Late breast cancer recurrence with bone marrow metastases and acute pulmonary hypertension

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ABSTRACT

Bone marrow is one of the most common sites of metastasis from breast cancer. Micrometastases to the bone marrow usually evade the systemic therapies used for the treatment of cancer and eventually lead to relapse later in the course of the illness. We report here a unique case of parallel progression of these bone marrow metastases in a patient with breast cancer who had a relapse a few years after treatment of her primary breast cancer, and she presented with diffuse marrow involvement and pulmonary hypertension without any definitive metastases elsewhere.

KEYWORDS Bone marrow; breast cancer; dormancy; metastases; pulmonary hypertension

Breast cancer is known to remain dormant for years and even decades before resurfacing as a relapse.¹ Bone marrow micrometastasis is a well-known phenomenon associated with breast cancer and is a poor prognostic marker, associated with poor overall survival and disease-free survival.² We present a unique case: a patient with breast cancer who had relapse in the bone marrow with cancer cells occupying almost all of the cellular space of marrow with no associated lytic lesions and without any definitive evidence of cancer elsewhere.

CASE PRESENTATION

A 64-year-old white woman presented to our facility in March 2009 with a lump in the right breast. A mammogram showed a 4-cm mass in the upper inner quadrant of the right breast. The patient subsequently underwent ultrasound-guided core biopsy of the mass that showed invasive ductal carcinoma, Nottingham grade II. It was found to be estrogen receptor (ER) positive, progesterone receptor (PR) positive, and HER-2/neu negative. Positron emission tomography (PET) scan showed no evidence of metastasis. Her cancer was staged as clinical stage IIA (T2N0M0). The patient received neoadjuvant chemotherapy in the form of docetaxel, gemcitabine, and bevacizumab followed by Adriamycin/cyclophosphamide (as part of the NSABP B-40 trial), and she also took anastrozole for 5 years. She underwent right partial mastectomy with axillary lymph node dissection after the completion of

neoadjuvant chemotherapy. During surveillance in October 2012, her mammogram showed a small mass in the upper outer quadrant of the right breast, and subsequent stereotactic biopsy revealed invasive ductal carcinoma, Nottingham grade III, negative for ER, PR, and HER-2/neu. This cancer was considered a new primary, and the patient received neoadjuvant FEC (fluorouracil, epirubicin, cyclophosphamide) and docetaxel. She underwent bilateral mastectomy with reconstruction in May 2013, and pathology revealed pathologic complete response (negative for malignancy in the breast; no further lymph node dissection was performed).

The patient was hospitalized in December 2015 for acute hypoxemic respiratory failure requiring supplemental oxygen. Blood counts, a basal metabolic panel, and liver function tests were unremarkable. Arterial blood gas on 2 L of oxygen showed a pH of 7.50, a partial pressure of carbon dioxide of 25 mm Hg, a partial pressure of oxygen of 61 mm Hg, and a bicarbonate of 19.5 mEq/L. Computed tomography with a pulmonary embolism protocol showed no evidence of pulmonary embolus. A ventilation/perfusion scan of the lung revealed no abnormalities. Right heart catheterization showed mild pulmonary hypertension with a pulmonary vascular resistance of 5.6 Wood units, a pulmonary artery pressure of 42/19 mm Hg, and a pulmonary capillary wedge pressure of 4 mm Hg. The left ventricle ejection fraction was within normal limits with no systolic or diastolic dysfunction. A PET scan showed no definitive metastasis, but

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Received October 31, 2017; Revised December 12, 2017; Accepted December 18, 2017.

Figure 1. Positron emission tomography–computed tomography (a) shows diffuse marrow uptake throughout the axial skeleton and (b) 3 months later shows significant improvement in the metabolic activity of the bone marrow.

diffuse marrow uptake throughout the axial skeleton was evident (*Figure 1a*). We subsequently decided to obtain a bone marrow biopsy that revealed marked involvement by metastatic adenocarcinoma comprising 80% to 90% of the cellular marrow space consistent with metastatic breast cancer (*Figure 2*). The biopsy was ER positive, PR negative, and HER-2/neu negative. We subsequently started her on capecitabine and sildenafil. She noticed significant improvement in her respiratory status over the next few weeks and was weaned off oxygen and sildenafil and continued on capecitabine. An interval PET scan has shown significant improvement in the metabolic activity of the bone marrow (*Figure 1b*). The patient has been continuing capecitabine for more than a year and is doing relatively well.

DISCUSSION

Cancer dormancy is defined as a stage in cancer progression when the tumor cells have entered into a quiescent phase and the cancer appears to be in remission with minimal residual disease. This period of dormancy can last for years or even decades before the tumor cells reactivate to cause locoregional

Figure 2. (a) Aspirate at low power ($\times 100$), demonstrating metastatic tumor cells. (b) High-power magnification of the metastatic tumor cells on aspirate ($\times 1000$). (c) The biopsy at low power ($\times 100$) demonstrates large areas of tumor and a focus of tumor necrosis (*). (d) High-power magnification of the metastatic tumor in the biopsy. (e–h) Immunohistochemical stains for (e) positive pan-cytokeratin, (f) positive GATA-3, (g) positive estrogen receptor, and (h) negative progesterone receptor.

relapse or distant metastasis.³ Tumor cell dissemination, also referred to as micrometastasis, can be seen in bone marrow in roughly one third of the patients with breast cancer.² Only a fraction of these disseminated tumor cells are able to survive the microenvironment of the metastatic site and flourish to cause a relapse later.^{4,5} The micrometastasis in the bone marrow in our patient persisted despite aggressive chemotherapy and endocrine therapy and continued to grow, eventually causing a relapse after 6 years. This metastasis fits the parallel progression model as described by Klein.⁶ The perplexing fact about our patient is that micrometastasis in the bone marrow grew to occupy almost all of the cellular space, appearing as a diffuse marrow uptake on the PET scan and comprising 80% to 90% of the cellular marrow space on bone marrow biopsy without causing any changes in the blood cell counts or any evidence of definitive metastasis elsewhere. Clarke and Cheung described a case of metastatic lobular breast cancer diagnosed on a peripheral blood film.⁷ The authors described only a scattered infiltrate of these cells in the bone marrow, though, unlike our patient.

We hypothesize that the tumor growth in the bone marrow of our patient was showering small tumor emboli that traveled to the pulmonary vasculature, causing mild pulmonary hypertension and acute respiratory failure. This hypothesis is supported by the fact that the patient noticed significant improvement in respiratory symptoms within a few weeks of starting capecitabine and after an interval PET scan showed significant improvement in the diffuse

uptake in the bone marrow. Murry et al described two patients, one with bladder cancer and one with breast cancer, who developed acute respiratory failure requiring intubation due to severe pulmonary hypertension that resulted in the death of both patients.⁸ Postmortem examination revealed innumerable carcinomatous microemboli massively showering pulmonary capillaries as the cause of severe pulmonary hypertension.⁸

1. Banys M, Hartkopf AD, Krawczyk N, et al. Dormancy in breast cancer. *Breast Cancer (Dove Med Press)*. 2012;4:183–191. doi: 10.2147/BCTT.S26431. PMID: 24367205.
2. Braun S, Vogl FD, Naume B, et al. A pooled analysis of bone marrow micrometastasis in breast cancer. *N Engl J Med*. 2005;353:793–802. PMID: 16120859.
3. Aguirre-Ghiso JA. Models, mechanisms and clinical evidence for cancer dormancy. *Nat Rev Cancer*. 2007;7:834–846. PMID: 17957189.
4. Luzzi KJ, MacDonald IC, Schmidt EE, et al. Multistep nature of metastatic inefficiency: dormancy of solitary cells after successful extravasation and limited survival of early micrometastases. *Am J Pathol*. 1998;153:865–873. PMID: 9736035.
5. Banys M, Krawczyk N, Fehm T. The role and clinical relevance of disseminated tumor cells in breast cancer. *Cancers (Basel)*. 2014;6:143–152. doi: 10.3390/cancers6010143. PMID: 24434543.
6. Klein CA. Parallel progression of primary tumors and metastases. *Nat Rev Cancer*. 2009;9:302–312.
7. Clarke L, Cheung C. Metastatic lobular breast cancer diagnosed from a blood film. *Br J Haematol*. 2016;173:177. doi: 10.1111/bjh.13899.
8. Murry C, Schneider AG, Nobile A, Rotman S, Liaudet L. Acute pulmonary hypertension caused by tumor embolism: a report of two cases. *Pulm Circ*. 2015;5:577–579.