DEVELOPMENT OF AUTOIMMUNE THROMBOCYTOPENIA AFTER HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS PERIPHERAL BLOOD STEM CELL SUPPORT FOR METASTATIC BREAST CANCER

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Abstract : Autoimmune thrombocytopenia (AT) occurs after not only allogeneic but also autologous SCT following high-dose myeloablative chemotherapy against malignant tumors. A 50-year-old woman was diagnosed with metastatic breast cancer (MBC) and received myeloablative chemotherapy followed by autologous peripheral blood stem cell transplantation. Purpura developed on day +40 after transplantation, and a diagnosis of AT was made based on her bone marrow picture and elevation of serum PA-IgG level. Her thrombocytopenia was refractory to treatment with high-dose intravenous immune globulin (IVIG) and steroids. Although her platelet count recovered to within the normal range after splenectomy, 14 months after receiving SCT she died of disseminated intravascular coagulation syndrome caused by progression of cancer metastasis. There have been 10 reported cases of AT developing after high-dose myeloablative chemotherapy against malignant tumors followed by autologous SCT. We suggest that the thrombocytopenia after engraftment was caused by activation of dormant auto-immunity, which our patient potentially had, in conjunction with an insufficient quantity and quality of suppressor T-cells before complete reconstruction of the immune system after myeloablative conditioning. The clinical course of our patient was specific and different from previously reported cases since a splenectomy was necessary due to her thrombocytopenia being refractory to both steroid and IVIG therapy.

Key words : autoimmune thrombocytopenia, breast cancer, high-dose chemotherapy, autologous stem cell transplantation

INTRODUCTION

Autoimmune thrombocytopenia (AT) is caused by autoimmune mechanisms that induce platelet destruction by the trapping of these cells by platelet-associated immunoglobulin G (PA-IgG) in the reticuloendothelial systems. In several recent cases myeloablative immunosuppressive therapy and autologous hematopoietic stem cell transplantation (SCT) have been attempted for patients with treatment-refractory AT and paraneoplastic syndrome

associated with lung cancer[1-3]. However, the development of AT has also been noted not only in patients who receive allogeneic SCT but also in those who receive autologous SCT following high-dose myeloablative chemotherapy against malignant tumors[4]. We report a metastatic breast cancer patient who developed AT following consolidation high-dose chemotherapy and autologous SCT after mastectomy and resection of a metastatic liver tumor.

CASE REPORT

A 50-year-old post-menopausal woman was diagnosed in April 1998 with metastatic breast cancer (MBC) involving a 5cm primary tumor in the right C region and a solitary liver metastasis in the S3 region. A modified radical mastectomy with axillary lymph node dissection was performed, and parasternal lymph node biopsy showed no metastasis in the lymph nodes. She then underwent one cycle of standard-dose chemotherapy with doxorubicin 50mg/m^2, cyclophosphamide 500mg/m^2 and 5-fluorouracil 500mg/m^2 (CAF) following resection of the primary and liver tumors with bilateral oophorectomy. The histological findings of the resected liver tumor were compatible with breast cancer metastasis. Two cycles of CAF followed, and autologous peripheral blood stem cells (PBSC) were mobilized with 4g/m^2 of cyclophosphamide and granulocyte-colony stimulating factor (G-CSF). A total of 2.68×10^6/kg CD34-positive cells were collected and frozen over 3 harvests. The standard dose of CAF was continued for 6 cycles and finished in November 1998. The patient's platelet count tended to decrease after January 1999 and was 96×10^9/l on January 22, 1999, although it had normalized after the transient decrease seen after each chemotherapy cycle. Conditioning chemotherapy with the CTCb regimen, which consists of cyclophosphamide 90mg/kg, thiotepa 6mg/kg and carboplatin 200mg/m^2 for 3 days, was started on January 27 and her PBSC were transplanted on February 1. Hematopoietic cell recovery was good; on transplant day +9 her WBC count was over 1×10^9/l and her neutrophil count was over 0.5×10^9/l. The period of febrile neutropenia was 3 days. Although red cell transfusion was never needed, platelet concentrate transfusion was required 6 times (total volume of 60 units). Her platelet count recovered to 93×10^9/l, which was the level before conditioning, on transplant day +17, and the patient was discharged on transplant day +18. Petechiae and purpura developed on her skin on about transplant day +40, and she was readmitted on March 23 because her platelet count had significantly decreased to 2×10^9/l. A diagnosis of AT was made based on her bone marrow picture, which revealed normoplastic megakaryocytes in addition to immature megakaryocytes and an elevated PA-IgG level of 114.0ng/10^7 cells in her peripheral blood. Cardiogenic shock occurred 2 hours after the bone marrow puncture, and echo-free space was observed in her pericardium on the echocardiogram. Under a diagnosis of cardiac tamponade caused by the sternal marrow puncture, her pericardial hematoma was drained of 240ml of fluid after immediate transfusion of platelet concentrate in the intensive care unit. Although high-dose intravenous immune globulin (IVIG) and pulse therapy with methyl-prednisolone followed by oral prednisolone (1mg/kg) were administered concurrently for AT, her platelet count increased to only $30\text{-}50\times10^9$/l. Although the response of AT was insufficient to keep her platelet count over 50×10^9/l, the subjective bleeding tendency disappeared and cardiac tamponade did not recur. In September, 7 months after SCT, we found multiple liver metastases, but cytotoxic

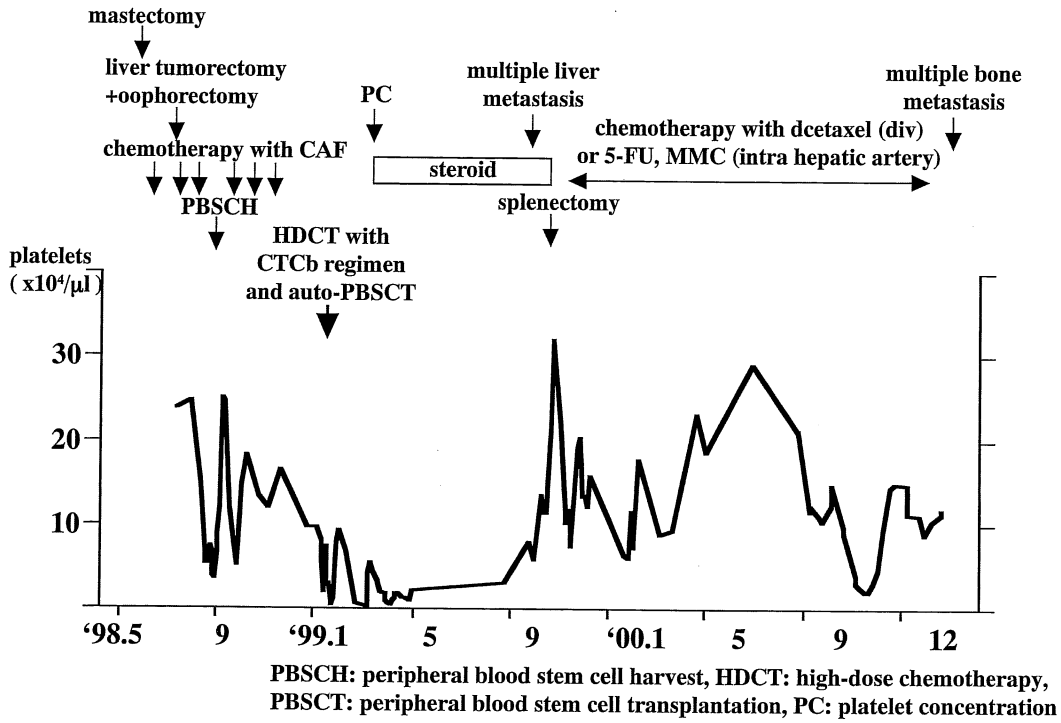

Fig. 1. Patient's clinical course with the transition of platelet count

therapy and invasive surgery were considered too difficult due to the thrombocytopenia. Her platelet count recovered to within the normal range after splenectomy in October, and systemic chemotherapy using docetaxel with fluorouracil injection through the hepatic artery followed. In spite of this chemotherapy, multiple bone metastases developed and liver metastasis could not be controlled. She died of disseminated intravascular coagulation syndrome on April 5, 2001 after palliative therapy with bisphosphonate, 14 months after receiving SCT (Fig. 1).

DISCUSSION

The disease entity of AT is characterized by platelet destruction caused by an auto-immune mechanism in the reticuloendothelial system. Some cases of AT have developed after high-dose chemotherapy or immunosuppressive therapy against malignant tumors, or severe congenital immunodeficiency followed by allogeneic SCT[5-10]. Recently, there have been 10 reports of AT developing after high-dose myeloablative chemotherapy against malignant tumors followed by autologous SCT[4, 11-17] (Table 1). The platelet count of these cases decreased after a transient increase with autologous SCT, and the patients were diagnosed with AT based on findings such as high serum PA-IgG level and an increase in the bone marrow megakaryocyte count. Their clinical courses suggest that the autoimmune platelet destruction occurred after engraftment of transplanted stem cells. Seven of these 10

Table 1. Reported cases of autoimmune thrombocytopenia after auto-hematopoietic stem cell transplantation (HSCT)

Patient	Age	Gendar	Disease for HSCT	Sourse of HSCT	Onset days after HSCT	Treatment	Outcome	Reference No.
1	16	M	LBL	BM	86	Danazol	Improve	11
2	28	M	AML	BM	300	Prednosolone	Improve	12
3	4	F	AML	PBSC	1 month	IV-IgG or Steroid	Improve	13
4	12	M	AML	PBSC	17 months		Improve	13
5	22	F	AML	PBSC	50	Prednosolone	Improve	14
6	19	M	LBL	PBSC	210	Untreated	Unknown	15
7	50	M	AML	BM	2400	-	Unknown	16
8	42	F	AML	BM	210	-	Unknown	16
9	4	F	ALL	PBSC	360	IV-IgG and Steroid	Improve	17
10	58	F	Breast cancer	PBSC	41	Steroid and IV-IgG	Improve	4
Our case	50	F	Breast cancer	PBSC	40	Steroid and IV-IgG	Fail	-
						Splenomegaly	Improve	

patients were under 30 years of age. The initial malignant tumors were acute leukemia in 7 cases and lymphoblastic lymphoma in 2 cases. A solid tumor was reported in the remaining one patient, who had a high-risk breast cancer with 21 metastatic axillar lymph nodes[4]. The source of transplanted hematopoietic stem cells was bone marrow in 4 cases and PBSC in 6 cases. The platelet count of all these reported SCT-related AT cases rapidly improved by treatment with steroids or IVIG, and one case with acute myelogenous leukemia who had a contra-indication for steroids responded promptly upon administration of danazol[11]. Although the mechanism for AT after allogeneic SCT is thought to be that the allo-immunity for the recipient, such as graft-versus-host disease, affects the production of auto anti-platelet IgG antibody, the period of onset of AT after autologous SCT varies and the exact mechanism for AT after autologous SCT is unknown. Several hypotheses have been proposed, such as transient immune system imbalance post transplant, impaired suppressor T-cell function, immune dysregulation due to thymic damage caused by chemo-radiotherapy, and the influence of viral infection [4,15]. In the present case, the platelet count already tended to decrease before high-dose chemotherapy, and AT developed early after SCT. We suggest that the thrombocytopenia after engraftment was caused by activation of dormant auto-immunity, which our patient potentially had, with an insufficient quantity and quality of suppressor T-cells before complete reconstruction of the immune system after myeloablative conditioning.

In summary, this is the second case report of AT developing after autologous SCT for a solid tumor, and the first case of AT developing after auto PBSCT for metastatic breast cancer. Furthermore, our patient's clinical course was specific and different from previously

reported cases, as she required a splenectomy because her thrombocytopenia was refractory to both steroid and IVIG therapy.

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