Clinicopathological characteristics of disseminated carcinomatosis of the bone marrow in breast cancer patients

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Abstract. Disseminated carcinomatosis of the bone marrow (DCBM) is characterized by diffuse infiltrative growth of tumor cells in the bone marrow and is associated with systemic hematological disorders. Bone marrow metastases from breast cancer are not rare, and they may lead to serious life-threatening conditions when there is an associated hematological disorder. Therefore, DCBM necessitates a definitive diagnosis and prompt systemic therapy. We herein present 4 such cases and a review of the previous relevant literature. Bone marrow biopsy is an effective method for diagnosing DCBM, and it may also be useful for selecting the optimal therapy. The malignant cells in the bone marrow biopsy specimens from all 4 patients were negative for progesterone receptor expression, and in 1 case, human epidermal growth factor receptor 2/neu expression was discordant between the primary tumor and the bone marrow metastases. Patients with DCBM often require granulocyte colony-stimulating factor and/or blood transfusions due to a DCBM-related hematological disorder. Although systemic chemotherapy for DCBM may temporarily exacerbate the need for hematological support, systemic chemotherapy may be effective for DCBM in breast cancer patients. In our experience, endocrine therapy has also been proven effective for DCBM. The aim of the present study was to review the clinical characteristics and the treatments used in 4 breast cancer patients with DCBM.

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Introduction

Bone marrow (BM) metastasis from malignant tumors was first reported as a type of 'diffusely infiltrative carcinoma' by Jarcho in 1936 (1). In 1979, Hayashi *et al* defined 'disseminated carcinomatosis of the BM (DCBM)' as a clinical entity distinct from the usual types of metastases to the bone and BM. They reported that diffuse infiltrative growth is a characteristic feature of DCBM, and pointed out the association between DCBM and systemic hematological disorders such as hematocytopenia, disseminated intravascular coagulation and microangiopathic hemolytic anemia (2). DCBM may also be referred to as 'symptomatic BM metastasis' (3) or 'BM carcinomatosis' (4); however, DCBM is considered to be the most appropriate term, as it suggests the diffuse infiltration of the BM by cancer cells and is associated with clinically important hematological disorders. Previous studies have reported that BM metastases from solid tumors are frequently detected in patients with breast, stomach, lung and prostate cancers (2,5-7).

Occult cancer cells in the BM have been reported to occur frequently, even in patients with early-stage breast cancer; however, whether the presence of isolated tumor cells in the BM has prognostic significance remains controversial (8-13). Furthermore, the association between isolated tumor cells in the BM and clinically symptomatic BM metastasis has not been fully elucidated (11,14), whereas clinically evident BM metastasis is relatively common and often progresses to DCBM in patients with metastatic or recurrent breast cancer. It was reported that BM metastases were identified in 6-79% of breast cancer patients at autopsy (15-17), and 27% of autopsy cases were clinically diagnosed with BM metastases prior to autopsy (15). When metastasis to the BM progresses to DCBM, a hematological disorder, such as hematocytopenia, is manifested (4). Therefore, prompt diagnosis and treatment are required to prevent the development of a life-threatening hematological disorder. The aim of the present study was to review the clinical characteristics and treatments of DCBM in breast cancer patients.

Patients and methods

Patients. The cases of 4 patients with breast cancer in whom DCBM was diagnosed between 2014 and 2016 at the Kyushu

Table I. Clinicopathological data on breast cancer patients prior to the development of disseminated carcinomatosis of the bone marrow.

Variables	Case 1	Case 2	Case 3	Case 4
Age at diagnosis of DCBM (years)	39	69	45	90
Sex	Female	Female	Female	Female
Primary lesion				
Histology	IDC	IDC	IDC	ILC
ER	-	+	+	+
PgR	-	+	-	+
HER2-neu	3+	1+	0	1+
NG	NA	3	3	1
Stage[a]	IIB	IV	IIA	IIA
DFS (months)	20	0	60	72
Time to DCBM after first diagnosis (months)	66	22	84	72
Other metastatic site at diagnosis of DCBM	Liver Bone Brain	Bone Lymph node Pleura	Liver Bone Brain Lung	None

[a]Stage was assessed using the TNM classification of malignant tumors, 7th edition (39). DCBM, disseminated carcinomatosis of the bone marrow; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; NG, nuclear grade.

University Beppu Hospital (Beppu, Japan) were retrospectively analyzed. All information was collected retrospectively from the medical records. The clinicopathological characteristics of the patients are summarized in Table I.

Results

Diagnosis of DCBM. All the patients had anemia and/or thrombocytopenia during their treatment for advanced or metastatic breast cancer. DCBM was diagnosed pathologically from a BM biopsy and systemic therapies were selected based on the results of the BM biopsy. The results of the BM assessments are listed in Table II. Notably, the immunohistochemical characteristics of the primary breast cancers were discordant with those of the metastatic BM lesions (Tables I and II). In one case, the BM metastatic lesion was human epidermal growth factor receptor 2 (HER2)/neu-positive, whereas the primary lesion was HER2/neu-negative. Based on the HER2/neu status of the BM lesion, the chemotherapy regimen for that patient was changed after she was diagnosed with DCBM (Fig. 1), which led to an improved response to treatment.

Treatment of DCBM patients. Two of the patients were treated with taxane and trastuzumab, and their hematological disorders improved. Another elderly patient was treated by endocrine monotherapy, and her hematological disorder was in remission for 20 months (Table II). The clinical course of 1 of the 4 patients with DCBM is shown in Fig. 1 (case no. 1 in Tables I and I). That patient developed pancytopenia and was diagnosed with DCBM from breast cancer. Following confirmation of DCBM, the patient was treated with paclitaxel + trastuzumab. Although pancytopenia worsened as a result of paclitaxel therapy, the hematological disorder went into remission following administration of granulocyte colony-stimulating factor and blood transfusions. A total of 3 of the 4 patients who received systemic therapies, such as chemotherapy and endocrine therapy, achieved remission of their hematological disorders and survived for 12-30 months (Table II).

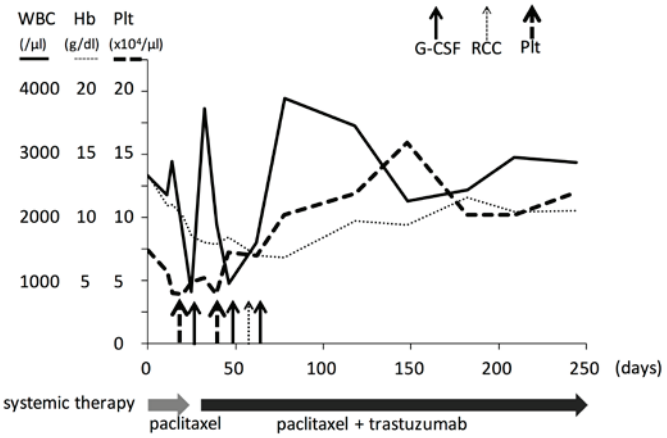

Figure 1. Clinical course of a breast cancer patient with disseminated carcinomatosis of the bone marrow (case no. 1 in Table I). WBC, white blood cell; Hb, hemoglobin; Plt, platelet; G-CSF, granulocyte colony-stimulating factor; RCC, red cell concentrates.

Discussion

The clinicopathological data from two literature reports and our breast cancer cases with DCBM were reviewed (Table III) (3,4).

Table II. Clinicopathological data on breast cancer patients after presenting disseminated carcinomatosis of the bone marrow.

Variables	Case 1	Case 2	Case 3	Case 4
Hematological data				
WBC count (/μl)	1,990	2,660	3,530	3,530
Hb (g/dl)	7.9	13.3	11.3	5.6
Plt count (/μl)	43,000	74,000	52,000	85,000
Bone marrow lesion				
ER	-	+	+	+
PgR	-	-	-	-
HER2-neu	3+	3+	1+	1+
Systemic therapy after diagnosis of DCBM	Paclitaxel + trastuzumab	Paclitaxel + trastuzumab	Failure	Anastozole
Survival after DCBM (months)	30 (alive)	12 (deceased)	3 (deceased)	24 (alive)

[a]Stage was assessed using TNM classification of malignant tumors, 7th edition (39). DCBM, disseminated carcinomatosis of the bone marrow; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor 2; WBC, white blood cell; Plt, platelet; Hb, hemoglobin.

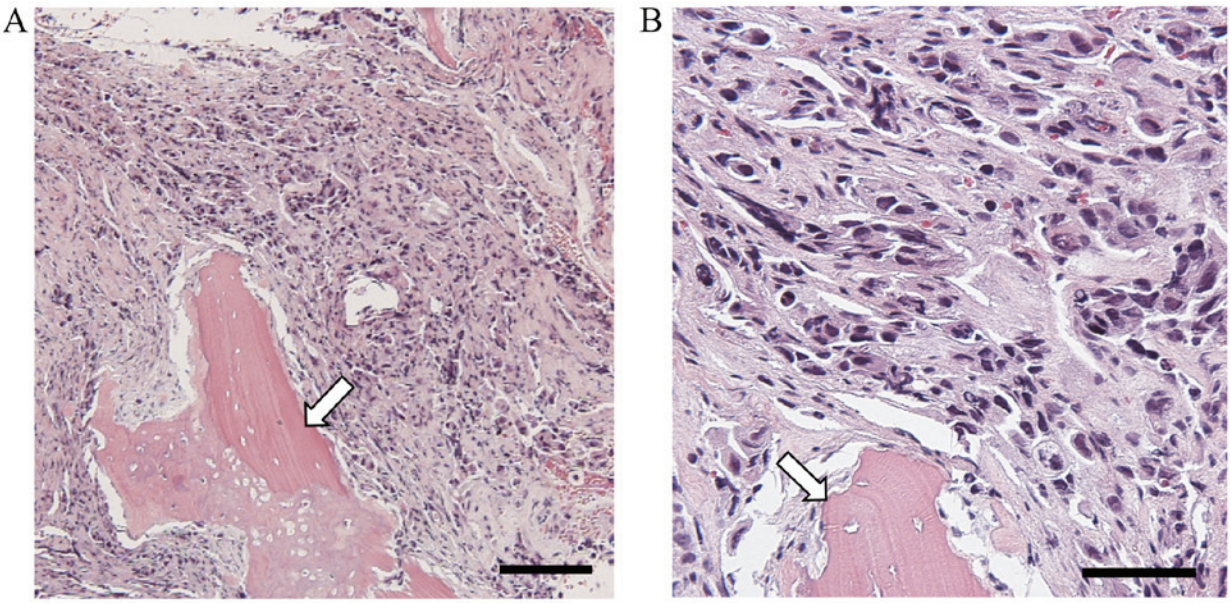

Figure 2. Bone marrow biopsy from the posterior iliac crest of a breast cancer patient with disseminated carcinomatosis of the bone marrow. Tumor cells have infiltrated the medullary cavity in the bone, and normal components other than bone trabeculae (white arrows) have been largely replaced by infiltrating tumor cells. Hematoxylin-eosin staining; magnification, (A) x100, scale bar 100 μm; (B) x400, scale bar 50 μm.

To the best of our knowledge, no clinicopathological characteristics of breast cancer, apart from advanced clinical stage, have been identified as risk factors for the development of DCBM in published reports (3). Clinically, it is important to suspect DCBM when a patient with advanced breast cancer manifests a hematological disorder, such as anemia or thrombocytopenia. Diagnostic tools, such as ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography and blood smear examination have been proposed for the diagnosis of DCBM (18-20); however, examination of a BM biopsy and/or aspirate remains the gold standard (3,14). Pathologically, DCBM is characterized by the diffuse infiltrative growth of tumor cells in the BM, and normal components, apart from bone trabeculae, are largely replaced by the tumor infiltrate (Fig. 2). BM biopsy is considered to be crucial for the accurate diagnosis of DCBM, and is also very important for deciding on a treatment regimen. Genetic heterogeneity of primary and metastatic tumors was recently reported (21-23), and there have been several reports on immunochemical discordance between primary breast cancer tumors and metastatic lesions (24-27). Clinically, the histopathological confirmation of metastatic tissue should be performed whenever possible, due to the potential discordance between the expression status of hormonal receptors and HER2/neu in primary and metastatic breast tumors. Discordant results affect the treatment regimens used for metastatic breast cancer patients (28).

Notably, in all 4 patients, the BM metastatic lesions were negative for progesterone receptor (PgR) expression, whereas

Table III. Clinicopathological characteristics of the primary tumor in patients with breast cancer who developed disseminated carcinomatosis of the bone marrow (3,4).

Characteristics	Kopp *et al* (4) N (%)	Demir *et al* (3) N (%)	Present study N (%)
Number of patients	22	27	4
Histology			
Invasive ductal	14 (64)	19 (71)	3 (75)
Invasive lobular	7 (32)	2 (7)	1 (25)
Other	1 (5)	6 (22)	0 (0)
Estrogen receptor			
Positive	16 (73)	21 (78)	3 (75)
Negative	6 (27)	6 (22)	1 (25)
Progesterone receptor			
Positive	13 (59)	18 (67)	2 (50)
Negative	9 (41)	9 (33)	2 (50)
HER2/neu			
Positive	3 (14)	3 (11)	1 (25)
Negative	14 (64)	24 (88)	2 (50)
Not available	5 (23)	0 (0)	1 (25)
Stage[a]			
I-II	9 (41)	4 (15)	3 (75)
III	6 (27)	9 (33)	0 (0)
IV	7 (32)	14 (52)	1 (25)
Median time to DCBM after the first diagnosis (months)	46	36	51
Median survival after the diagnosis of DCBM (months)	11	6	17
Systemic therapy[b]			
Taxane + anthracycline	6	0	0
Taxane	4	4 (3)	2 (2)[c]
Anthracycline	3	6 (5)	0
Other	7	3 (0)	0
Endocrine therapy	0	1 (1)	1 (1)

[a]For cases in the present study, the clinical stage was assessed using the TNM classification of malignant tumors, 7th edition (39); for other cases, stages were shown according to each article. [b]Number of patients without disease progression after treatment are shown in parentheses. [c]Two cases were treated using taxane plus trastuzumab. DCBM, disseminated carcinomatosis of the bone marrow; HER2, human epidermal growth factor receptor 2.

the primary lesions of 2 patients (50%) were PgR-positive (Tables I and II). PgR-negative patients with luminal breast cancer are well-known to have a worse prognosis compared with PgR-positive patients (29,30). The PgR expression status has been reported to be frequently discordant between primary and metastatic sites (31-35), and the loss of PgR expression has been associated with worse prognosis due to acquired resistance to hormonal therapy (26,32). The effect of PgR status on DCBM progression is unknown, and additional clinical reviews and molecular studies are warranted.

Prompt systemic treatment is needed for breast cancer patients with DCBM, as DCBM is associated with hematological abnormalities. Among the various treatment regimens for breast cancer, the preferred regimen for DCBM from breast cancer remains unknown. DCBM has been treated by various chemotherapy regimens (Table III) (3,4). Although the therapeutic effects of chemotherapy have not been comprehensively reported, anthracycline and taxane regimens have been more effective compared with other chemotherapy agents. Demir *et al* reported disease control rates (complete response + partial response + stable disease) of 83% (5/6), 75% (3/4) and 0% (0/3) for anthracycline, taxane and other regimens, respectively (3). Endocrine therapy was administered to 1 patient, who achieved stable disease (3). Based on the patient response to therapy reported previously and observed by us, systemic chemotherapy is recommended for DCBM of breast cancer patients. Endocrine (hormonal) therapy may be added in estrogen receptor-positive cases. Due to myelotoxicity,

chemotherapy appears to lead to temporary exacerbation of the hematological disorder, and blood transfusion is often required after the initiation of systemic chemotherapy.

According to previous studies (3,4) and our experience, the median time to DCBM following initial breast cancer diagnosis ranged from 36 to 51 months, and the median survival after diagnosis of DCBM ranged from 6 to 17 months (Table III). Breast cancer patients with DCBM who received systemic chemotherapy were reported to survive significantly longer compared with patients without chemotherapy (3).

The molecular pathogenesis of DCBM in breast cancer is not completely understood. We recently reported that the inhibition of the F-box protein FBXW7 in BM promoted cancer metastasis in mice (36). *FBXW7* is a gene that regulates the cell cycle, and it may maintain cancer-initiating cells (37). Despite advances in the understanding of the mechanism and significance of the dissemination of tumor cells in BM, the molecular mechanism underlying the progression of DCBM from a metastasis in the BM remains unknown. The BM environment is considered to have unique biological properties for the homing, survival and proliferation of circulating tumor cells (38). DCBM is considered to progress from BM micrometastases, but further studies are required to elucidate the mechanism of DCBM development in breast cancer patients.

In conclusion, DCBM is a type of metastasis that is characterized by diffuse infiltrative growth, and is associated with poor prognosis and hematological disorders in patients with advanced breast cancer. A definitive diagnosis by BM biopsy and prompt systematic therapy may prolong patient survival.

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