International Journal of
HEMATOLOGY

Case Report

Successful Cord Blood Stem Cell Transplantation for Myelodysplastic Syndrome with Behçet Disease

Kazumi Yamato

Department of Pediatrics, Osaka City University Graduate School of Medicine, Osaka, Japan

Received June 13, 2002; received in revised form August 21, 2002; accepted September 3, 2002

Abstract

A 10-year-old girl who had been treated as an outpatient for neurofibromatosis type 1 was admitted with fever, 10% weight loss, and abdominal pain that had persisted for 1 month. The clinical manifestations and the results of endoscopy led to the diagnosis of intestinal Behçet disease. Blood cell dysplasia appeared during the hospitalization. The patient subsequently developed blast cells, and the diagnosis of myelodysplastic syndrome (MDS) was made. Behçet disease was first controlled with steroids and diet followed by chemotherapy and cord blood stem cell transplantation (SCT). Both the MDS and Behçet disease went into remission after transplantation. The use of hematopoietic SCT has the potential not only to cure but also to help explicate the mechanism of Behçet disease. *Int J Hematol.* 2003;77:82-85.

Key words: Behçet disease; Myelodysplastic syndrome; Cord blood transplantation

1. Introduction

Behçet disease is a chronic inflammatory disorder of unknown etiology. It is predominantly characterized by recurrent mouth ulcers, external genital ulcers, and skin and eye lesions. Inflammation of tissue and organs throughout the body, including the gastrointestinal tract, central nervous system, and vascular system, occasionally occurs [1]. Many cases of Behçet disease are found in the Mediterranean region, countries of the Middle East, and Japan. Onset of the disease in childhood is rare, accounting for only 2% to 3% of all cases [2]. Although inflammatory bowel disease (Crohn disease in particular) is a well-known manifestation of myelodysplastic syndrome (MDS) with gastrointestinal complications [3], only 9 cases of MDS associated with Behçet disease have been reported [4]. We describe the case of a patient with MDS associated with intestinal Behçet disease. In this case we first controlled the Behçet disease and followed the treatment with cord blood transplantation from unrelated donors. The treatments seemed to cure the Behçet disease and the MDS.

Correspondence and reprint requests: Kazumi Yamato, 1-4-3 Asahi-cho, Abenoku, Osaka 545-8585, Japan; 81-6-6645-3817; fax: 81-6-6636-8737 (e-mail: yamatomi@med.osaka-cu.ac.jp).

2. Case Report

A 10-year-old girl was admitted with fever, 10% weight loss, and abdominal pain that had persisted for 1 month and intensified after meals. At 8 months of age, the patient had been found to have neurofibromatosis type 1 (NF1). The medical history was significant for a leukemoid reaction triggered by *Salmonella* septicemia that occurred when the patient was 1 year old. The patient's case was followed on an outpatient basis for an increase in leukocyte count, slight thrombocytopenia, and mild hepatosplenomegaly. Although no other family members had NF1, the patient's brother, who was 6 years older, developed chronic myelogenous leukemia 2 years after the patient's admission. Examination of the patient when she was admitted revealed café-au-lait spots on the skin over the entire body. The patient had slight anemia, and ulcers were found in the oral mucosa. No enlarged lymph nodes were palpable. Both the liver (3 cm) and the spleen (3 cm) were palpable. No genital ulcers, iridocyclitis, or uveitis were detected. No neurological abnormalities were found.

Laboratory results revealed a white blood cell count of 6900/μL; hemoglobin, 10.3 g/dL; platelets, 64,000/μL; C-reactive protein, 1.5 mg/L; erythrocyte sedimentation rate, 109/154 mm/h; immunoglobulin G (IgG), 3210 mg/dL; IgA, 635 mg/dL; and IgM, 142 mg/dL. The test result for occult blood in stool was positive. Even after admission, the

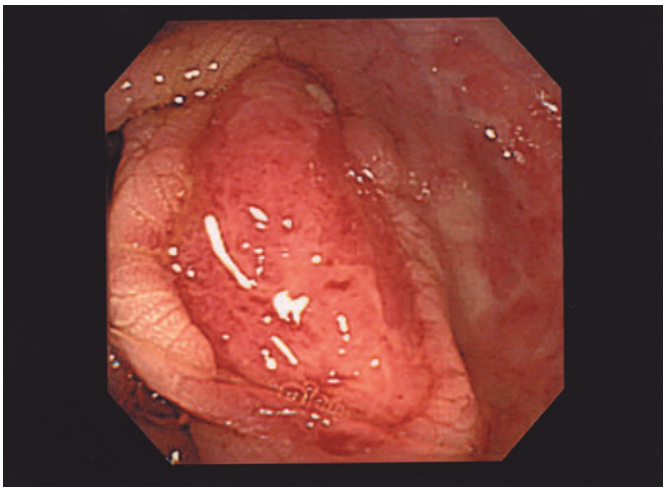

Figure 1. Punched-out ulcer at ileocecal valve.

patient continued to have fevers above 38°C, mild abdominal pain, and mouth ulcers. The mouth ulcers had repeatedly appeared and disappeared over the course of the previous year. The appearance of erythema nodosum was then noticed on the lower legs and trunk. Laboratory findings did not suggest an autoimmune disease. Neither blasts nor dysplasia was detected by examination of the bone marrow. Because the stool occult blood test results were positive, gastrointestinal endoscopy was performed. The examination revealed multiple punched-out ulcers and aphthae in the large and small intestine and aphthae in the esophagus (Figure 1). On the basis of these findings and the observed symptoms, a diagnosis of intestinal Behçet disease was made.

A pseudo-Pelger anomaly in the peripheral blood neutrophils with few granules was noticed after the diagnosis of Behçet disease was made. Because of the findings of thrombocytopenia and giant platelets and because a repeated bone marrow puncture examination revealed small mononuclear megakaryocytes, megaloblastic changes in erythroid series, and the presence of type 1 blast cells, a diagnosis of MDS (refractory anemia with excess of blasts) was made. Chromosomal abnormalities, such as ring 6, which had not been identified earlier, became apparent, although monosomy 7 was not observed. Because the patient's condition was hematologically stable, the Behçet disease was treated first. Although the symptoms were relieved and the endoscopic findings dramatically improved with steroids and diet therapy, a reduction in the steroid dose resulted in recurrence of symptoms, such as abdominal pain, mouth aphthae, and fever. The endoscopic findings also worsened again. Because the MDS had progressed to overt leukemia, temporary remission of the Behçet disease was attempted with pulse steroid therapy followed by initiation of remission-induction chemotherapy for acute myelogenous leukemia (AML). The patient received a second course of therapy, after which the bone marrow reached M1 marrow status. Because there was no HLA-matched family donor, cord blood transplantation from unrelated donors who were a 1-locus mismatch (Table 1) was performed. Although endoscopy performed prior to treatment identified small aphthae, the ulcers had disappeared. Pretransplantation conditioning included cyclophosphamide 60 mg/kg for 2 days, 12 Gy total body radiation, and high-dose cytarabine (Ara-C) (3 g/m^2 × 2 for 4 days) (Figure 2). Cyclosporine and methotrexate were used for prevention of graft-versus-host disease (GVHD). Neutrophil recovery (500/μL) occurred on day 28. The platelet count exceeded 50,000/μL on day 68. GVHD manifested as a skin rash (stage 2) on day 23. The patient experienced diarrheal stools of 500 mL/d and abdominal pain (grade II) on day 56. These symptoms were ameliorated with methylprednisolone pulse therapy. Results of a cytomegalovirus antigenemia assay turned positive on day 40, and ganciclovir administration was initiated. However, because the abdominal symptoms again worsened, colonoscopy was performed on day 77. Although acute GVHD findings were observed and cytomegalovirus was detected with a polymerase chain reaction assay, no evidence of Behçet disease was found. The result of the cytomegalovirus antigenemia assay turned negative and ganciclovir administration was completely stopped on day 150. Pneumatosis cystoides intestinalis subsequently developed and persisted over long periods, but the patient's condition improved with conservative treatment. Steroid administration was discontinued, and endoscopic examinations performed on days 329 and 510 showed the mucous membrane was completely normal without any indication of Behçet disease.

3. Discussion

The diagnosis of Behçet disease must include the presence of recurrent oral ulcers concomitant with any 2 of the following symptoms: recurrent genital ulcers, eye lesions, skin lesions, or a positive result of a pathergy test [5]. Behçet disease is classified according to the organ involved: incomplete, intestinal, vascular, and neuro-Behçet disease [6]. The incomplete type is frequently found among children with Behçet disease, and genital ulcers are rare before adolescence [7]. Eye symptoms, which are uncommon, are seen during the early stages in only 35% of patients in France and 10% in Japan [8].

Cases of MDS associated with Behçet disease are rare, and all reported cases have been adult cases. Eye symptoms were observed in 2 of the 9 patients in these reported cases, and 7 of the 9 patients had incomplete Behçet disease with multiple intestinal lesions [4]. Our patient had mouth and skin lesions. Endoscopy of the gastrointestinal tract revealed circular, punched-out ulcers on the antimesenteric side of the intestine between the terminal ileum and the colon. Neither skip lesions nor epithelioid cell granuloma was identified. The lesions were similar to those found in typical Behçet dis-

Table 1.
Donor and Patient Characteristics

			HLA Type		
	Sex	Blood Type	HLA-A	HLA-B	HLA-DR
Patient	F	A+	24, 33	44, 52	1302, 0901
Donor	M	B+	24, 33	44, 52	1302, 0405

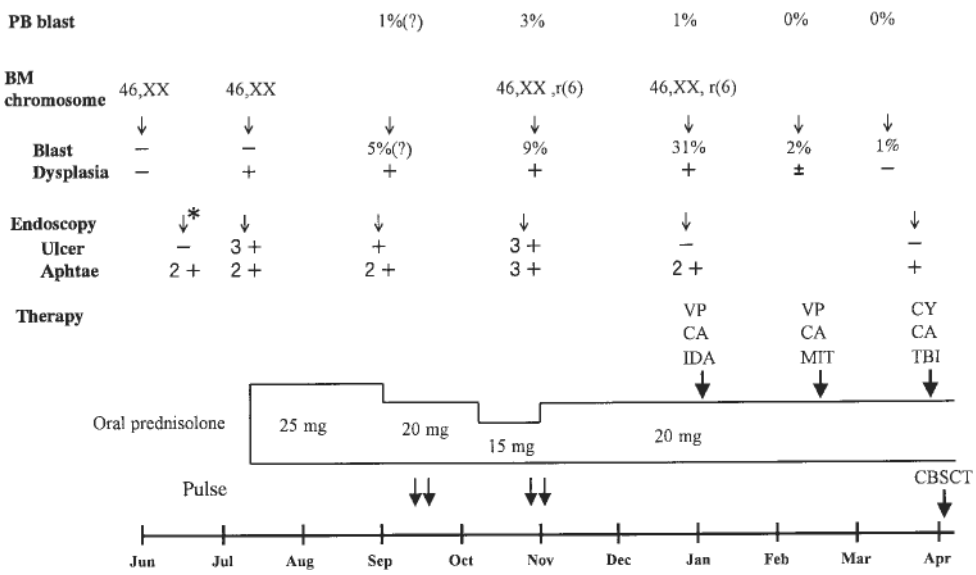

Figure 2. Clinical course before cord blood transplantation. PB indicates peripheral blood; BM, bone marrow; VP, etoposide; CA, cytarabine; IDA, idarubicin; MIT, mitoxantrone; CY, cyclophosphamide; TBI, total body irradiation; Pulse, methylprednisolone; CBSCT, cord blood transplantation; *, esophageal lesion.

ease [9]. The diagnosis of intestinal Behçet disease was made on the basis of these factors.

Steroids and immunosuppressants are used in the treatment of Behçet disease; however, no radical treatment exists today, largely because the etiology is unknown. The causal factors suggested so far include autoimmune disease, abnormalities of T-cells, enhanced neutrophil function, HLA subtype (B-51), and an abnormal coagulation system [10]. A recent study showed that allogeneic transplantation in patients with blood dysplasia associated with a refractory autoimmune disease resulted in cure of both diseases [11]. Allohematopoietic stem cell transplantation (SCT) can be effective in the treatment of abnormal T-cells and enhances neutrophil function. The prognosis of MDS in children is extremely unfavorable, except for RA (refractory anemia) or MDS with Down syndrome [12]. Allohematopoietic SCT may be the best hope for a cure [13]. Unfortunately, our patient did not have an HLA-matched family member. The following considerations were taken into account in the search for an alternative source of hematopoietic stem cells. (1) The overall event-free survival with umbilical cord blood transplantation is not statistically different from that with bone marrow transplantation [14]. (2) The outcome of cord blood SCT in children with malignant blood disorders often is favorable [15]. (3) The management of intestinal Behçet disease is difficult, and a surgical procedure often is required [16], so pretransplantation conditioning is not possible in the presence of active intestinal lesions. (4) Long-time use of steroids is avoided. (5) For patients with disease that progresses to RAEB-T (refractory anemia with excess blasts in transformation) with excess blasts in transformation or AML, the outcome after transplantation may be improved by transplantation as soon as possible [17]. We selected cord blood because it allowed transplantation to be carried out when the Behçet disease was stabilized.

For a patient with MDS associated with Behçet disease, we performed cord blood SCT and obtained a favorable outcome. It is unclear that the cure of Behçet disease was brought about by T-cell replacement after SCT or by high-dose chemotherapy at preconditioning. Further study is required to cure and to explicate the mechanism of Behçet disease.

Acknowledgments

I thank Dr. Tetsuo Arakawa and Dr. Nobuhide Oshitani, Department of Gastroenterology, Osaka City University Graduate School of Medicine, for endoscopic examinations.

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