrow examination, which showed myeloid hyperplasia with tri-lineage dysplasia and an increase of blasts. She was diagnosed with MDS and RAEB. The karyotype of her bone marrow cells showed complex abnormality with trisomy 8. Endoscopic examination of her gastrointestinal tract revealed multiple ulcers in the ileocecal region (Fig. 1, panel d). Histopathologic examination of the ulcers showed non-specific inflammation. She had intractable oral aphthae. Despite intensive treatment with antibiotics, colchicine, salazosulphapiridine and intravenous hyperalimentation, attacks of fever with massive melena recurred at short intervals. Eight months after the initial diagnosis of MDS, blast cells increased in her peripheral blood, indicating leukemic transformation. She died of leukemia with uncontrollable bacterial and fungal infection two months after leukemic transformation.

Discussion

More than 30 MDS cases complicated with inflammatory intestinal lesions have been reported to date. Most cases have been classified as intestinal BD, while some have been diagnosed as Crohn's disease or ulcerative colitis (2-13). The reported cases of MDS complicated with BD are listed in Table 1. The majority was the incomplete type with intestinal involvement, especially in the ileocecal region, and trisomy 8 was a very common chromosomal abnormality. Interestingly, most of these reports are from Japan, suggesting the importance of the regional or racial background in this clinical condition. The incidence of BD itself is endemically high in Turkey, Iraq, Iran, Korea and Japan; these populations were derived historically from the ancient Silk Road (14). HLA-B51, one of the common allele types among Japanese, has been implicated in the higher occurrence of BD in Japanese. In Japanese living in Hawaii, the frequency of BD is very low, therefore some environmental factors in addition to inherited factors may be important for the occurrence of BD (15). Among the present three cases, only Case 1 had HLA-B51. Together with the reported cases, trisomy 8 seems to be a much more important risk factor for BD rather than HLA-B51 in patients with MDS. The order of onset of MDS and BD varies. In some cases, the diagnosis of MDS preceded the manifestation of BD symptoms. In other cases, MDS developed years after the onset of BD symptoms; three of these cases had been treated with chlorambucil, which could induce secondary MDS, for BD (16-18). In the present three cases, the diagnosis of BD was preceded by the diagnosis of MDS in Case 1, which was reversed in Case 2. In Case 3, both intestinal symptoms and hematological abnormalities co-existed at her first visit. As for treatment, Kuttikat et al reported a case of steroid-refractory BD associated with MDS with trisomy 8, whose symptoms were significantly improved by thalidomide, an immunomodulating agent, although it had to be discontinued due to peripheral neuropathy (19). Two relatively young cases had cord blood transplantation and achieved remission of both MDS and BD (20, 21).

Among the present cases, Cases 1 and 2 were diagnosed as BD, and were successfully treated with salazosulphapiridine. In Case 2, each attack was accompanied by an elevated serum CK level, suggesting the presence of myositis in the acute phase (Fig. 2). Antibiotics seemed effective, at least transiently, in each attack in Cases 1 and 2 in terms of fever and CRP elevation, but were not effective for oral aphthae or melena. Bacterial infection which could trigger an overreaction of the immune system might have caused mucosal and skin lesions in these cases. Case 3 did not fulfill the criteria of either BD or inflammatory bowel diseases, but similar to the other cases, had intractable oral aphthae as well as inflammatory intestinal ulcers in the ileocecal lesion with recurrent melena, indicating a pathologic condition

Table 1. Reported Cases of MDS Complicated with BD

Age	Sex	MDS		BD onset	BD		Country	Others	Ref
		type	Karyotype		symptoms				
72	M	RA	+8,der(20)(q11)	1.6y after MDS	O,G,S,F		Japan		(2)
35	M	RA	normal	3y after MDS	O,G,S,U,A		Japan		(3)
57	M	RA	+8	6m after MDS	O,G,I,S,F		Japan		(3)
52	M	RA	+22,t(9;22)(q34;q11)	4y after MDS	O,S,A,F		Japan		(3)
59	M	RAEB	Complex with -5,-7,+8	4m after MDS	O,F,U,A,V		Japan		(32)
45	F	RARS	+8,+15	Simultaneously	O,G,S,F		Japan		(33)
41	F	RARS	+8	At diagnosis	O,I,S,F		Japan		(4)
54	F	RA	+8	1y after MDS	O,G,S,F,P		Japan	*2	(5)
23	F	RA	+8	18y before MDS	O,G,I,S		Japan		(6)
34	F	RA	+8	3y after MDS	O,G,I,F,U		Japan		(7)
50	M	RARS	+8	Simultaneously	O,G,I,S,F,P		Italy		(8)
59	M	RA	+8	1m after MDS	O,G,S,F		Japan		(9)
50	F	RA	Complex with +8	ND	O,G,I,F,A,P		Korea		(10)
39	F	RAEB-T	-7	4y before MDS	O,G,I,S,U		Germany	*1	(17)
39	M	RA	+8	Simultaneously	O,G,I,F,A,V		Japan		(34)
25	M	RA	+8	ND	O,G,I,S		Japan		(13)
41	F	RA	Complex with +8	17y before MDS	O,G,I,S		Japan		(13)
67	M	CMML	ND	ND	O,G,S,F,A,E		USA		(11)
35	M	MDS-AL	-7	3y before MDS	V(CNS)		Italy	*1	(16)
74	F	RA	Complex with +8	ND	O,I,T		Japan	*2	(12)
36	F	RA	dup(1)(q12;q44),+8	ND	I,S,T		Japan	*2	(12)
31	F	RA	+8	ND	I,V		Japan		(12)
56	F	RA	+8	6y before MDS	O,G,S,F		Japan		(35)
64	M	RA	+8	Simultaneously	O,G,I		Japan		(36)
28	F	RA	+8	5y before MDS	O,G,I,S		Japan		(37)
39	F	RA	+8,+9	10y before MDS	O,G,I,S		Japan		(37)
10	F	RAEB	Ring 6	Simultaneously	O,F,I,S		Japan	*3	(21)
55	M	RAEB	Complex	3m after MDS	O,G,S,Eso		Japan		(38)
27	F	RAEB	+8	8y before MDS	O,G,S,F		Japan	*3	(20)
49	M	RA	Constitutional trisomy 8	4y before MDS	O,G,I,T,A		Japan		(39)
45	F	RAEB-T	Complex with +i(8q)	8y before MDS	O,G,I,A,S,F		Israel	*1	(18)
54	M	RA?	+8	Simultaneously	G,A,S		UK	*2	(19)
69	M	RAEB-T	Complex with -5,+8	Simultaneously	O,I,S,F		Japan		(40)
76	F	RA	+8	3y after MDS	O,G,I,S,F		Japan		Present
					O,G,I,S,F,A,				
75	M	RAEB	+8	1y before MDS	P		Japan		Present
67	F	RAEB	Complex with del(5q),+8	Simultaneously	O,I,F		Japan		Present

Abbreviations: RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; RAEB-T, RAEB in transformation; ND, not described; 'complex' indicates abnormalities involving more than two chromosomes; O, oral ulcers; G, genital ulcers; I, intestinal ulcers; Eso, esophageal ulcers; S, skin lesions; F, fever; A, arthralgia; P, positive pathergy test; T, thrombosis; U, uveitis; V, vasculitis. *1; chlorambucil was used to treat BD. *2; G-CSF was used to treat MDS. *3; cord blood transplantation for MDS was performed.

similar to the other two cases. Bone marrow cells of all our cases had chromosomal abnormalities with trisomy 8.

As mentioned above and reported by others, trisomy 8 is likely a risk factor for BD, especially the intestinal type, in patients with MDS (12). Excessive production of inflammatory cytokines and abnormal neutrophil functions are frequently observed in MDS (22, 23). These abnormalities can possibly cause the skin and mucosal inflammatory lesions observed in BD, because the abnormal neutrophil functions, the overproduction of inflammatory cytokines as well as other immunological abnormalities are thought to be involved in the etiology of BD (14). Granulocyte colony-stimulating factor, which may stimulate the production of inflammatory cytokines, administered for cytopenia in MDS,

could elicit or aggravate the symptoms of BD (12). A number of case reports have implicated the relationship between BD and MDS with trisomy 8, but no reasonable etiological link between them has been proposed. Chen et al (24) recently analyzed the gene expression pattern in purified CD 34-positive hematopoietic progenitor cells obtained from MDS patients with either trisomy 8 or monosomy 7. In cases with trisomy 8, up-regulated genes included those primarily involved in immune and inflammatory responses (such as TGF-beta, TGF-beta receptor, interleukin-6, interleukin-7 receptor and VCAM-1), while genes up-regulated in cells with monosomy 7 did not include these genes but included those involved in leukemia transformation (HOX9A, BRCA2, and PLAB) and apoptosis (TRAIL

and TRAIL-DR5) (24). This expression profile of CD34-positive cells with trisomy 8 may be related to the pathogenesis of BD-like symptoms occurring in MDS patients with this chromosomal abnormality.

Trisomy 8 is a cytogenetic abnormality frequently observed not only in MDS but also in myeloproliferative disorders (MPD) such as polycythemia vera, idiopathic myelofibrosis, essential thrombocythemia and chronic myelogenous leukemia (CML) as well as in acute myeloid leukemia (AML) (25). However, BD-like symptoms are not common in patients with MPDs (26), except for those with chronic myelogenous leukemia treated with interferons (27-30). In these CML patients, interferons might induce BD-like symptoms by activating neutrophil functions (27-30). In AML patients, BD-like symptoms are not common. In these patients, the number of mature neutrophils is usually decreased, or their function may be impaired; this may explain why BD-like symptoms are rare. In fact, in our Case 3, intestinal hemorrhage was diminished after leukemic transformation.

Apart from BD, some MDS patients develop other immune-mediated complications such as vasculitis, Sweet's syndrome, immune thrombocytopenia and Hashimoto's thyroiditis (31). Billstrom et al reported that the incidence of chromosomal abnormalities is higher in these MDS patients than in those without immune-mediated complications (31). To date, however, no clear relationship between trisomy 8 and immune-mediated complications other than BD has been documented in MDS patients. In our Case 2, transient thrombocytopenia and CK elevation were observed in each attack, which may be related to some immune-mediated mechanisms.

In conclusion, for hemorrhagic intestinal ulcers observed in BD patients, the possibility of underlining clonal hematological disorders should be considered. On the other hand, if MDS patients have fever with either abdominal pain or melena, caution should be taken for the possibility of complications with intestinal BD. Further studies are needed to clarify the association between BD and MDS with trisomy 8.

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