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A Case of Male Breast Cancer with a BRCA Gene Mutation

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Background: Male breast cancer (MBC) is an uncommon malignancy with an incidence that accounts for about 1% of all breast cancer cases. It commonly presents as a locally advanced tumor that has already spread to the regional nodal basin. Similar to female breast cancers, MBC gene expression profiling and tumor studies help to detect molecular subtypes of tumors that correlate with clinical outcome and mortality rates.

Case Report: We report a relatively uncommon case of a 64-year-old male with a BRCA1+ gene mutation that is also found to be HER2+ on receptor analysis. Initial diagnostic studies with mammography and ultrasound revealed a left-sided hypoechoic mass measuring 2.3 cm, located at the 11 o'clock position adjacent to the nipple-areolar complex. Whole body positron emission tomography–computed tomography scan revealed a hypermetabolic retroareolar left breast mass and enlarged, hypermetabolic left axillary lymph nodes. Final pathology revealed an infiltrating ductal carcinoma with a Nottingham histologic score of 3 (mitotic count score, 3; nuclear pleomorphism score, 3). Of the 19 lymph nodes examined, 15 had evidence of macrometastatic disease.

Conclusion: This report highlights a novel case of MBC with a rare genotypic presentation. A need exists to further explore this disease process because the literature is scant with information regarding the long-term treatment and outcomes of MBC, especially in the genotypic form presented here. Subsequent studies in the long-term outcomes of various MBC cases will need to be pursued to better understand the optimal screening and treatment strategies for this disease.

Keywords: *Breast neoplasms–male, neoplasms, receptor–ErbB-2*

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INTRODUCTION

Male breast cancer (MBC) is an uncommon malignancy with an incidence that accounts for about 1% of all breast cancer cases.[1] Although stage per stage, MBC outcomes appear similar to the outcomes of breast cancer in women, noted differences exist in presentation, prognosis, and treatment. MBC commonly presents as a locally advanced tumor that has often metastasized to the regional nodal basin upon presentation.[2,3] The incidence of locally advanced tumors at presentation is partially because routine screening mammography is not commonly done in men, and the early detection of breast cancer in men is a rare occurrence.[3] Similar to female breast cancers, MBC gene expression profiling and tumor studies help to detect molecular subtypes of tumors that correlate with clinical outcome and mortality rates. BRCA2 mutation carriers correlate with the overall incidence of MBC.[4] Additionally, the frequency of endocrine receptor positivity in males is higher compared to females. More than 90% of tumors in men are positive for either estrogen receptor (ER) or progesterone receptor (PR).[4,5] The presentation of locally advanced breast cancer in males is attributed to the combination of receptor positivity and minimal screening in the male population.

This case report presents a relatively uncommon case of a male with a BRCA1+ gene mutation that is also found to be HER2+ on receptor analysis.

CASE REPORT

A 64-year-old man initially presented to his family practitioner in December 2013 complaining of a left breast mass. He reported that earlier that summer, he accidentally bumped his left chest area while moving some boxes. He subsequently noticed a visible mass at the nipple-areolar complex that started to bleed and erode through the skin (Figure 1). Mammogram and ultrasound of the left breast demonstrated a left-sided hypoechoic mass measuring 2.3 cm and located at the 11 o'clock position adjacent to the nipple-areolar complex. Ultrasound also revealed a suspicious-appearing left axillary lymph node (Figure 2).

Ultrasound-guided biopsy of the breast mass and axillary lymph node demonstrated an infiltrating ductal carcinoma of the left breast with metastatic breast cancer to the lymph node. Both specimens were ER 100%, PR 75%, HER2/neu amplified (positive) by fluorescence in situ hybridization analysis, with a Ki-67 proliferative index of 75%. As part of a thorough evaluation of the possible risk of inherited cancer, the patient underwent genetic counseling that revealed a

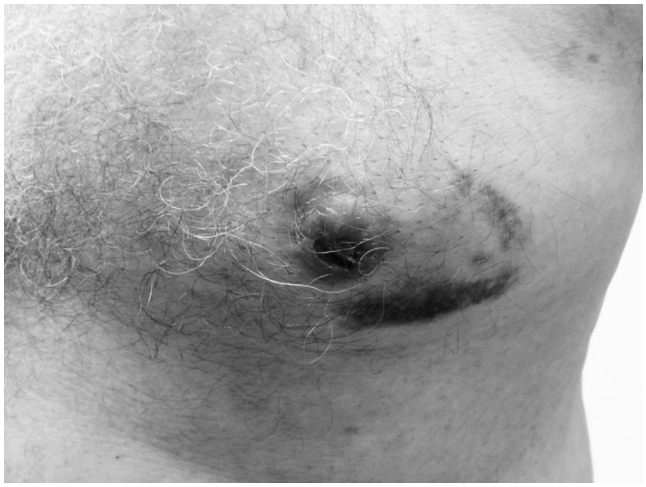

Figure 1. Initial presentation of chest mass with nipple ulceration.

biological sister with a history of breast carcinoma (unknown type) treated in her 40s. Genetic testing for mutations in the BRCA genes revealed a positive mutation in the BRCA1 gene.

The patient's medical history was significant for gastroesophageal reflux disease and his surgical history for tonsillectomy, appendectomy, and back surgery for a herniated disk. The patient's social history included two-pack per day tobacco abuse for 40 years and moderate alcohol consumption, mainly on the weekends. The patient's family history included hypertension and myocardial infarction in his father, as well as an unidentified cancer in his mother that resulted in her death in her early 40s. A 12-point examination of the review of systems was negative.

Several positive findings were noted during the breast physical examination. Within the left breast was an area of ecchymosis with skin breakthrough of approximately 2.2 cm adjacent to the left side of the left nipple and at the 3 o'clock position fixed to the underlying tissue. A palpable mass extended posteriorly to the nipple-areolar complex approximately 3 cm in overall diameter. No evidence of nipple discharge was noted; however, the mass had visibly eroded through the skin. Evidence of lymphadenopathy was seen within the left axilla, with the largest lymph node measuring 2 cm in diameter. In comparison, the right breast was negative for masses, tenderness, nipple inversion, discharge, or retractions noted to deep palpation. The right axilla did not reveal any lymphadenopathy. No areas of chest wall crepitus or tenderness were noted throughout the rest of the chest wall physical examination. The remainder of the physical examination was within normal limits and negative for any other findings.

Staging workup with a whole body positron emission tomography–computed tomography scan revealed a hypermetabolic retroareolar left breast mass consistent with his known breast cancer and enlarged hypermetabolic left axillary level I, level II, and level III lymph nodes. The largest of these lymph nodes measured 1.8 cm. A mildly hypermetabolic left supraclavicular lymph node was also identified and considered slightly suspicious for possible neoplastic involvement.

At our weekly comprehensive multidisciplinary breast cancer planning and treatment conference, the consensus was to begin treatment with neoadjuvant chemotherapy. The patient received 6 cycles of docetaxel (Taxotere), trastuzumab (Herceptin), and pertuzumab, and a relatively good clinical response was noted with shrinkage of the primary tumor, as well as the lymph nodes within the left

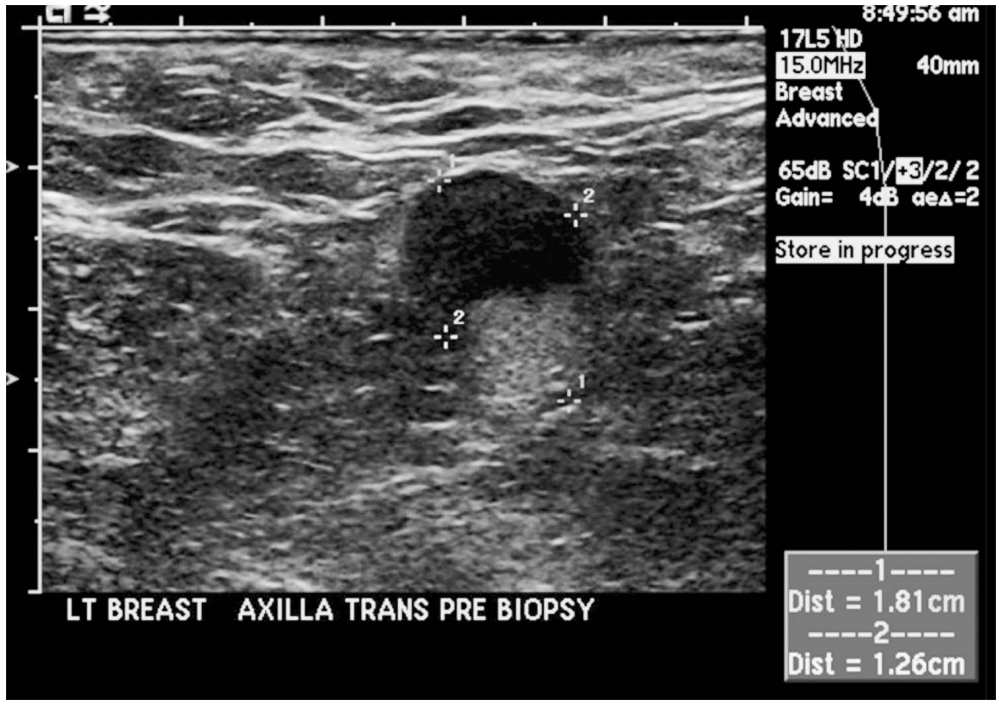

Figure 2. Diagnostic ultrasound demonstrates hypoechoic mass at initial presentation (pre-biopsy).

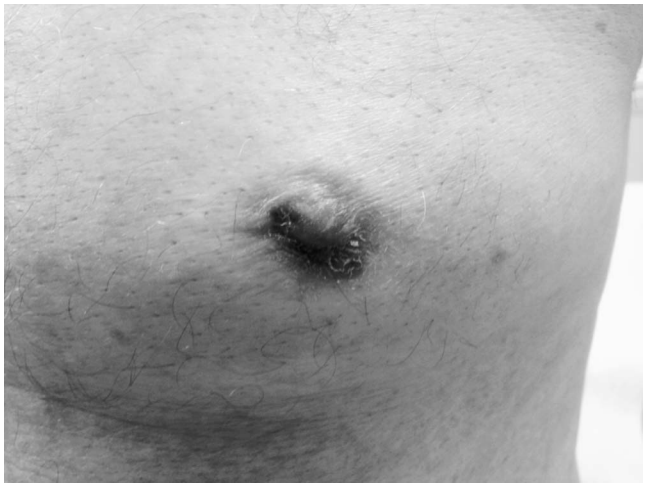

Figure 3. Chest mass after neoadjuvant therapy during preoperative assessment is visible and palpable.

axilla. The breast cancer remained visible and palpable with a large portion of the underlying mass no longer palpable (Figure 3).

Six weeks later, the patient underwent a left modified radical mastectomy and a right prophylactic simple mastectomy with a right axillary sentinel lymph node biopsy. The patient tolerated the procedure well, and his postoperative course was uncomplicated. The final pathology revealed that the mass was an infiltrating ductal carcinoma with a Nottingham histologic score of 3 (mitotic count score, 3; nuclear pleomorphism score, 3). Nineteen lymph nodes were examined; 15 contained metastatic breast cancer. The patient will continue with a full year of therapy with trastuzumab and was also started on adjuvant therapy with tamoxifen. He will also undergo chest wall and axillary irradiation because of the number of involved lymph nodes with metastatic disease, with specific attention to the supraclavicular fossa.

DISCUSSION

The cloning of the BRCA1/2 genes in 1994 made it possible to identify women with a germ line mutation whose cumulative risk for breast cancer is 43%-75% by age 70.[6] Without preventive intervention, the survival probability by age 80 for BRCA1 and BRCA2 mutation carriers has been estimated at 33%-52% in comparison to 66% for the general US female population.[2] A BRCA1 gene mutation is typically associated strictly with breast and ovarian cancers in women, while the BRCA2 gene mutation has been implicated in Fanconi anemia, various leukemias, ovarian cancer, prostate cancer, and melanoma. To date, treatment of breast cancer in males has been tailored around antiestrogen therapy with tamoxifen for hormone receptor–positive tumors and trastuzumab for HER2+ tumors.

However, the literature demonstrates that HER2 positivity in MBC is a rare event for reasons unknown. Current studies report that only 3%-11% of total MBC cases are HER2 amplified compared to approximately 15%-20% of female breast cancers.[4] In addition, only approximately 20% of men with breast cancer report having a first-degree relative with breast cancer.[4] A reported 4%-40% of all MBCs are estimated to result from BRCA1/2 inheritance compared to 5%-10% in women.[7]

Similar to chemotherapy treatment for female cancers, treatment regimens for MBC generally consist of taxanes and anthracyclines. Particularly, a number of studies have suggested a potential correlation between HER2 amplification and topoisomerase IIA (topo IIA) gene alterations.[4] Other studies have shown a chromosome 17 centromere (CEP17) duplication correlating with an improved tumor response to the adjuvant anthracyclines used to commonly treat breast cancer.[4] Topo IIA is a target of anthracyclines, and the fact that the HER2 and topo IIA gene are located close to one another on chromosome 17 might help identify a link between HER2 positivity and anthracycline responsiveness.

Little data are published about the MBC population, especially with the uncommon subset of our case: BRCA1 gene mutation combined with an HER2/neu (+) tumor type. Brinton et al explored the similarities between anthropometric and hormonal risk factors associated with MBC.[2] They noted that within their patient population, low levels of testosterone and high levels of estrogens (high estrogen/androgen ratios) correlated with an increased incidence of MBC. The association with obesity that was observed in men was of interest, given a similar risk in obese postmenopausal women with breast cancer.[2] The study concluded that the 30% increased risk in breast cancer observed in obese men was nearly identical to the increased risk of similar breast cancers seen in populations of obese female patients.

Kreiter et al examined the overall MBC incidence rate worldwide.[7] The group analyzed 104 populations where the male population contributed at least 5 million person-years during 1998-2002 and ethnically stratified geographically defined populations. They showed that the MBC incidence closely correlated with the female breast cancer incidence. MBC incidence rates increased with age as in female breast cancer. In one of the US population–based studies by Anderson et al, MBC was statistically significantly more likely to be reported as ER+/PR+ than in female breast cancer.[8] This descriptive study was limited in its ability to demonstrate causal associations but strongly suggested a geographic (and possible environmental) distribution of both male and female breast cancer.

Soliman et al analyzed a cohort of 69 MBC patients surgically treated from 2000-2007.[9] The patient population had below-average overall survival that was attributed to poor quality in dose calculation for different chemotherapeutic agents, lack of HER2 status testing, lack of stereotactic planning and application of radiation, and large tumor burden on presentation. The two significant prognostic factors that affected survival in this cohort were lymph node status and tumor grade. Using tumor grading as a negative predictor of outcomes has been a controversial issue in the literature. Some authors have found tumor grading to be a prognostic factor in their retrospective, single-institutional reviews while others have not.[9]

Another series studying the outcomes of MBC matched 99 consecutive cases of MBC with 198 female breast cancer cases at a single institution.[5] Iorfida et al matched variables that included year of surgery, age, primary tumor size, nodal involvement, hormone receptor status, status of HER2, Ki-

67, and grade to compare outcomes between male and female breast cancer patients. When the 2 cohorts were matched for the above variables, disease-free survival was 75.5% vs 80.1% and 51.7% vs 66.5% at 5 and 10 years, respectively, in men vs women. Overall survival was 88.6% vs 91.5% and 70.7% vs 84.2% at 5 and 10 years in men vs women as well. However, no differences were observed between male and female patients in distant metastasis and local recurrence in the respective cohorts.[5] In addition, no male patients had the HER2+E subtype identified in the Iorfida et al study. The researchers concluded that men with MBC ultimately have poorer outcomes than female breast cancer patients. Therapy, counseling, and close follow-up are essential to improve the outcomes in MBC patients.

Close follow-up for treatment outcomes and recurrence will be necessary to better understand MBC. We already understand that MBC commonly presents as advanced local disease with lymphatic involvement.[10,11]

CONCLUSION

We presented an MBC patient with a unique genotype that is rarely seen or published in the literature. This case reemphasizes the need to further explore this rare disease process and seek treatment correlations to its female counterpart for breast cancer. Subsequent studies in the long-term outcomes of MBC cases need to be pursued to better understand optimal screening and treatment strategies for this disease.

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