



# Bone Marrow Only Metastases from Lobular Carcinoma: Insights into Responses to Endocrine Therapy

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## Abstract

Two patients with lobular carcinoma of the breast previously treated with curative intent presented with anemia and multiple areas of bone pain. CT/PET, bone scan and a panel of laboratory tests including peripheral blood smears were not abnormal except for their CA27-29 values. Bone marrow aspirates and biopsies were performed. In both patient's lobular carcinoma was identified. They both failed on aromatase inhibitor-based regimens. Fulvestrant and abemaciclib were used as the first palliative option. Responses to this combination were marginal and brief. Substituting everolimus for the abemaciclib resulted in marked, rapid improvements in pain, anemia and CA27-29 levels. One patient demonstrated a tumor flare event.

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## Introduction

Bone marrow metastasis from breast cancer is uncommon. Bone marrow only metastasis is rare. Lobular carcinoma of the breast is the most common subtype observed. Almost all cases reported have one or more hormone receptor positivity. Most patients do not have a leucoerythroblastic blood picture [1-7]. Data on treatment efficacy is sparse at best [8-11]. The positive responses of both the patients in this report to endocrine therapy supports its upfront role particularly in view of the tumor flare observed in one patient. Treatment should usually not be interrupted when tumor flare occurs. This event is important to recognize so that a useful treatment is not abandoned prematurely.

## Materials and methods

The first patient was a 58-year-old lady who presented with invasive lobular carcinoma of the right breast. The cancer was ER/PR positive and negative for HER-2-neu overexpression. It was 5/9 according to the Bloom -Richardson grading scale. It was a T2N2MO lesion in the upper outer quadrant of her breast. She received neoadjuvant Adriamycin with Cytosan followed by

Taxol. At surgery her stage was ypT2N3aM0. She had 12 positive nodes out of 15 harvested. She received adjuvant radiation. She was then started on adjuvant Anastrozole. Thirty -four months after diagnosis and 26 months after completing neoadjuvant chemotherapy she presented with diffuse headaches and multiple areas of bone pain not localized to joint spaces. Laboratory data was normal except for an elevated CA 27-29. She underwent CNS imaging with MRI. CT/PET imaging and later a bone scan were all negative for evidence of metastatic disease. Her CA 27-29 continued to increase, and her bone pain fluctuated but persisted. A bone marrow aspiration and biopsy were performed. Her CBC and peripheral blood smear were normal at this point. Lobular carcinoma was identified in the marrow space adjacent to the bone. It had the same ER/PR positivity as the original cancer. It was also negative for HER-2-neu overexpression. The Anastrozole was stopped, and she was started on fulvestrant and abemaciclib. The abemaciclib was started at 50 mg po bid and titrated up to full dose over a 6 week time period. Her bone pain improved temporarily but her CA 27-29 began to rise again as did her bone pain. She had been on combined fulvestrant and abemaciclib for 6 months. She was switched fulvestrant and everolimus. Two weeks after the change she experienced a marked rise in bone pain severity and a marked rise



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in her CA 27-29. Approximately 2 weeks after this her symptoms abated and her CA 27-29 levels fell by over two thirds from over 6000 to less than 2000. She did not have cytopenias until just before the change in endocrine treatment. These cytopenias resolved more slowly than her symptoms and CA 27-29.

The second patient is at the opposite end of the spectrum in terms of risk of recurrence. The second patient was a 64 year old lady who presented with a mammogram detected T1bN0M0 7/9, ER/PR positive, HER-2-neu negative lobular carcinoma of right breast. Her OncotypeDX recurrence score was 11. She underwent partial mastectomy, adjuvant radiation and then started adjuvant Anastrozole therapy. Two years after diagnosis she had a CBC done due to her complaints of fatigue. She was noted to have a normocytic, normochromic anemia. Her anemia work up was normal. A CA 27-29 was collected because she also began to complain of multiple areas of bone pain not localized to joint spaces. Her CA 27-29 was elevated. She was imaged with CT/PET and later bone scan, but no evidence of metastatic disease was detected. A bone marrow aspirate and biopsy were done. Lobular carcinoma was identified in the marrow spaces. It had the same features as the original cancer. Her Anastrozole was stopped. She was started on fulvestrant and abemaciclib. The abemaciclib was started at 50mg po bid and dose escalated to 150 mg po bid. It was at higher doses diarrhea occurred that would not respond adequately to antidiarrheals. Her bone pain and CA 27-29 elevations improved but her anemia persisted. After 6 months her symptoms and CA 27-29 worsened, and she was switched to fulvestrant with everolimus. Her symptoms, anemia and CA 27-29 have improved.

### Results and discussion

The two patients we present had radiographically occult disease. This is similar to what was reported by Fan et al [2]. These data high light the need for through investigations of patients with breast cancer with new symptoms. An endocrine approach was used for both patients since there was no imminent severe end organ failure. The tumor flare reaction could have been misinterpreted as disease progression. It is critical to be aware of this phenomenon and to avoid premature discontinuation of a valuable treatment. Tumor flare was recognized as an event during successful treatment of advanced breast cancer over 45 years ago [12]. Flare is a transient increase in symptoms and signs of hormonally sensitive breast cancer. It may be accompanied by severe hypercalcemia and other electrolyte disturbances. Supportive care and reassurance can manage most patients' issues. Letrozole has been reported to cause a similar event [13]. Aromatase inhibitors with Palbociclib have as been noted to cause a pseudoprogression of breast cancer. This is the first report of fulvestrant and everolimus causing a tumor flare reaction.

Sun et al [1] reported 19 cases of bone marrow metastases from breast cancer seen in their cancer center. They noted all cases were ER positive, the incidence of skeletal adverse events was higher in this group and survival was shorter in this group compared to patients with bone metastases. Pain was an adverse finding. Combination therapy in bone marrow metastases was numerically superior to single agent treatment, 21 vs 5 months. Fan et al [2] reported a case of diffuse bone marrow metastases as the initial clinical presentation of occult estrogen positive breast cancer. The patient's initial complaint was headache. Atwal et al [3] also reported a case of estrogen receptor positive diffuse bone marrow metastases occurring 6 years after the initial diagnosis. Kopp et al [4] reported 22 cases of

breast cancer patients with bone marrow metastases. These 22 cases represented 0.17% of all the breast cancer patients seen over a 14-year time span. All patients had other sites of metastases. Only 4 of the 22 were negative for hormone receptors. Over half were invasive ductal carcinoma. Five patients had abnormal peripheral blood smears. Both patients we report had areas of bone pain, estrogen and progesterone receptor positivity and neither had abnormal blood smears. One patient presented with anemia and the other developed it after treatment was started. The patient with less extensive disease had anemia. This is consistent with the observations of Kopp et al [4] that the blood smear abnormalities did not correlate with the extent of disease.

Bitter et al [5] noted extreme difficulty with the accurate diagnosis of bone marrow metastases by lobular breast cancer. Reasons cited for the poor specificity and sensitivity of diagnosis by hematoxylin-eosin-stained bone marrow samples included 4 issues. First off lobular carcinoma cells are similar in size to hematopoietic cells. Lobular carcinoma infiltrations often include single cells, the cells lack distinctive features and there is limit normal tissue reaction to the presence of the cancer cells. They recommend pancytokeratin stains for all bone marrow samples from breast cancer patients. Clarke and Cheung [6] reported a case of lobular carcinoma metastatic to the bone marrow. Their illustrations of the peripheral smear and marrow emphasize the difficulties in diagnosis reported by Bitter et al [5]. Anecdotally a patient with a similar presentation of lobular carcinoma had over 1500 cells/ml by circulating tumor cell assay but the peripheral smears were repeatedly read as normal (personal observations). Neither one of the patients we are reporting had abnormal peripheral blood smears collected on multiple occasions. These peripheral blood smears were reviewed by multiple Pathologists.

He et al [7] reviewed the unusual sites of metastases seen in patients with lobular carcinoma. They noted diffuse marrow replacement by lobular carcinoma may cause signal reversal of bone marrow on T-1 weighted MRI. On FDG-PET scans diffuse marrow metastases may appear as numerous "hot spots" throughout the skeleton. Neither one of the patients we are reporting had CT/PET, bone scan or MRI of skull findings pointing to bone marrow metastases.

Akagi et al [8] reported the successful control of estrogen positive lobular breast carcinoma with metastasis to multiple sites including bone marrow using Adriamycin and Cytosan. The patient's cytopenias and disease burden were well controlled. She progressed 15 months later and received erbulin with good results. Pahouja et al [9] also noted success with Adriamycin in a very similar patient. The 2 patients in this report only had bone marrow metastasis. Certainly, bone marrow metastasis can be viewed as a visceral crisis and treated with cytotoxic chemotherapy but endocrine treatment was successful in the 2 patients reported herein.

Nakagawa et al [10] reported the control of cytopenias from widely metastatic lobular carcinoma of the breast involving the bone marrow initially with letrozole. When the patient progressed, control was achieved with fulvestrant and Palbociclib. Garufi et al [11] reported a similar case in which control of the patient's disease was achieved with leuproline, letrozole and Palbociclib. The 2 patients in this report both developed metastasis while on adjuvant anastrozole. Initial responses to fulvestrant and abemaciclib were salutary but both progressed on therapy. Both have improved on using everolimus in place of the

CDK 4/6 inhibitor. Gao et al [15] noted the responses of metastatic lobular breast carcinoma to combined endocrine and CDK 4/6 inhibitor treatment 6.9 month improvement in progression free survival over single agent endocrine therapy. Progression free survival improvements in other breast cancer subgroups were numerically superior at 9.1-9.6 months. The responses of our 2 patients to CDK 4/6 inhibition were also relatively short.

Martin et al [16] reported data on second line treatment in hormone receptor positive breast cancer patients failing endocrine therapy and a CDK4/6 inhibitor. Chemotherapy was the most frequent choice. Treatment with everolimus was associated with an improved overall survival compared to chemotherapy while single agent fulvestrant was not. Lee et al [17] looked for genomic signals of resistance to CDK 4/6 inhibitor treatment in hormone receptor positive breast cancer. They noted FGFR1 amplification, PTEN loss and DNA repair pathway gene mutations showed significant associations with shorter progression free survival for patients receiving CDK 4/6 inhibitor therapy. Some of these mutations activate downstream MAPK/AKT/Mtor which confers resistance to CDK 4/6 inhibition. These observations hint at the mechanism the positive role for everolimus in combination with fulvestrant that we report for our 2 patients.

### Conclusions

Bone marrow only metastases are very uncommon. More often they occur with other sites of metastatic disease with bone being the most common. Most of the cases reported were hormone receptor positive patients. Well over half of all cases were due to lobular carcinoma. Most patients do not have a leucoerythroblastic peripheral blood smear. Beneficial, effects of treatment with chemotherapy and endocrine therapy have been seen. Failure on one line of endocrine therapy can be salvaged by second line endocrine therapy. Everolimus with fulvestrant was an effective salvage endocrine treatment for the 2 patients reported. A tumor flare reaction was observed in the patient with more extensive disease. This is the first report of tumor flare reaction in patients treated with fulvestrant and everolimus. Early discontinuation of this treatment would have missed the opportunity to control this patient's disease had this not been recognized.

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