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Letter to the Editor

Autologous Hematopoietic Recovery with Aberrant Antigen Expression after Allogeneic Bone Marrow Transplantation

Hiroyuki Kobayashi,[1)] Tomohiro Matsuyama,[1)] Satoko Oka,[2)] Shin-ichiro Fujiwara,[1)] Iekuni Oh,[1)] Takahiro Suzuki,[1)] Katsutoshi Ozaki,[1)] Masaki Mori,[1)] Tadashi Nagai,[1)] Keiya Ozawa,[1)] and Kazuo Muroi[1)]

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TO THE EDITOR

A 50-year-old woman was admitted in December 2006 with progressive petechiae. Bone marrow (BM) aspiration showed massive proliferation of leukemic myeloblasts with myeloperoxidase staining. Three-color flow cytometry (FCM) with a CD45 gate for the BM cells was performed in our laboratory[1] ; the blasts were positive for CD7, CD11c, CD13, CD15, CD33, myeloperoxidase and HLA-DR and negative for CD34 and CD117. Karyotypes of the BM cells were normal. A diagnosis of acute myeloblastic leukemia (AML)-M2 was made on the basis of French-American-British classification. The patient needed standard induction chemotherapy twice to achieve complete remission. Refractoriness to platelet transfusions due to anti-HLA antibody developed. She received an allogeneic BM transplant from an ABO-matched and HLA-DR-mismatched unrelated female donor in September 2007. The conditioning regimen consisted of total body irradiation (2 Gy twice daily for 3 days) followed by cyclophosphamide (60 mg/kg/day for 2 days). On day 0, 4.0×10^8 BM cells per recipient body weight were infused. Tacrolimus and short-course methotrexate were used as prophylaxis for graft-versus-host disease. After BM transplantation, severe pancytopenia persisted. BM aspiration on day 22 revealed marked hypocellularity, suggesting graft rejection. Peripheral blood neutrophils gradually increased from day 50. BM aspiration smears on day 75 showed recovery of the BM cells, especially myeloid cells, without significant morphologic abnormalities and proliferation of myeloblasts, indicating that complete remission was maintained. Chromosomal analysis of the BM cells showed various cytogenetic abnormalities (Table 1). A chimerism-based analysis of the BM cells using short tandem repeat-polymerase chain reaction showed that 100% of the cells originated from the recipient. A diagnosis of autologous (recipient) hematopoietic recovery after graft rejection was made. Multiparametric FCM based on a four-color method (ReproCELL, Yokohama, Japan), which had been approved by the Jichi Medical University Institutional Review Board (no. 06-70), did not show the abnormal expression of antigens in the blasts in the BM on days 75 and 183. However, it showed small populations of $CD34^+CD7^+$ cells and $CD34^+CD15^+$ cells in the blasts on day 253 (Fig. 1). The latter cells were characterized by a high intensity of CD34, which indicates abnormal expression of the antigen. BM aspiration was performed every three to six months ; various chromosomal abnormalities of BM cells were found in each sample (Table 1). After day 253, routine three-color FCM instead of the multiparametric FCM was conducted to analyze phenotypes of the blasts in the BM. This FCM can detect $CD34^+CD7^+$ cells but not $CD34^+CD15^+$ cells because of antibody combinations. The proportions of $CD34^+CD7^+$ cells among the blasts of the BM were as follows : on day 323, 37.2% ; on day 421, 30.9% ; on day 603, 35.5% ; on day 785, 21.5% ; on day 975, 49.2% ; on day 1,149, 36.0% ; and on day 1,232, 24.5%. Although chromosomal abnormalities were detected on and after day 75, obvious dysplastic features associated with myelodysplastic syndrome (MDS) were not found. The patient is clinically well with normal peripheral blood cell counts.

There are several reports on autologous (recipient) hematopoietic recovery after allogeneic hematopoietic stem cell transplantation.[2-6] All patients received total body irradiation

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[1)]Division of Cell Therapy, Jichi Medical University Hospital, Tochigi, Japan
[2)]First Department of Internal Medicine, Osaka Medical College, Osaka, Japan
Address correspondence and reprint requests to : Kazuo Muroi, M. D., Division of Cell Therapy, Jichi Medical University Hospital, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan. E-mail : muroi-kz@jichi.ac.jp

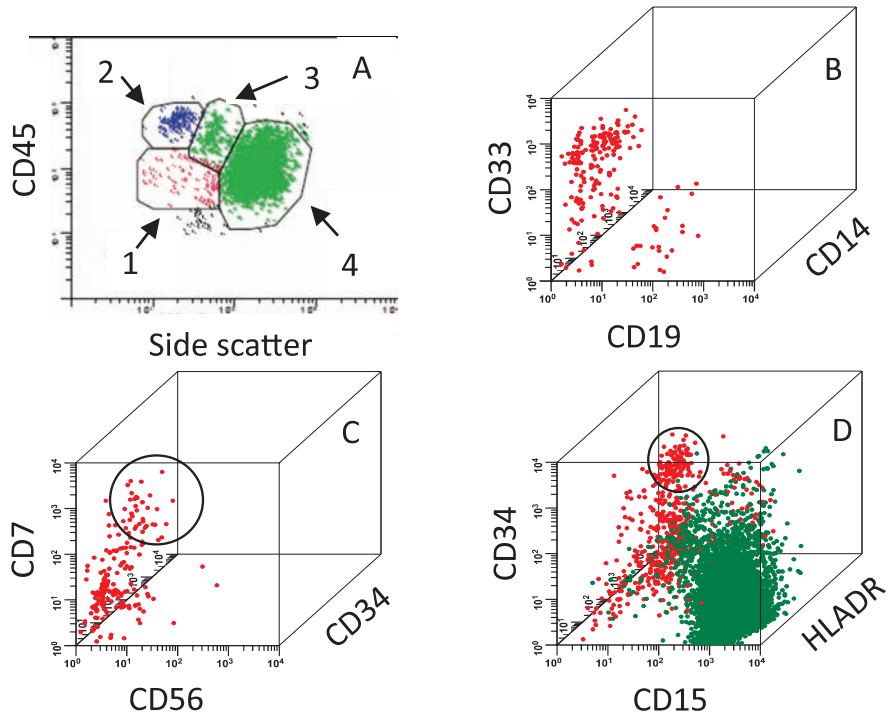

Fig. 1. Flow cytometric analysis of bone marrow cells on day 253 after bone marrow transplantation. 1, blasts ; 2, lymphocytes ; 3, monocytes ; 4, granulocytes. Antigen levels in the blasts are plotted in *1B* (right upper), *1C* (left lower) and *1D* (right lower), while those in granulocytes are plotted in *1D*. The cycle indicates the blasts expressing abnormal antigens.

with a total of 12 Gy or more as conditioning. In these patients, various chromosomal abnormalities in the BM cells were found to be associated with autologous hematopoietic recovery. Because chromosomal abnormalities in these patients were random and not related to the patients' underlying diseases, such aberrations indicate that normal hematopoietic progenitors may have been injured by the irradiation used for conditioning. In our case, various chromosomal abnormalities were found concomitantly with small populations of $CD34^+CD7^+$ cells and $CD34^+CD15^+$ cells in the BM, which have been used as markers for aberrant antigen expression in AML.[7-10] Taking these findings together, the $CD34^+CD7^+$ cells and $CD34^+CD15^+$ cells in the blasts of our patient were derived from injured normal hematopoietic progenitors that have self-renewal activity. Although the reason why neither $CD34^+CD7^+$ cells nor $CD34^+CD15^+$ cells were detected on day 75 or 183 is not known, it may be due to clonal changes to the injured hematopoietic stem cells. To the best of our knowledge, there is no report on progression to MDS or AML in patients who showed autologous hematopoietic recovery.[2-6] It is necessary to follow up the patient carefully for the long term to clarify whether the disappearance of $CD34^+CD7^+$ cells in the BM leads to the normalization of BM karyotypes or an increase in these cells causes hematopoietic diseases including MDS and AML.

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Table 1. Karyotypes of the bone marrow cells before and after bone marrow transplantation

Day	Karyotype
At diagnosis	46, XX (20/20)
Day-14	46, XX (20/20)
Day 22	No metaphases because of insufficient specimen
Day 75	46, X, -X, add(1)(p32), -5, add(6)(q21), add(11)(p15), +mar1 (4/16)
	46, XX, -8, del(15)(q22), +mar2 (2/16)
	46, XX (10/16)
Day 183	45-46, X, X, -2, -6, -10, -16, -22, +1-3mar (8/20)
	46, XX (12/20)
Day 253	46, XX, add(7)(p11) (7/17)
	46, XX, add(7)(q32) (5/17)
	46, XX, t(3;15)(q29;q15) (1/17)
	46, XX(4/17)
Day 323	No metaphases because of insufficient specimen
Day 421	46, XX, -3, add(7)(q32), +1 (3/5)
	46, XX (2/5)
Day 603	46, XX, -3, add(7)(q32), +1-5mar (3/5)
	46, XX (2/5)
Day 785	45, XX, add(11)(p15), -22, +mar (4/9)
	46, XX, del(10)(q24) (3/9)
	44-45, XX, add(7)(q36) (2/9)
Day 975	46, XX, add(3)(q23), add(7)(q32) (2/6)
	46, XX (4/6)
Day 1,149	45-46, XX, -7, -9, +1-8mar (4/7)
	46, XX (3/7)
Day 1,232	46, XX (3/4)
	AK (1/4)

AK, unidentified abnormal karyotypes.
The numerators and denominators in parentheses indicate identified karyotype numbers and total metaphase numbers.

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