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Case Report

Early Breast Cancer Following Treatment of Myelodysplastic Syndrome: Report of a Case

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A 45-year-old woman was admitted to our hospital complaining of a mass in her left breast. She had previously been diagnosed with myelodysplastic syndrome (MDS), a type of refractory anemia, based on bone marrow findings and chromosome analysis. She received a preoperative transfusion of fresh packed platelets and a recombinant human granulocyte colony-stimulating factor (rhG-CSF) injection. Left partial mastectomy and axillary lymph nodes dissection were performed to treat early breast cancer. Postoperatively, prophylactic radiotherapy of the residual breast and administration of medroxyprogesterone acetate (MPA) were performed because the tumor tissue was positive for progesterone receptors. She has remained clinically stable, with no evidence of recurrence, for more than three years to date. We report a rare case of breast cancer with MDS, treated with breast-conserving therapy. The strategy of pre- or postoperative platelet transfusion, rhG-CSF injections, and hormonal therapy (MPA) appears to be suitable treatment for progesterone receptor (PgR)-positive breast cancer patients with MDS.

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Key words: Myelodysplastic syndrome, Breast cancer, Breast-conserving therapy, Medroxyprogesterone acetate

Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic disorders characterized by ineffective hematopoiesis with abnormal cellular maturation and cellular dysfunction[1]. Moreover, the incidence of MDS in Japan was estimated to be 1.3 per 100 000 person-years in 1988. The 2.7 per 100 000 person-years figure obtained in 1992 suggests a gradual increase in this disorder[2,3].

Although there have been many reports[4-6] of secondary MDS induced by chemotherapy or radiation therapy for malignant tumors, there have been few reports of non-hematological malignant tumor occurring in primary MDS[5,7]. We present a case of surgically treated early breast cancer with primary MDS.

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Abbreviations:
MDS, Myelodysplastic syndrome; ER, Estrogen receptor, PgR, Progesterone receptor; rhG-CSF, Recombinant human granulocyte colony-stimulating factor; MPA, Medroxyprogesterone acetate

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Case Report

A 45-year-old woman presented in September 1993 with a small mass in the left breast. A diagnosis of MDS, a type of refractory anemia (RA) had already been made by an internist at our hospital in February 1990, based on purpura of the extremities and persistent nasal bleeding due to thrombocytopenia. On bone marrow biopsy, the number of all nucleated cells was $26.9\times10^4/\mu l$ and the megakaryocyte/erythrocyte (M/E) ratio was 1.04. There was also slightly increased megakaryocytic proliferation within normocellular marrow, consistent with ineffective hematopoiesis. Furthermore, there was abnormal cellular maturation in two cell lineages, with some giant-metaneutrophils and atypical erythrocytes, and 1% granulocytic or erythrocytic blasts (less than 5%). Chromosome analysis of the bone marrow sample revealed the following karyotype (G-band assay): 46, XX/−12, der(1)t(1;12) (p11;q11). Thus, MDS, as a type of RA, was diagnosed based on bone marrow biopsy findings and the results of chromosomal analysis.

On physical examination, two small elastic hard tumors in close proximity to each other were

palpated in the lower-inner quadrant of the left breast. There was neither abnormal nipple discharge nor swelling of the bilateral axillary, supraclavicular and infraclavicular lymph nodes. Although mammography showed neither tumor nor microcalcification, ultrasonography revealed two well-defined, small hypoechoic tumors measuring 2.0 cm and 1.0 cm in diameter. Fine needle aspiration biopsy yielded a cytological diagnosis of breast cancer. Cytological findings raised a strong suspicion of ductal carcinoma because of extreme atypia and irregular nuclei, and the absence of naked bipolar cells (Fig 1). The cancer was Stage I ($T_{1a}N_0M_0$, TNM Stage classification, The General Rules for Clinical and Pathological Recording of Breast Cancer, The Japanese Breast Cancer Society), and she was admitted to our department in October 1993.

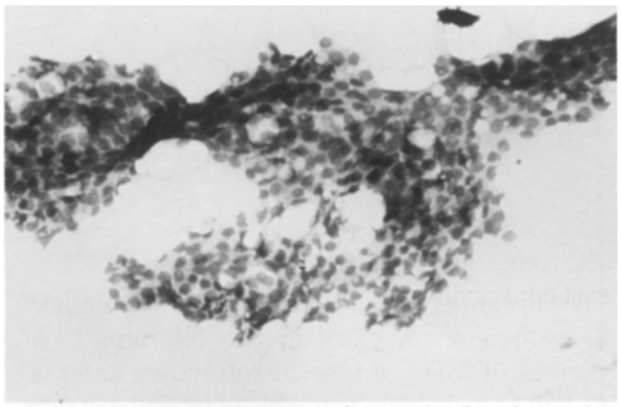

Fig 1. Cytological appearance of atypical cells with irregular nuclei, with no naked bipolar cells in the background (May-Grunwald-Giemsa-staining, original magnification ×200).

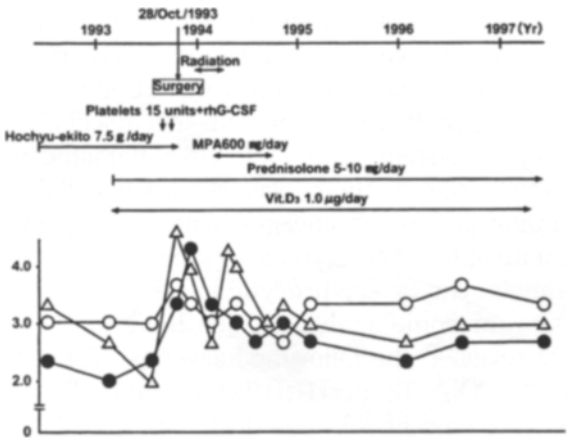

Fig 2. Clinical course. The patient received a total radiation dose of 59 Gy (including a 14 Gy boost) to the residual breast. ●, WBC ($\times 10^3/mm^3$); ○, RBC ($\times 10^6/mm^3$); △, Platelet ($\times 10^4/mm^3$).

Laboratory data on admission are shown in Table 1. Peripheral blood cell counts showed pancytopenia, and the platelet count was particularly low at 11 000/mm^3. Serum ferritin was also low (15.7 ng/ml), but serum Fe was within the normal range (117 μg /dl). Furthermore, various tumor markers (CEA, TPA, CA15-3, NCC-ST439, and BCA225) were all within normal limits.

Breast conserving surgery (Bp+Ax+Ic, R_2) was performed on October 28. The operation was performed after pre-operatively transfusing 15 units of platelets and injecting rhG-CSF, to manage the pancytopenia associated with MDS. There were no perioperative or postoperative complications or difficulties (Fig 2). Histopathologically, both the resected breast tumors were diagnosed as invasive ductal carcinomas (papillotubular type), without lymph nodal metastasis (Fig 3). Fortunately, no cancer cells were detected at the surgical margin, although extensive intraductal components in a cribriform pattern were observed.

In the initial 3 postoperative weeks she completed radiotherapy, receiving a total dose of 59 Gy (including a 14 Gy boost) to the residual mammary gland in accordance with our breast-conserving therapy schedule. Hormonal examination of the resected tumor showed the tissue to be estrogen receptor (ER) negative, but progesterone

Table 1. Laboratory Data at Admission

Blood cell counts		GPT	11 U/l	
WBC	2500/μl	LDH	240 U/l	
Neu.	38.2%	AlP	170 U/l	
Lym.	42.8%	CH-E	283 U/l	
Mo.	16.8%	CPK	36 U/l	
Eo	1 0%	FBS	94 mg/dl	
Ba.	1.2%	T.P.	6.0 g/dl	
Blast	0.0%	AlB	3.4 g/dl	
RBC	$309\times10^4/\mu$l	BUN	7 mg/dl	
Hb	9.2 g/dl	Cr.	0 49 mg/dl	
Ht	28.3%	S-Na	141 mEq/l	
Platelets	$1.1\times10^4/\mu$l	S-K	4.0 mEq/l	
Coagulation studies		S-Fe	117 μg/dl	
PT	140%	Ferritin	15.7 ng/ml	
APTT	26.8 sec	Tumor markers		
Fibrinogen	218 mg/dl	CEA	(≦2.5)	1.0 ng/ml
FDP	1.24 μg/ml	TPA	(≦100)	25 U/l
Chemical studies		CA15-3	(≦30)	20 U/l
T. Bil	0 6 mg/dl	NCC-ST439	(≦7.0)	5.2 U/l
GOT	12 U/l	BCA225	(≦160)	70 U/l

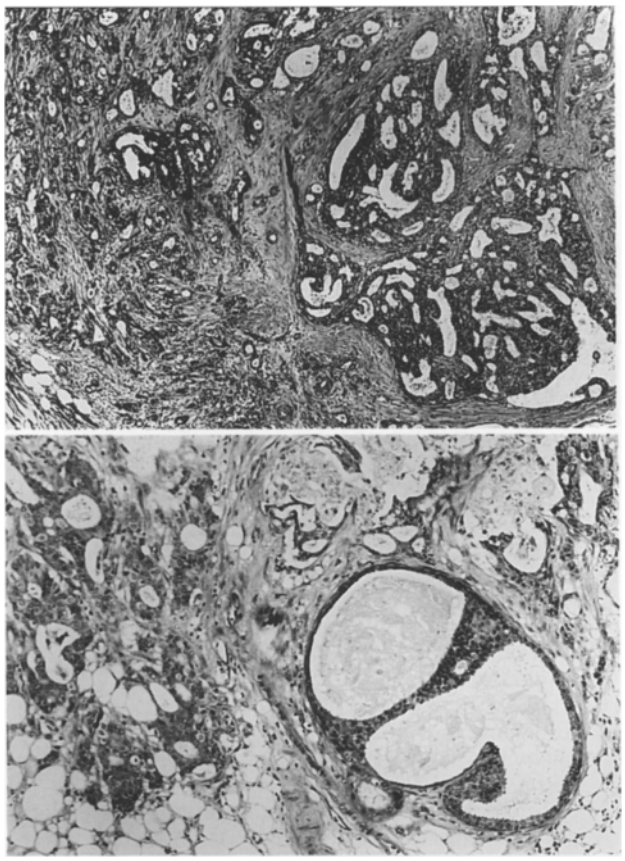

Fig 3. Cross section of the breast tumor showing stroma infiltrated with atypical cells, having a papillary appearance and extensive intraductal components (HE-staining, original magnification ×100 [top], ×200 [bottom]).

receptor (PgR) positive. The patient was thus administered 600 mg/day of medroxyprogesterone acetate (MPA) for about six months postoperatively. Chemotherapy was not indicated because of the early stage of the breast cancer. In the more than 3 years and 5 months to date since surgery, there has been no evidence of breast cancer recurrence nor any change in her MDS.

Discussion

MDS is a preleukemic hematopoietic disorder that was defined and classified by a French-American-British (FAB) co-operative study group in 1982[1]. It is characterized by malformation (dysplasia) and dysfunction of abnormal clonal hematopoietic precursor cells, ineffective hematopoiesis, and differentiation abnormalities in peripheral blood and bone marrow[2,3]. In the usual clinical course of MDS there is progression to a chronic stage. However, if a shift to an irreversible progressive stage (acute leukemia) occurs, treatment is usually ineffective, prognosis is poor, and evolution of marrow failure leads to death due to infection, hemorrhage, etc[1-3] (median survival is 3-4 years). In general, the incidence is reported to be somewhat higher in elderly males than in elderly females[3,4].

Our case (a 45-year-old female) was diagnosed as the RA-type of MDS based on a bone marrow biopsy and chromosome analysis. Although patients with the RA-type of MDS are considered to have the best prognosis in the FAB classification, there is eventual progression to leukemia in about 10% of these patients[1,2] (almost always within 5 years).

Although there have been many reports[1,5,6] of secondary MDS induced by chemotherapy or radiation therapy for malignant tumors, reports of primary MDS promoting non-hematological malignant tumors have only increased very recently[7,8]. Clark *et al*[7] reported that MDS was associated with neoplasms of other organs in 7 of their 198 MDS cases, and that the incidence rate of malignant neoplasms was 2.9 times higher than in healthy controls. However, there have been few reports of cancer involving non-hematopoietic organs in patients treated for MDS[7-10]. Furthermore, to our knowledge, this is the first report of breast-conserving therapy for early breast cancer associated with MDS.

Various treatments for MDS have been attempted in the past, but nearly all have failed because of associated morbidity[2,5-8]. Although the treatment of MDS generally aims at promoting the maturation and differentiation of hemocytes, because the abnormal clones in MDS represent a disturbance of hematopoietic differentiation, there are no spontaneous remissions (as in anaplastic anemia) and about 50% of all MDS patients die of bone marrow failure or acute leukemia[1-3,11]. Our patient, who had an associated breast cancer, was treated with MPA postoperatively because the tumor was PgR-positive and because of the protective effect of MPA on bone marrow hematopoietic function.

Administration of high-dose MPA has been shown to counteract the bone marrow toxicity of several anti-cancer agents[12,13]. The anti-leukopenic mechanism of MPA is still not well understood, and various hypotheses have been proposed to explain its action; (a) the recruitment of pluripotential stem cells from the G_0 phase into the cell

cycle, (b) the induction of differentiation of committed progenitor cells into proliferating precursors of granulocytes and megakaryocytes, (c) shifting of leucocytes from reserve compartments to the blood pool, and (d) ability to protect committed progenitor stem cells from the cytotoxic activity of antiblastic drugs. The report by Amadori *et al*[12] supports the hypothesis that the myeloprotective effect of MPA is due to its ability to induce mitotic rest in stem cells, thereby protecting them from the action of chemotherapeutic drugs. There have been few reports on MPA administration in MDS, although the androgen Danazol has been reported to be an effective hormonal treatment for MDS[14,15]. Therefore, MPA administration should be considered for the treatment of selected cases, such as PgR-positive breast cancer patients with MDS. On the other hand, progress in chromosome analysis and molecular biological techniques in recent years has been remarkable. Therefore, new insights into the mechanism triggering MDS crisis and the development of effective therapies for MDS are anticipated in the near future.

Acknowledgments

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