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CASE REPORT

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Behçet's disease accompanied by myelodysplastic syndrome with trisomy 8: two case reports and a review of 15 Japanese cases

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Abstract We describe two cases of Behçet's disease associated with myelodysplastic syndrome (MDS) with trisomy 8. Both cases developed ulceration in the cecum as a gastrointestinal complication of Behçet's disease, after a diagnosis of MDS. We summarized recent case reports of Behçet's disease associated with myelodysplastic syndrome, and studied the clinical manifestations. Most cases showed trisomy 8 as a chromosomal abnormality. Gastrointestinal involvement without eye lesions seems to be characteristic of Behçet's disease associated with MDS.

Key words Behçet's disease · Entero-Behçet's disease · Myelodysplastic syndrome (MDS) · Trisomy 8

Introduction

Behçet's disease is an inflammatory disease characterized by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions.[1,2] The pathogenesis of Behçet's disease is still unclear. Some cases show an involvement of the gastrointestinal tract, most commonly ileocecal ulceration. The prevalence of gastrointestinal involvement is high in Japanese patients with Behçet's disease.

Myelodysplastic syndrome (MDS) is an acquired blood disorder that often progress to acute leukemia, and is characterized by pancytopenia with overt morphological abnormalities or dysplastic changes in the bone marrow.[3] Chromosomal abnormalities such as trisomy 8, monosomy 7, and 5q− are frequently observed in MDS.[4,5]

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Recently, reports of Behçet's disease associated with MDS have been increasing in Japan. We describe two cases, and discuss the clinical manifestations of Behçet's disease associated with MDS.

Case reports

Case 1 (Fig. 1a)

A 28-year-old woman with a 14-year history of aplastic anemia was admitted to this hospital because of high fever caused by a gingival abscess. Pancytopenia due to aplastic anemia had continued despite treatment with anabolic steroids and cyclosporin A. Occasional folliculitis had been present for 9 years before admission. For the past 5 years, she had recurrently developed painful oral aphthae and genital ulceration. Toothache was present from 5 months before admission, and persisted despite treatment. The toothache and gingival pain worsened several days before admission. After admission, peripheral blood analysis showed pancytopenia. Bone marrow examination revealed hypocellular bone marrow with dysplasia of erythroblasts. Chromosomal analysis of bone marrow cells revealed 47,XX,+8 in 16 of 20 dividing cells (Fig. 2a). Chromosomal analysis of bone marrow cells in this patient done 6 years earlier had shown no abnormalities. Her hematological diagnosis was changed from aplastic anemia to refractory anemia in MDS because of the new appearance of dysplasia of erythroblasts and chromosomal abnormality. No eye lesions were evident. A gingival abscess was present, but subsided after the extraction of one tooth and antibiotics. Several days after admission, she developed right lower abdominal pain. Total colonoscopy showed extensive ulceration in the ileocecal region. The patient was diagnosed as having Behçet's disease with intestinal involvement. The patient did not possess HLA-B51. Prednisolone at 40 mg/day and sulfasalazine at 1 g/day were administered. However, the ulceration in the cecum was resistant to these therapies and the patient developed repeated high fever. High-dose corticosteroid therapy,

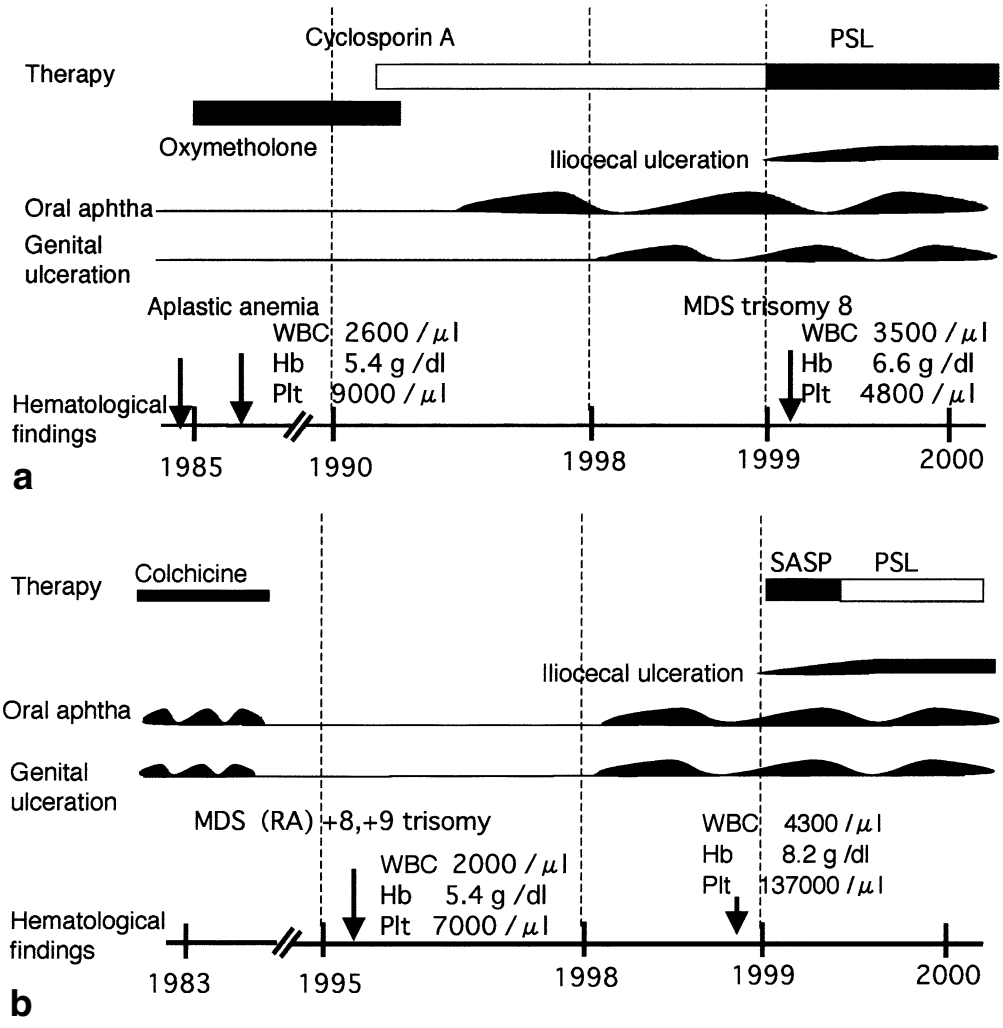

Fig. 1. Clinical course of the reported cases. **a** Patient 1. **b** Patient 2. *PSL*, prednisolone; *SASP*, salazosulphapyridine; *MDS*, myelodysplastic syndrome; *WBC*, white blood cells; *Hb*, hemoglobin; *Plt*, platelets

including several administrations of pulse therapy (methylpredonisolone 1 g/day for 3 days), was not effective for the ulceration in cecum, and the high fever did not respond to broad-spectrum antibiotics. Repeated bacterial examinations were negative. Mesalazine was also not effective.

Ileocecal resection was performed 1 year after admission. The surgical specimen revealed multiple ulcers (7 × 4.5 cm and 1.5 × 1 cm) of the cecum with focal peritonitis that was compatible with intestinal involvement in Behçet's disease. After the operation, the fever disappeared and the general condition of the patient improved. Predonisolone was gradually tapered off to 10 mg/day. The patient remains moderately well, with periodical oral or genital ulcers. Pancytopenia is persistent, necessitating occasional blood transfusion.

Case 2 (Fig. 1b)

A 39-year-old woman was admitted to this hospital because of lower abdominal pain. The patient had been well until the age of 23 years, when she developed recurrent oral aphthae, genital ulceration, and pseudofolliculitis of the skin. No eye lesions were evident. Behçet's disease was diagnosed. Oral administration of colchicine was effective, and the patient's condition was good for 14 years. Two years before admission, the patient developed pancytopenia without blasts in peripheral blood. Bone marrow examination revealed hypocellular bone marrow with dysplasia of erythroblasts. Chromosomal analysis of bone marrow cells revealed 48,XX,+8,+9 in 16 of 20 dividing cells (Fig. 2b). The patient was diagnosed with refractory anemia in MDS, with trisomy 8 and 9. The patient had been kept under observation without any treatment for the MDS.

After admission, total colonoscopy showed a large ulceration in the ileocecal region. The patient was diagnosed as having Behçet's disease with intestinal involvement. The patient did not possess HLA-B51. Recurrent ulceration in the cecum was resistant to salazosulphapyridine or large amount of prednisolone, including several administrations of pulse therapy. Mesalazine was started, but was discontinued because of liver dysfunction. Because the maintenance dose of prednisolone could not be reduced from 40 mg/day, and the patient had depended on intravenous hyperelementation for 7 months, ileocecal resection was performed. After the operation, her general status improved and she remains well with 17 mg/day of prednisolone. The patient's MDS was stable during this period.

Table 1. Features of Japanese reported cases of Behçet's disease accompanied by myelodysplastic syndromes

Case	Age	Sex	Eye	Skin	Oral	Genital	GI	Onset	Chromosome	Reference
1	72	M	−	+	+	+	−	M → B 1.6 y	47XY,+8,del(20)(q11)	6
2	35	M	+	+	+	+	−	M → B 3 y	46XY	7
3	57	M	−	−	+	+	+	M → B 6 m	47XY,+8	7
4	52	M	−	+	+	−	−	M → B 4 y	47XY,+22,t(9;22),(q34;q11)	7
5	41	F	−	+	+	+	+	B → M 15 y	47XX,+8	8
6	59	M	+	−	+	−	−	M → B 4 m	43XY,−5,−7,+8,−16,−18,−3p−,7q+,12p−,+2mar	9
7	45	M	−	+	+	+	−	M = B	48XY,+8,+15	10
8	57	M	−	+	+	+	+	M → B 4 y	ND	11
9	23	F	−	+	+	+	+	M → B 1 y	47XX,+8	12
10	54	F	−	+	+	+	−	M → B 1 y	47XX,+8	12
11	34	F	+	+	+	+	+	M → B 3 y	47XX,+8	13
12	39	M	−	+	+	+	+	M = B	47XY,+8	14
13	59	M	−	+	+	+	−	M = B	47XY,+8	15
14	28	F	−	+	+	+	+	B → M 5 y	47XX,+8	Case 1
15	39	F	−	+	+	+	+	B → M 10 y	48XX,+8,+9	Case 2

Eye, skin, oral, genital: presence or absence of symptoms characteristic of Behçet's disease in these organs
GI, gastrointestinal involvement; M → B, myelodysplastic syndrome occurred before Behçet's disease; B → M, Behçet's diseases occurred before myelodysplastic syndrome; M = B, myelodysplastic syndrome and Behçet's disease were diagnosed on the same occasion
y, year; m, month

Discussion

MDS is a rare complication of Behçet's disease. In the world literature, we found a total of 17 case reports of Behçet's disease associated with MDS, including these two cases, since 1985. Among these, 15 reported cases were in Japan.[6–15] The other cases were from Korea and Germany. The clinical manifestations of the 15 Japanese cases are summarized in Table 1. The mean age was 46.3 years (range 23–72 years). The subtypes of MDS included 11 refractory anemia (RA), 3 refractory anemia with ringed sideroblast (RARS), and 1 refractory anemia with excess of blasts (RAEB), based on French–American–British (FAB) MDS classification criteria.[3] In both of our cases, the type of MDS was refractory anemia.

Most cases had recurrent oral and genital ulceration and skin lesions. However, eye lesions were present in only 3 of the 15 cases. Interestingly, more than half of the cases (8/15) had gastrointestinal involvement, mainly ileocecal ulceration. It seems that gastrointestinal involvement without eye lesions is one of the characteristic clinical findings in Behçet's disease associated with MDS. Our two cases are consistent with this conclusion.

Behçet's disease was preceded by MDS in nine cases, although our two cases had long histories of Behçet's disease before the onset of MDS. In our case 1, the patient had been suffering from aplastic anemia for 14 years. Strictly speaking, we cannot determine exactly when MDS developed in this patient, although chromosomal analysis was normal 6 years before admission. This patient presented with ileocecal ulceration with Behçet's disease after the diagnosis of MDS. In this case, gingival abscess may have triggered the exacerbation of Behçet's disease, causing the first appearance of ileocecal ulceration. Similarly, in two other cases, gingival abscess preceded Behçet's disease.[9,10] Since some bacterial infection by oral flora has been suggested as a possible cause of Behçet's disease, increased susceptibility to infection due to hematological disorders may play a role in the complication of Behçet's disease with MDS.

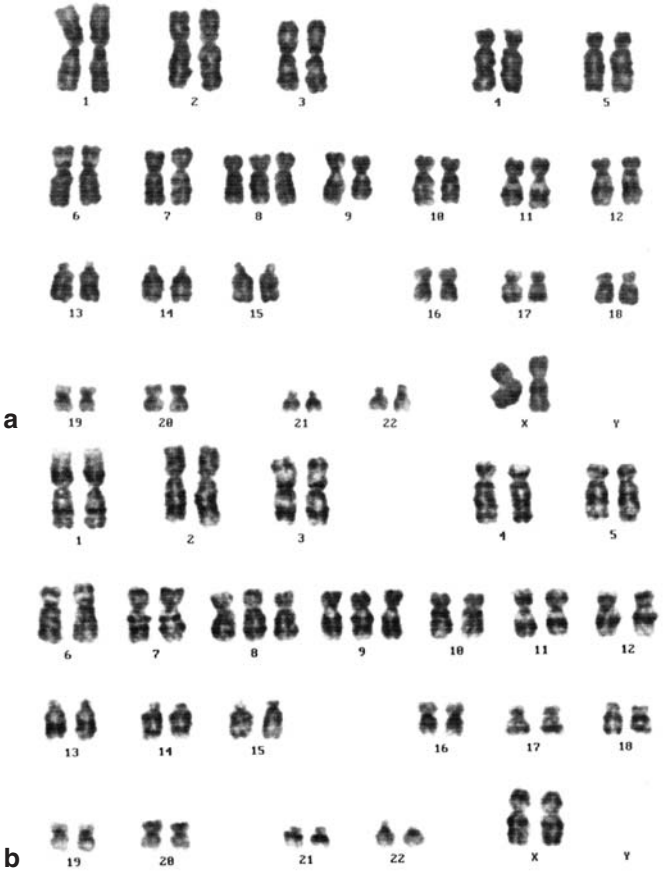

Fig. 2. Chromosomal analyses of reported cases. **a** Patient 1, showing trisomy of chromosome 8. **b** Patient 2, showing trisomies of chromosomes 8 and 9

On cytogenetic examination, most cases (13/15) showed chromosomal abnormalities (Fig. 2). In particular, trisomy 8

was detected in 12 cases. Among these cases, nine had trisomy 8 as the single abnormality (47 XY or 47 XX, +8) and three had trisomy 8 with other abnormalities. Trisomy 8 is one of the common chromosomal abnormalities in MDS. However, the frequency of trisomy 8 is around 20% of MDS cases in general.[4,5] Therefore, the presence of trisomy 8 seems to be a characteristic of MDS associated with Behçet's disease. The relationship between trisomy 8 and the pathogenesis of MDS is unknown. To date, we do not have a hypothesis to explain the high incidence of MDS with trisomy 8 in Behçet's disease patients. Detailed analyses with more patients may give an insight into the pathogenesis of Behçet's disease. Viewed from another perspective, Kimura et al.[16] reported that among patients with MDS, patients with trisomy 8 have high prevalence of multiple intestinal ulcers. They concluded that trisomy 8 may be a risk factor for intestinal ulcers. Thus, MDS, trisomy 8, intestinal ulcers, and Behçet's disease seem to be connected in some way. However, these reports, including ours, are mostly from Japan, and it is not clear whether this relationship is present worldwide, or in Japan only. A large-scale multinational survey of MDS patients is necessary to confirm this relationship. In addition, the relationship between the progression of MDS and the disease activity of Behçet's disease is yet to be determined. In previous reports, features of Behçet's disease responded to therapy without any improvements in hematological disorders,[7,10,14,15] fluctuated independently,[8,11] or were refractory to conventional therapies, as in our two cases. In the case reported by Takishita et al.,[9] Behçet's disease responded to 100 mg/day oral prednisolone, but MDS progressed from refractory anemia with excess of blasts to refractory anemia with excess of blasts in transformation (RAEB-T), and the patient died from renal and respiratory failure.

Case 1 had presented with repeated high fever for 1 year, which is a rare symptom on Behçet's disease and suggests an infection rather than Behçet's disease, but no infection was detected throughout the long clinical course. Interestingly, Nawata et al.[15] reported a similar case which presented with repetitive high fever. They found an elevation of serum inflammatory cytokines, such as IL-6, IL-8, and G-CSF. However, the high fever responded to 30 mg/day prednisolone in their case, while in our case 1, the high fever resisted a high dose of prednisolone, but completely disappeared after surgical removal of the ileocecum. The surgical specimen showed large ulcers with focal peritonitis, suggesting that the large inflammatory lesion in the ileocecal area was the cause of the repeated high fever in this case.

As for therapy for Behçet's disease, both our cases were resistant to a high level of steroid therapy for more than half a year, and surgical treatment was needed, although it is considered that surgical procedures are risky in MDS patients. After the operation, the patients' general condition improved, and amount of steroid could be reduced in both patients. At least in our cases, surgical removal of the affected intestine lead to an eventual remission of the disease. The indications for surgical treatment for intestinal involvement in Behcet's disease are controversial. Surgical treatment may trigger a deterioration of the Behçet's disease. In addition, relapses of intestinal ulceration frequently arise after the operation.[17,18] In the 15 reported Japanese cases of Behçet's disease with MDS, an emergency operation was performed for the perforation of an ulcer in only one case in addition to our two cases. Careful and continued observation is necessary for our two cases, although to date surgical treatment seems to have been successful in both cases. Recently, Travis et al.[19] reported successful treatment of refractory intestinal Behçet's disease by infusion of the monoclonal anti-TNFα antibody infliximab. Dramatic improvements were observed in two cases. The use of infliximab, after fully informed consent, may be considered for patients who are unresponsive to conventional therapies. A bone marrow transplant may be the final option for extremely refractory patients.

In conclusion, we reported two cases of Behçet's disease accompanied by MDS. Intestinal manifestations and trisomy 8 seem to be characteristics of this condition. Thus, when refractory anemia occurs in intestinal Behçet's disease patients, MDS should be ruled out, and MDS patients with trisomy 8 should be followed with intestinal manifestations in mind.

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