A 33-year-old female was referred to our hospital with a complaint of left nipple retraction and mass (HER2), protein overexpression and HER2 gene amplification. Patients suffering from TNBC face a high risk of early metastasis and death within five years after diagnosis but high rates of complete pathological response occur following neoadjuvant chemotherapy. One of the current criteria in the guidelines of the National Comprehensive Cancer Network (NCCN) for the test of BRCA1 and BRCA2 includes patients with TNBC diagnosed before the age of 60 years and no family history. Patients with BRCA mutations face an increased risk of getting cancers such as breast, ovary, pancreas, and melanoma. Some studies recommend bilateral risk-reducing mastectomy and bilateral salpingo-oophorectomy for these patients.

Introduction

Breast cancer is the most common malignant disease among women across the world. A recent study found that conversion in breast cancer hormone receptors takes place during the metastatic progression. Triple-negative breast cancer (TNBC) is an aggressive subgroup of breast cancer. Accounting for 12% to 17% of breast cancers, TNBC is characterized by the lack of expression of estrogen receptor (ER) and progesterone receptor (PR), absence of human epidermal growth factor receptor 2 (HER2), protein overexpression and HER2 gene amplification. Patients suffering from TNBC face a high risk of early metastasis and death within five years after diagnosis but high rates of complete pathological response occur following neoadjuvant chemotherapy. One of the current criteria in the guidelines of the National Comprehensive Cancer Network (NCCN) for the test of BRCA1 and BRCA2 includes patients with TNBC diagnosed before the age of 60 years and no family history. Patients with BRCA mutations face an increased risk of getting cancers such as breast, ovary, pancreas, and melanoma. Some studies recommend bilateral risk-reducing mastectomy and bilateral salpingo-oophorectomy for these patients.

Case presentation

A 33-year-old female was referred to our hospital with a complaint of left nipple retraction and mass...
sensation for the past three months. The patient had no family history of breast or ovarian cancer. She was married and had a child. In her physical examination, a 30 mm fixed mass was palpated in the retro areolar region. The lymph nodes (LNs) in the axillary region were palpable. Mammography showed a spiculated mass with suspicious microcalcification (BIRADS 5). Malignancy was suggested in ultrasonographic evaluation (BIRADS 5) with cortical thickening in at least two LNs in the axilla. After a core needle biopsy from the breast lesion and fine needle aspiration (FNA) from the LNs, invasive ductal carcinoma with positive LNs was confirmed (Clinical T2, N1). Immunohistochemical (IHC) analysis of the specimen showed that the tumor was ER, PR, and HER2 positive with Ki67 %30. We recommended the patient to undergo adjuvant chemotherapy, but she preferred to do the surgery first. Central resection and axillary dissection were done. In permanent pathology reports, all surgical margins were free, and the tumor involved four out of ten lymph nodes. Metastatic workups were negative in thoracic and abdominal CT scan as well as whole-body bone isotope scan. After surgery, the patient received chemotheraphy (Adriamycin and Taxol followed by Herceptin) and radiotherapy for the whole breast and radiation therapy, the patient received hormone therapy (tamoxifen 20 mg/day). She followed up on a regular basis with clinical examination (every six months) and mammography (every 12 months). Two years after treating the primary tumor, she presented with progressive pain in the hip area. Investigations for the source of the pain with a bone scan, plain X-ray, and MRI showed a highly suspicious metastatic lesion in the right femoral head. CT scan of the thoracic and abdominopelvic cavity did not show any other metastatic lesion (PET was not affordable for the patient at that time).

According to the recommendation of the multidisciplinary team, the patient underwent orthopedic surgery and femoral head replacement by an implant. The metastatic infiltrative carcinoma with breast origin pattern was approved in pathology evaluation although the IHC profile of the tumor was converted to ER, PR, and HER2 negative with a Ki67 45%.

Question
The case was presented at the weekly breast multidisciplinary team session at the Department of Breast Surgery, Tehran University of Medical Sciences. The questions were as follows: Does the patient need genetic assessment because of TNBC in the metastatic lesions? And does the new specimen need CISH/FISH techniques to confirm TNBC tumors?

Discussion
The conversion of the receptors during the metastatic progression or local recurrence of breast cancer is a common topic affecting the therapeutic measures and outcome.1 Up to 50% of treatment plans have been changed due to this conversion. Cejalvo et al. identified 47 genes that were expressed differently in metastatic versus primary disease.10 There are several possible mechanisms for the conversion of breast cancer hormone receptors expression. Technical errors and the variability in the accuracy of IHC reports may contribute to the difference of hormone receptors status between primary and metastatic tumors.11 Some studies have showed associations between changes in receptors and the duration from primary tumor diagnosis to metastasis, sites of metastasis, or breast cancer subtypes, but some others contradict such reports.12,13 Tumor markers conversion could be a result of genetic drift during tumor progression.14 The negative conversion of tumor markers is a predictor of poor prognosis. Therefore, biomarker change evaluation in the metastatic site is a crucial concern that may not only affect the treatment options but also predict the prognosis of patients. For reassessment of PR and ER, pathology review and IHC may be sufficient. However, a repeat biopsy is also recommended, particularly when the specimen is small, and there is the possibility of some technical problems such as prolonged cold ischemic time. Some authors also recommend rebiopsy when there is any discrepancy between histomorphologic findings on H&E and the results of biomarkers (e.g., the potential technical error in tubular or mucinous carcinoma with positive HER2 results).15-17 In-situ hybridization assays, such as Chromogenic in situ hybridization (CISH), Silver in situ hybridization (SISH), and fluorescent in situ hybridization (FISH) are also recommended for HER2 overexpression reassessment.18 Real-time qPCR is an alternative option to evaluate breast cancer hormone receptors.19 Bone metastases may be biased by false-negative IHC results for both hormone receptors and HER-2 due to decalcification.20-22 Therefore, we cannot be sure whether a genuine conversion in tumor markers has occurred or not, although bone and bone marrow samples can be used for the evaluation of HER2 status and compared with the status of the primary tumor.23 Although in situ hybridization may be helpful in this case, the possibility of DNA degradation during calcification cannot be excluded. This may result in false-negative ISH results as well. Therefore, a sufficient sample of tumoral tissue without decalcification should be available at the time of tissue processing and evaluation. There are often some softer parts in the metastatic bone samples which can be processed without decalcification. Also, other methods of calcification, e.g., using EDTA can be applied instead of acid.
There is a consensus in the international guidelines over the necessity of genetic counseling for patients whose primary breast tumors are TNBC. Overall, about 15–20% of breast cancers are triple-negative. Among them, the majority of TNBC patients are young women or women with a mutation in the BRCA genes.²⁻⁴ This subtype differs from the others in the natural history of the disease and patients’ outcome. In fact, TNBC tumors grow and spread faster, have more limited treatment options, and have a worse prognosis.²⁻⁴ National Comprehensive Cancer Network (NCCN) guideline recommended hereditary cancer testing for the patients diagnosed at age <60 years with TNBC.³ The guidelines also recommend genetic testing in TNBC patients at any age, although this is applicable when the primary tumor is triple-negative. To the best of our knowledge, there is no definite recommendation for TNBC when it is found in metastasis, especially when the primary tumor is not TNBC.

**Multidisciplinary team (MDT) recommendation**

For this patient with breast cancer biomarkers conversion (luminal type in the primary tumor and triple-negative in bone metastasis), members of breast MDT in the Breast Surgery Department, Imam Hospital, Tehran University of Medical Sciences, did not recommend genetic counseling and BRCA testing. They thought that the evidence was not sufficient enough to support BRCA2 tests. In fact, this topic was so controversial among the members that they could not make a unanimous decision. They recommended talking to the patients and providing her with the latest findings of the studies. We suggested designing a survey to compare BRCA results between primary TNBC and breast cancer patients with triple-negative in metastatic lesions. Regarding re-assessing the specimen for ER, PR, and HER-2, the members recommended re-evaluating the profile using FISH or CISH methods.

**Conflict of Interest**

The authors have nothing to disclose.

**Ethical Consideration**

The patients agreed to present her medical information anonymously by singing an informed consent.

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