

Bone Marrow Involvement as the Initial Presentation of Breast Cancer

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Received May 04, 2015; Revised May 09, 2015; Accepted May 20, 2015

Abstract Breast cancer has a predilection for spreading to the bone, brain, liver and lung, however metastasis to bone marrow resulting in bone marrow failure is considered rare. Here, we discuss a case of breast cancer presenting with bone marrow involvement and diffuse bone lytic lesions. The patient was an 81 year old female presenting with back pain in the lumbar region for four months, progressively worsening despite physical therapy and oral analgesics. She was referred for magnetic resonance image which revealed diffuse bone lytic lesions. Follow up computed tomography of chest, abdomen and pelvis confirmed bone lesions but was negative for any primary malignancy. Peripheral blood studies showed white blood cell count of $4.5 \times 10^3/\mu\text{L}$, hemoglobin of 6.6g/dL, hematocrit of 21% and platelet count of $120,000/\mu\text{L}$. She also had renal dysfunction with creatinine of 1.41mg/dL and calcium of 9.8mg/dL. Due to concern for a plasma cell neoplasia, the patient was referred to our oncology clinic. Physical examination was unremarkable and peripheral blood studies revealed IgG 1411mg/dL, IgA 292mg/dL, IgM 122mg/dL with undetectable serum and urine M spikes. She underwent a bone marrow biopsy which was negative for multiple myeloma but showed a neoplastic component in the marrow (approximately 5%) positive for Pan-Keratin, GATA3, ER and Cyclin D1, consistent with mammary carcinoma. During further questioning, she reported a normal screening mammogram one year prior to the onset of symptoms. Positron emission tomography (PET) was remarkable for extensive bony metastatic disease and a heterogeneous hyper-metabolic adrenal mass concerning for metastasis. She was started on endocrine therapy with a daily aromatase inhibitor and monthly Denosumab for bone metastasis. At her six month follow up, PET-scan showed stable disease. Currently, she remains on the same hormonal regimen with monthly follow up at the oncology clinic.

Keywords: metastatic breast cancer, bone marrow involvement, plasma cell neoplasm, cytopenias

Cite This Article: Narjust Duma MD, Zhen Wang MD, and Claudia Miranda MD, "Bone Marrow Involvement as the Initial Presentation of Breast Cancer." *American Journal of Medical Case Reports*, vol. 3, no. 6 (2015): 177-180. doi: 10.12691/ajmcr-3-6-8.

1. Introduction

Breast cancer is the most common cancer affecting women in the United States and worldwide. Estimated global incidence in 2010 was roughly more than 1.5 million cases [1]. Representing the second most common cause of cancer death in women in the United States [1]. While metastatic breast disease generally carries a dismal prognosis, survival rates for patients with metastatic breast cancer have improved significantly given the availability of new therapies. Breast cancer has a predilection for spreading to the bone, brain, liver and lung and metastasis to these sites are well documented. However, metastasis to bone marrow with resultant bone marrow failure is considered rare [2]. There is limited literature regarding bone marrow involvement in early breast cancer, as most of the patients developed bone marrow involvement during the last stages of the disease [3]. Here we present our experience with a patient with diffuse lytic bone lesions; renal dysfunction, anemia and thrombocytopenia,

initially suggestive of a plasma cell disorder but found to be the first manifestation of metastatic breast cancer.

2. Case presentation

81 year old Caucasian female with past medical history of hypertension, hyperlipidemia, atrial fibrillation, coronary arterial disease and no history of chronic kidney disease, presented to our clinic complaining of back pain of four months duration. Pain was located in the lumbar region, initially rated 4 out of 10 but progressively worsening to reach 10 out of 10 intensity. Pain was described as constant, radiating bilaterally to the lower extremities, without any alleviating factors. She was initially seen by an orthopedist. Subsequent x-rays were obtained which did not reveal any pathology. Due to worsening of the symptoms, patient was referred for a spine magnetic resonance image (MRI) which revealed multiple lytic bone lesions highly concerning for bone metastases (Figure 1), including an expansile lesion at L4 resulting in narrowing of the central canal and right lateral recess at this level with contact to the right descending

nerve root. There was a high suspicion for a primary malignancy of unknown origin, the patient underwent a computed tomography (CT) of chest, abdomen and pelvis; this confirmed the multifocal bone lytic lesions throughout the spine, pelvis, and left proximal femur as well as pathologic fractures of T6 and L1. No primary malignancy was identified.

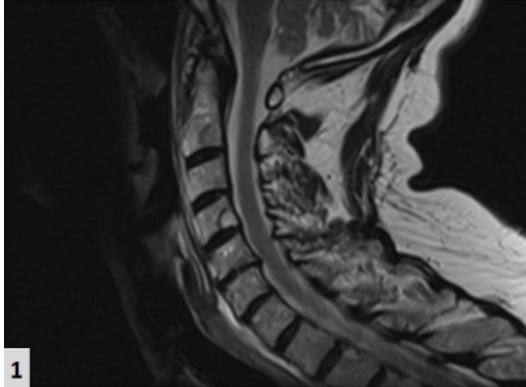


Figure 1. Cervical spine MRI reveals diffuse bone lytic lesions in the vertebral bodies of C2 to C6

Blood tests revealed normocytic anemia and thrombocytopenia, with a white blood cell count of $4.5 \times 10^3/\mu\text{L}$, hemoglobin of 6.6 g/dL (baseline hemoglobin 12.5 g/dL, 6 months prior), hematocrit of 21%, mean corpuscular value (MCV) of 90.7 fL, reticulocyte count of 0.4% and platelet count of $120,000/\mu\text{L}$. She also had renal dysfunction with creatinine of 1.41 mg/dL (creatinine one year prior was 0.7) and calcium of 9.8 mg/dL. Due to the presence of decreased blood counts and diffuse bone lytic lesions she was considered to be a high risk for a plasma cell neoplasia and she was referred to our oncology clinic. On physical examination, she was a well-developed, well-nourished female with diffuse pallor, no icterus, clear lungs to auscultation, abdomen was soft, non-tender, non-distended. There was tenderness to palpation of the lumbar spine, but strength was full in all extremities. Despite her back pain, the patient reported she was able to perform her activities to daily living with an Eastern Cooperative Oncology Group (ECOG) performance status of 1.

Peripheral blood studies revealed IgG 1411 mg/dL, IgA 292 mg/dL, IgM 122 mg/dL, with serum M spike undetectable, and serum immunofixation undetectable as well. A Serum free kappa level of 37.9 mg/dL, free lambda of 19.2 mg/dL and a kappa-lambda ratio of 1.97 was obtained. 24 hour urine resulted with a total protein of 92 mg and negative urine M spike. In spite of these findings, there was a high suspicion for multiple myeloma and she underwent a bone marrow biopsy. Immunophenotypic analysis of the bone marrow revealed less than 0.2% of plasma cells without evidence of light chain restriction. Further testing showed a neoplastic component in the marrow (approximately 5%) positive for Pan-Keratin, GATA3, ER and Cyclin D1, consistent with a mammary carcinoma. Given the presence of diffuse cytoplasmic staining of p120 Catenin and apparent lack of membranous staining of E-cadherin, these findings suggested a lobular origin. An antigen CA27.29 was obtained, with reported value of 2641 U/ml (normal range <30 U/ml). Further testing revealed the breast cancer was

estrogen and progesterone receptor positive and HER2/Neu negative (human epidermal growth factor receptor 2/ proto-oncogene Neu).

Based on these results, an extensive review of the patient's gynecologic history was undertaken. She had a screening mammogram one year prior to the onset of symptoms which has been negative for malignancy. She never had any abnormal results on previous mammography. She had three normal pregnancies with no history of hormonal replacement therapy or oral contraceptive use. There was no family history of breast, ovarian, uterine and colon cancer. She underwent a positron emission tomography (PET) scan; which was remarkable for extensive bony metastatic disease and a heterogeneous hyper-metabolic adrenal mass concerning for metastatic disease (Figure 2-Figure 3). Patient was started on endocrine therapy that included a daily aromatase inhibitor and monthly Denosumab for bone metastasis. At her six month follow up, PET-scan showed stable disease. Currently, she remains on the same hormonal regimen with monthly follow up at the oncology clinic.



Figure 2. Whole body PET-scan reveals diffuse bone lytic lesions, with hyper-metabolic adrenal mass but no signs of a primary malignancy



Figure 3. Whole body PET-scan reveals diffuse bone lytic lesions, with hyper-metabolic adrenal mass but no signs of a primary malignancy

3. Discussion

Diffuse infiltration of the bone marrow by malignant cells can result in cytopenia and thus poses a difficult problem in the treatment of affected patients. However, despite its clinical relevance, this complication has received little attention [2]. Prostate cancer and gastric adenocarcinoma are the malignancies which are primarily associated with bone marrow involvement (BMI) [3]. With breast cancer being the most prevalent cancer in women in the United States and worldwide, special attention should be directed to the identification of bone marrow involvement in these patients, as this represents an unfavorable prognostic factor. Occult micro-metastatic spread of breast cancer cells to the bone marrow has been described in up to one third of patients with stage I-III disease at the time of diagnosis and is known to be prognostic in regard to risk of relapse [4].

Most patients with breast cancer BMI have no particular symptoms and show normal complete blood counts. In patients with symptomatic BMI, anemia is the most frequent finding, present in 40-60% of patients, with most of them having a hemoglobin value of less than 12 g/dL. Leukopenia and thrombocytopenia is seen in 12-25% of patients. Other manifestations include bone pain secondary to diffuse osteolytic lesions, anorexia, and worsening in performance status [5]. In our patient the anemia can be considered of acute onset, she had hemoglobin of 12.5 g/DL 6 months prior to the onset of symptoms, without any history of acute blood loss or other pathology that could explain the decrease in her hemoglobin and platelet count besides the BMI secondary to her breast cancer.

Regarding specific tumor characteristics, no special subtypes of breast cancer – based on histology, grading, or receptor status – have been identified to be at increased risk of developing BMI [2]. A high level of suspicion is advisable in patients suffering from intermediate or poorly differentiated tumors with bone metastases and otherwise unexplained anemia [2]. A close association between bone metastasis and bone marrow involvement have been described. In clinical routine, the presence of a leukoerythroblastic peripheral blood smear is considered a sign of marrow infiltration [6,7], as long as other causes such as hemolysis, myelodysplastic syndromes, and myeloproliferative syndromes are ruled out.

Bone marrow aspiration is the definite diagnostic test to reveal BMI in breast cancer patients but due to the invasive nature of this procedure is not considered a routine exam in patients with metastatic breast cancer. Whole-body PET could be suggested as the best non-invasive diagnostic test for BMI, as most the patients undergo PET scans at the time of disease staging. Whole-body PET with ¹⁸F-FDG exploits the high glycolytic rate of malignant tissue compared with that of nonmalignant cells, and can be useful in uncovering previously unknown metastatic disease to the marrow [8].

Great percentage of patients with breast cancer and BMI also have cortical or lytic bone lesions, while PET scan can identify bone marrow involvement, MRI is considered the preferred imaging study when trying to differentiate bone marrow involvement versus cortical bone disease; because the bone marrow contains a high percentage of adipose tissue, T1 weighted MRI scans

generally reveal metastases as focal areas of low signal intensity, this approach has been shown to be very sensitive to solid tumors that metastasize to bone marrow such as breast and lung cancer. Due to a high rate of false-positive cases with non-contrast MRI, it is recommended to use gadolinium-enhanced bone imaging, invasion of the bone marrow commonly demonstrate high or inhomogeneous signal intensity after gadolinium injection, which is not seen in fractures or cortical bone disease [9,10].

Very limited data exists as to the safest and most efficacious manner to treat patients with breast cancer and bone marrow involvement. The therapeutic approach can be divided into symptomatic management with the use of analgesic medications, corticosteroids, bisphosphonates and erythrocyte/platelet transfusions and, hormone therapy consistent of anti-estrogens, LH-RH agonists, aromatase inhibitors, and progestin derivatives [2]. In our case, the patient had stable disease after six months of hormonal therapy and bisphosphonates and did not require systemic chemotherapy. However a significant percentage of patients are progesterone or estrogen receptor negative or may have disease progression despite hormonal therapy. These patients require a more aggressive management with systemic chemotherapy.

Chemotherapy can provide symptomatic improvement as well as survival benefit if appropriate drug regimens are used, both in terms of expected toxicities and patients' quality of life. The administration of standard, full-dose chemotherapy regimens in patients with BMI poses a risk of infection (around 20% in previous reports) and toxic death [3,11]. Moreover, intensive hematological support is required in more than 50% of cases [11,12]. The rationale of cytotoxic chemotherapy administration is to favorably affect erythro-, leuco- and thrombopoiesis exerting a cytotoxic effect on tumor cells in the bone marrow. Due to the high risk of toxicity induced by chemotherapy, particularly in patients presenting with cytopenias, standard full-dose myelotoxic chemotherapy is not feasible in patients with BMI [13]. For these reasons, several small studies have shown benefit in the use of dose reduced therapy with doxorubicin and capecitabine. Nonetheless, further research is needed before a standard regimen is established.

The prognosis of breast cancer patients with BMI is variable, but it is usually considered to be poor. Indeed, the extent of marrow involvement is an important indicator of tumor burden and, the patient's potential resistance to treatment. In a multivariate analysis of prognostic factors in metastatic breast cancer patients, the poor prognostic impact of a pretreatment hemoglobin value of less than 11 g/dl and a platelet count below 100,000 was underlined. Poor performance status at baseline and the combination of both osseous and visceral involvement have also been described as negative prognostic factors [14]. The estimated median overall survival from the time of diagnosis of BMI is approximately 19 months. Individual patients may experience longer disease control despite this difficult condition [1,15].

In summary, we present a case of 81 year old female with metastatic breast cancer whose initial presentation included diffuse bone lytic lesions, anemia and thrombocytopenia. Based on our literature review, we

conclude that, while breast cancer has a tendency to metastasize to the bone marrow, it does not commonly cause bone marrow failure. BMI needs to be suspected in patients suffering from high- or intermediate-grade breast cancer with bone metastases and otherwise unexplained cytopenia. As was the case with our patient, some patients can present in a manner suggestive of a plasma cell neoplasm and only bone marrow aspiration will provide the definite diagnosis. The treatment of these patients should be conducted holistically, including symptomatic, hormonal and cytotoxic therapies. Despite the usual poor prognosis associated with BMI, our patient achieved stable disease after six months of treatment, which suggests that even patients with marked symptomatic BMI can achieve varying levels of disease control.

Acknowledgement

We want to thank all our mentors for their support during our residency.

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