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Case Report

Bone Marrow Carcinomatosis in a Stage IV Breast Cancer Patient Treated by Letrozole as First-Line Endocrine Therapy

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Keywords
Breast cancer · Bone marrow carcinomatosis · Endocrine therapy

Abstract
Bone marrow carcinomatosis (BMC) associated with breast cancer is a rare but often difficult-to-treat condition; we report a case of a female stage IV breast cancer patient in her seventies with BMC that improved with endocrine monotherapy. The patient had hemoglobinopenia and thrombocytopenia at the time of diagnosis. The diagnosis of BMC due to estrogen receptor-positive invasive lobular carcinoma was confirmed. After transfusion of 4 units of concentrated red blood cells, endocrine treatment with letrozole improved the hematopenia. Ten months after the treatment started, bone metastases worsened, so the patient was changed to combination therapy with palbociclib and fulvestrant, after which there was no worsening of the disease.

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Introduction

Bone marrow carcinomatosis (BMC) in breast cancer is a relatively rare condition, and it is commonly seen in breast cancer patients with diffuse bone marrow metastases, with anemia and thrombocytopenia as the first clinical symptoms [1]. As a result, chemotherapy may be difficult to administer. On the other hand, BMC is also common in lobular carcinoma, and since lobular carcinoma has a high frequency of estrogen receptor positivity, endocrine therapy may restore hematopoietic function [2]. A case of BMC with severe anemia and thrombocytopenia treated with endocrine therapy and in whom second-line treatment with a CDK4/6 inhibitor and fulvestrant combination was performed for subsequent disease progression, after improvement of hematopoiesis, is reported.

Case Report

A woman in her 70s came to our hospital with a chief complaint of exertional dyspnea. The hemoglobin level (Hb) was 5.7 g/dL, and the platelet count (Plt) was 44,000/μL. Severe anemia and thrombocytopenia were observed. Erythroblasts were seen in the peripheral blood, and a bone marrow puncture was performed. The tumor cells with eosinophilic cytoplasm showed substantial growth in the trabecula, and the diagnosis of BMC was confirmed. Immunostaining results were positive for AE1/3 and GATA3, negative for E-cadherin, J-Score 3b for ER, J-Score 0 for PgR, and Score 0 for HER2. Thus, bone marrow metastasis of primary invasive lobular carcinoma of the breast was considered (Fig. 1).

Physical examination showed a hand-fist-sized tumor in the lateral region of the left breast. There was no exposure of the tumor to the skin. The mammogram showed extensive architectural distortion in the lateral area of the left breast. Ultrasonography showed a 33-mm hypoechoic region in the outside of the left breast, and a needle biopsy was performed from the same area; a diagnosis of invasive lobular carcinoma was made (ER: J-Score 3b, PR: J-Score 1,

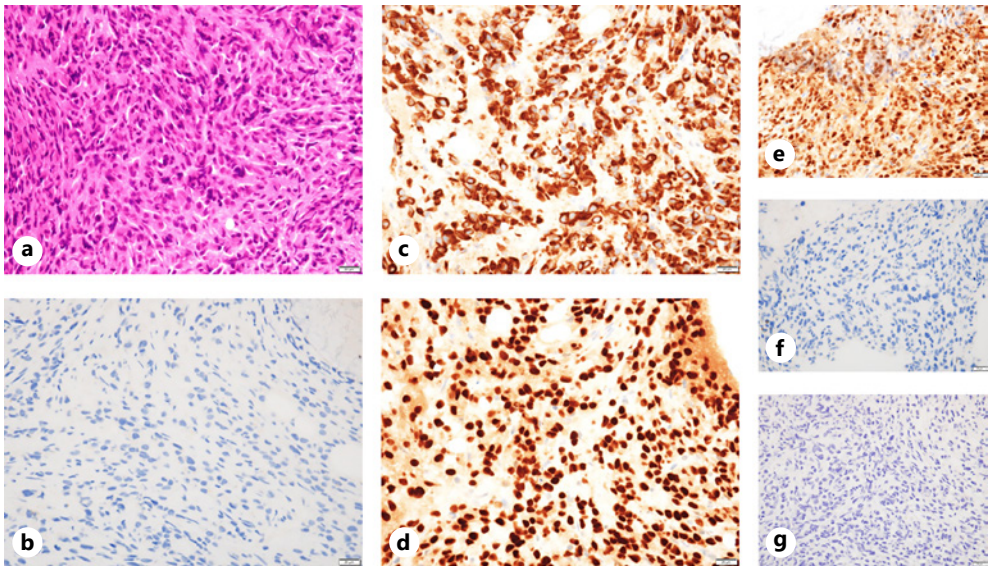

Fig. 1. Pathological diagnosis of bone marrow puncture specimens. Magnification is ×400. H&E staining (**a**), E-cadherin-negative (**b**), AE1/3-positive (**c**), GATA3-positive (**d**), estrogen receptor-positive (**e**), progesterone receptor-negative (**f**), and HER2-negative (**g**).

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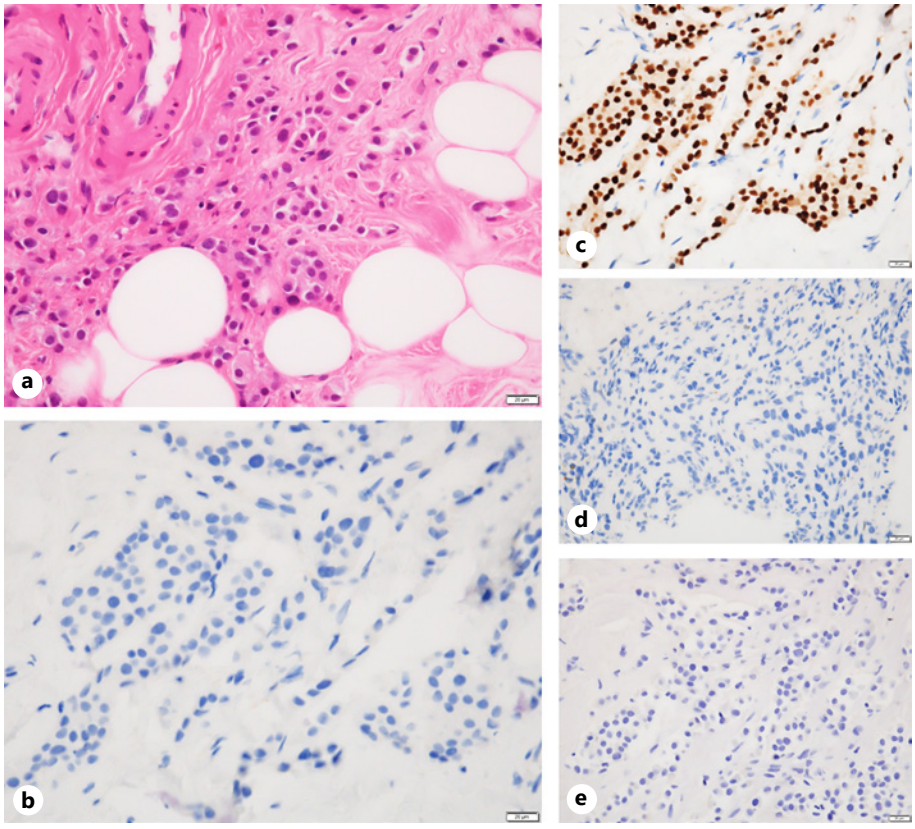

Fig. 2. Pathological diagnosis of needle biopsy specimen of breast tumor. Magnification is ×400. H&E staining (**a**), E-cadherin-negative (**b**), estrogen receptor-positive (**c**), progesterone receptor-negative (**d**), and HER2-negative (**e**).

HER2[−]) (Fig. 2). PET-CT showed left breast cancer, lymph node metastasis, bone metastasis, and peritoneal dissemination (Fig. 3a). The patient was started on letrozole as endocrine therapy. A total of 4 units of packed red blood cells were transfused at the start of treatment. No platelet transfusion was performed.

Four months later, her Hb recovered, and her platelets were normal. Tumor markers had also decreased. Six months after the start of treatment, PET-CT showed reduction of the primary tumor and improvement of bone metastasis (Fig. 3b). Ten months after letrozole monotherapy, PET-CT was performed because of an increase in tumor markers, which showed progression of bone metastases. At that time, no hematopenia occurred, and palbociclib (100 mg/body/day) and fulvestrant combination therapy was started as second-line therapy. There was no increase in carcinoembryonic antigen, and there was no hematopenia that could be considered a side effect. The clinical courses of tumor markers and blood findings are shown in Figures 4 and 5.

Discussion

BMC is a relatively rare condition with a poor prognosis caused by diffuse invasive metastasis of a malignant tumor to bone and bone marrow, resulting in hematological disorders such as disseminated intravascular coagulation. The life expectancy after diagnosis of BMC in breast cancer is 6.4–19 months [2–4]. Breast cancers presenting with BMC are often invasive

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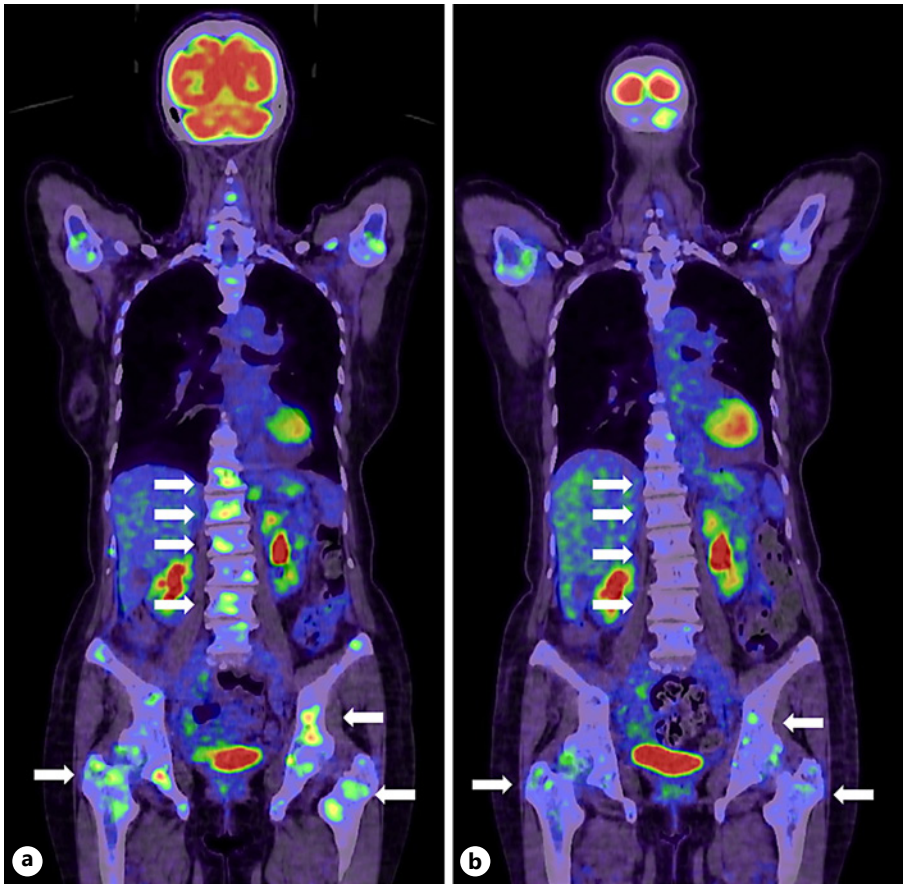

Fig. 3. PET-CT image. **a** PET-CT before the start of treatment. **b** PET-CT image 6 months after the treatment started, showing improvement in bone metastasis.

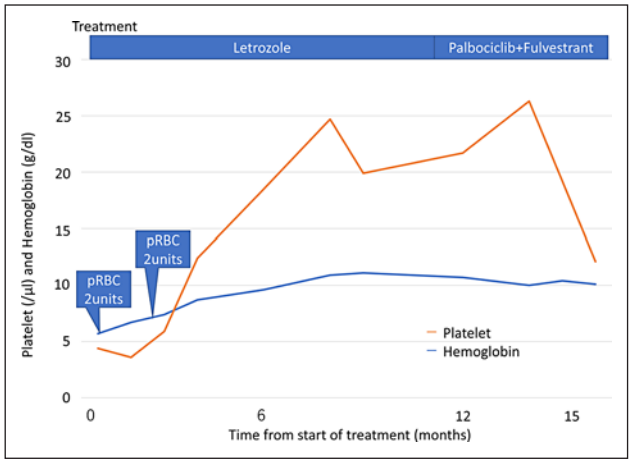

Fig. 4. Changes in Hb and Plts during treatment. pRBC, packed red blood cells.

lobular carcinomas and often estrogen receptor-positive [2]. However, BMC can be considered a life-threatening condition, and paclitaxel, which is considered to cause relatively little myelosuppression, is often administered. The treatment strategy depends on whether the BMC appears during treatment for relapse. Chemotherapy is always considered for BMC that appears after the failure of endocrine treatment for recurrence.

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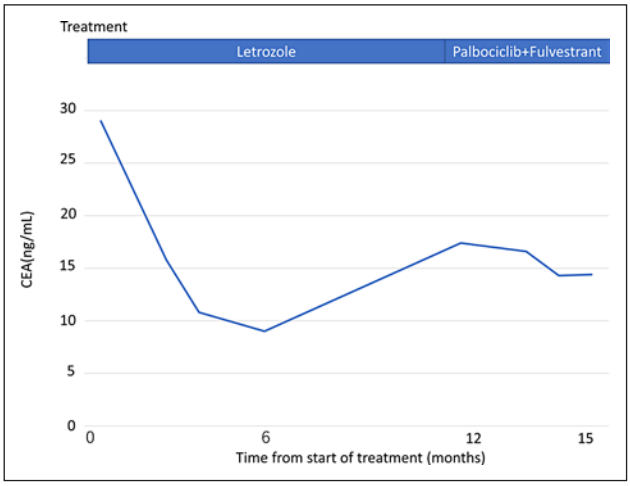

Fig. 5. Changes in carcinoembryonic antigen levels during treatment.

In this case, endocrine monotherapy was chosen because the patient had poor activities of daily living and there was no previous treatment. The patient required two transfusions of concentrated red blood cells, but the red blood cell count and Plts recovered with endocrine monotherapy.

According to previous reports, chemotherapy is chosen as the first treatment for most BMC cases. Kopp et al. [4] reported 22 cases of BMC (16 were ER-positive), of which 20 were treated with chemotherapy, 2 with palliative care, and none with endocrine therapy [2]. Okamoto et al. [3] reported that 47 of 54 cases of BMC were of the luminal type, but endocrine treatment was given in only 9 cases. In Demir et al.'s [2] report of 27 cases of BMC, of the 7 cases of stage IV breast cancer with BMC at the time of initial diagnosis, only 1 case was started on endocrine therapy [4].

There are few reports of a response to endocrine therapy for BMC. In addition, whether or not to use CDK4/6 inhibitors in combination with initial therapy is controversial. Garufi et al. [5] reported a case of a Stage IV BMC patient with Hb 7.5 g/dL and Plt 110,000/μL who achieved CR with a combination of CDK4/6 inhibitors and aromatase inhibitors as first-line endocrine therapy and continued treatment for 26 months. Yamaguchi et al. [6] started letrozole monotherapy for 2 years for BMC in latent breast cancer, and pancytopenia improved. The patient was then treated with a combination of a CDK4/6 inhibitor and fulvestrant for second-line therapy [6]. The present case had a similar course. Treatment was started with endocrine therapy alone, and after improvement of the hematopenia, the patient developed progressive disease, so the patient was shifted to CDK4/6 inhibitor and fulvestrant combination therapy. Fortunately, neither hematopenia associated with the progression of BMC nor CDK4/6 inhibitor-induced hematopenia occurred. Therefore, it is safe to start the primary endocrine therapy of BMC with hematopenia as a single agent and consider a CDK4/6 inhibitor as a second-line therapy after progressive disease or add a CDK4/6 inhibitor in the course of the first-line monotherapy.

Conclusion

This was a case of stage IV breast cancer with BMC in which the primary endocrine therapy improved activity of daily life and the transition to the secondary endocrine therapy was successful after the disease progressed.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Tsuyoshi Nakagawa contributed to the writing of the manuscript. Toshiaki Ishikawa, Kentaro Okamoto, and Hiroyuki Uetake supervised the study. Tsuyoshi Nakagawa, Kumiko Hayashi, Ayumi Ogawa, Goshi Oda, Iichiro Onishi, Masahide Yamamoto, Mio Mori, and Tomoyuki Fujioka served as the attending physicians for the presented patient. All the authors have read and approved that final version of this manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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