American Journal of Cancer Prevention, 2016, Vol. 4, No. 2, 33-35
Available online at http://pubs.sciepub.com/ajcp/4/2/3

DOI:10.12691/ajcp-4-2-3

A Case of Second Primary Multiple Myeloma Mimicking Bone Metastases in a Patient with Breast Cancer: An Approach to Osseous Metastases

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Abstract A 62-year-old female patient received adjuvant chemotherapy after a mastectomy due to a locally advanced invasive ductal carcinoma eight years ago. During the follow-up, she complained of extensive backache, so a plain radiography was taken. The radiography showed diffuse lytic lesions located primarily around the vertebrae and sternum. Given that the bone lesions could be related to osseous metastases of the breast cancer, a bone scintigraphy was performed and no positive involvement was observed. Magnetic resonance imaging was subsequently applied and diffuse hypointense areas were found on the vertebrae. The patient had also accompanying bicytopenia (thrombocytopenia and luecocytopenia), albumin/globulin inversion and hyperglobulinemia. As the patient did not have such involvement in regard to her overall body scintigraphy and there were accompanying abnormal biochemical parameters, it was concluded that the patient's bone lesions were an outcome of a hematological malignity. Bone marrow aspiration and the biopsy result were found to be consistent with multiple myeloma (MM). It was thus confirmed that the lytic lesions were not related to breast cancer but rather MM bone lesions. We are able to conclude, based on the case presented herein, that newly-developing bone lesions on patients with breast cancer must be approached with suspicion, and their other laboratory analyses and imaging diagnostic processes must be evaluated carefully. It is necessary to keep in mind that such a condition might be related to other diseases, however rare the occurrence.

Keywords: *second primary cancer, breast cancer, multiple myeloma, bone metastasis, bone scintigraphy*

Cite This Article: Nurhan Onal Kalkan, Muhammed Aslanboga, and Erkan Dogan, "A Case of Second Primary Multiple Myeloma Mimicking Bone Metastases in a Patient with Breast Cancer: An Approach to Osseous Metastases." *American Journal of Cancer Prevention*, vol. 4, no. 2 (2016): 33-35. doi: 10.12691/ajcp-4-2-3.

1. Introduction

Despite the fact that breast cancer is one of the most common cancers worldwide, in recent years related mortality has decreased due to advanced imaging systems and treatments [1,2]. Seventy percent of patients with metastatic breast cancer develop osseous metastasis. Bone is the first location of metastasis for around one-fourth of the patients. After a follow-up of four years, the recurrence rate is found to be 36%, and for most of these, the first focus of the recurrence is the skeletal system [3].

Multiple myeloma (MM) is a plasma cell malignancy characterized by osteolytic bone lesions, cytopenias (especially anemia), hypercalcemia and renal insuffiency. It involves an increase in abnormal monoclonal plasma cells which primarily infiltrate the bone marrow and, rarely, other visceral organs, as well as abnormal immunoglobulin (Ig) secretion by these pathologic cells. Lytic bone lesions are often observed radiologically, especially around the proximals of vertebrae and extremities [4]. Vertebral column involvement is common in MM; hence, if the patient presents with lower back pain and backache, MM should be considered during differential diagnosis. Twenty-seven percent of all bone tumors which biopsied due to bone lesions and 1% of all malignities are caused by MM **[5].**

2. Case Report

A 62-year-old female patient was admitted to the local government hospital for a breast lump in July 2007. Due to the palpable mass at her lower outer quadrant left-breast, an ultrasonography was taken, and she was found to have a ''lobular, irregular shaped solid mass, 2.4 cm in size, located at the lower outer quadrant left-breast". An excisional biopsy was performed. Pathological diagnosis was consistent with invasive ductal carcinoma which was low grade, ER, PR and HER2 negative, with no vascular or neural invasion. The patient underwent a left modified radical mastectomy (MRM) plus axillary lymph node dissection in August 2007 at the university hospital. Pathological examination showed no sign of a residual tumor, however accompanying fibrocystic changes were observed. At the same time, thirteen reactive lymph nodes were observed. Beginning in September 2007, the patient was given 4 cycles of Adriamycin plus cyclophosphamide treatment as adjuvant chemotheraphy. Adjuvant radiotheraphy

was not recommended. Subsequently, the patient's follow-up without treatment was started. The patient had no medical complaint for eight years.

Then, in late 2014, she started to complain of widespread lower back pain. The plain radiographic examination showed diffuse lytic lesions on the sternum and vertebrae. Bone scintigraphy was then performed and no pathological involvements were found which could be considered metasteses. Diffuse hypointensities with heterogeneous enhancement in the peduncle, corpus and thoracolumbar vertebrae, observed by means of vertebral magnetic resonance imaging (MRI), were initially considered to be diffused metastases; however, extramedullary hematopoiesis was not conclusively excluded. Following the MRI, fluorodeoxyglucose positron emission tomography combined with computed tomography (PET-CT) scan was performed and pathological involvement, more distinct around the vertebral coloumn and sternum and increased on the axial skeleton, was observed. The patient's laboratory findings were as follows: leucocyte 6900, platelet 78000, MCV 84,3 fL, hemoglobulin (Hb) 9.1 gr/dL, albumin 3.3 g/dL, globulin 8.1 g/dL, lactate dehydrogenase 168 U/L, alkaline phosphatase (ALP) 24 U/L, creatinine 0.61 mg/dL, calcium 7.5 mg/dL, beta-2 microglobulin 5.63 mg/L, IgG 61,9 gr/L, IgA 0.5 gr/L, IgM 0.173 gr/L, CRP 3.48 mg/L, CA-125 1.1 U/mL, CA15-3 15.2 U/Ml and CEA 0.97 ng/mL. Taking into account the bicytopenia, normal ALP values and albumin/globulin inversion, it was decided that a bone marrow aspiration and biopsy should be performed. The results of the bone marrow biopsy and aspiration, performed in March 2015, were found to be compatible with monoclonal plasma cells nodular infiltration. Considering the above-mentioned findings, the patient was diagnosed with MM. Following the diagnosis, zoledronic acid treatment for the lytic lesions on the bones and bortezomib plus steroid treatment for the MM was begun.

3. Discussion

The primary question in this case is which breast cancer patients with suspicious osseous metastases should undergo bone marrow and/or bone biopsies. Clayer and Duncan, in their prospective study, have tried to discover the nature of the condition by means of conducting biopsies on the newly-developing bone lesions of patients with identified localized visceral carcinoma who were developing the lesions during their follow-up [6]. Newly-developing bone lesions were found to be second primary cancers on 15% of the patients and 4% of these were found to have MM. In consideration of the aforementioned results, they suggested that a biopsy of the new-developing bone lesions must be performed, especially when the patient's primary cancer is breast cancer [6].

Guidelines concerning which patients and which metastases caused by which tumors require confirmation by biopsy are not yet very clear. Many factors can assist us in this issue. Radiological properties of metastatic lesions, location of the involvement, age of the patient, and accompanying laboratory abnormalities (biochemical and hematological cytopenia) can be considered such factors. In bone scintigraphy, an increase in radiopharmaceutical involvement in any part of the skeletal system indicates an increase in osteoblastic activity and/or local blood flow. Changes in the above-mentioned factors result in abnormal bone scintigraphy. While there may be osteoblastic and osteolytic lesions in cases of metastatic breast cancer, what is observed in cases of multiple myeloma are pure osteolytic lesions due to the increase in osteoclastic activity during which osteoblastic activity is suppressed [7]. Apart from this, a radiotracer is held only by active osteoblasts which can cause false imaging in cases of multiple myeloma [8]. Despite the presence of lytic lesions in our patient around the vertebra and sternum, as shown by the plain radiography, there was no involvement in the patient's bone scintigraphy. This is a rare occurrence for breast cancer bone metastasis, hence it is necessary to diagnose the lytic lesions on bones definitively. In connection with increased osteoblastic activity in breast cancer patients, two-thirds of the patients have increased levels of serum ALP [9,10]. Through the same mechanism, as the osteoblastic activity is suppressed in cases of MM, no increase in osteoblastic activity is observed. Instances of new bone formation in MM are quite low, hence the increase in ALP levels are found to vary from 4% to 17%. The ALP level in our patient was within the normal range. This finding also supported a diagnosis of MM [11]. Additionally, in patients with metastatic breast cancer, only 16% do not have extra-skeletal system visceral organ involvement despite their diffuse skeletal system involvement, while the majority of patients with multiple sclerosis have been found to have bone involvements [12].

In identifying osteolytic lesions which develop in cases of MM, the sensitivity of MRI is remarkably high [13]. On the bone scintigraphy taken due to our patient's extensive bone pain, there were no findings indicating the spread of the disease to the skeletal system. However, the vertebral MRI presented diffuse patchy hypointensities with heterogeneous enhancing around the corpus and pedincules. There were no scintigraphic involvements with bone lesions, while the MRI indicated presence of lesions, bringing to mind MM.

Neoplastic plasma cells which replace bone marrow cells suppress the production of normal bone marrow cells, possibly causing normochromic normocytic anemia, thrombocytopenia and leucopenia in the meantime. Accordingly, examinations of the patients have revealed anemia (Hb 9.1 gr/dl) and thrombocytopenia (78000). Furthermore, albumin (3.1gr/dl) was found to be low, globulin (8.1 gr/dl) was high, and the sedimentation rate was also high. MM often shows abnormal monoclonal immunoglobulin (Ig) synthesis; IgG was found to be high in 60% of the patients, IgA in 20% of the patients, and 20% of the patients had high Ig light chains [14]. What pointed to MM in our patient were anemia, albumin/globulin inversion, thrombocytopenia, high sedimentation rate and weight loss. One of the immunoglobulin levels related to MM which was analyzed, IgG, was found to be high (61.9 g/l). Results of the bone marrow aspiration and biopsy were consistent with plasma cell myeloma.

In conclusion, biopsies from metastatic lesions must be considered wherever possible for the treatment of metastatic disease which develops during follow-up of patients treated for localized carcinoma. If a biopsy is

contraindicated, secondary primary diseases must be carefully looked into and any additional examinations must be included as well.

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