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Loss of Human Epidermal Growth Factor Receptor 2 (HER-2) Expression after Trastuzumab Treatment in Locally Advanced Breast Cancer: A Case Report.

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ABSTRACT

Amplification of the human epidermal growth factor receptor 2 (HER-2) oncogene is present in approximately 15% of primary invasive breast cancers and trastuzumab is a monoclonal antibody that targets HER-2. In this case report we present a case of locally advanced breast carcinoma who lost expression of HER-2 after treatment with trastuzumab and also discuss the clinical implications of this change. A 28 years female presented with complaints of painful lump in left breast, measuring 2 x 3 cm firm, mobile and tender in outer-upper quadrant of left breast. Core biopsy from larger lesion revealed invasive ductal carcinoma Grade III. Immuno-histochemical assessment revealed estrogen receptor (ER) negative (0%), progesterone receptor (PR) positive (80%) and HER-2 3+ positive. Fluorescent in situ hybridization (FISH) analysis revealed more than six signals per nucleus with HER-2/CEP-17 signal ratio of more than six confirming HER-2 positivity by FISH. She was treated with neo-adjuvant chemotherapy with docetaxel, carboplatin and trastuzumab for 6 cycles and the disease became metabolically inactive. She underwent left modified radical mastectomy and axillary clearance a month later. Six months postoperatively, she presented with complaints of headache for 20 days. Magnetic Resonance Imaging of brain revealed enhancing T2 heterogenously hyperintense lesion in the right occipito-parietal lobe with extensive perilesional edema, few foci of susceptibility weighted imaging hypointensities with effacement of adjacent sulci, occipital horn and body of right lateral ventricle and midline shift of 5 mm to the left side was suggestive of metastasis. Additionally, repeat FISH analyis revealed that patient's HER-2 status became negative. Our patient had a change in HER2 status pre and post treatment, which has shown to affect relapse free survival in patients, as in our case.

Keywords: Breast, Carcinoma, Trastuzumab, Imaging

INTRODUCTION

Globally, breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death in women. Amplification of the human epidermal growth factor receptor 2 (HER-2) oncogene is present in approximately 15% of primary invasive breast cancers and trastuzumab is a monoclonal antibody that targets HER-2. For the 15% of patients with breast cancer whose tumors overexpress HER-2, trastuzumab therapy is important in the treatment of both early and advanced disease. Trastuzumab's beneficial role as a component of neoadjuvant therapy for HER-2 positive tumors is well substantiated. In this case report we present a case of locally advanced breast carcinoma who lost expression of HER-2 after treatment with trastuzumab and also discuss the clinical implications of this change.

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CASE REPORT

A 28 years female with no-comorbidities presented with complaints of painful lump in left breast for 15 days. On examination, there was a 2 x 3 cm firm, mobile, tender lump present in outer-upper quadrant of left breast. On examination, the skin over the swelling and nipple areolar complex appeared to be normal. The underlying muscles and chest wall were free. Left axillary lymph nodes were palpable and the right breast was normal. Ultrasonography (USG) of left breast revealed two thick walled lesions with tightly packed internal echoes. The smaller lesion measured 2.5 x 2.4 x 2.4 cm, the larger one which was closely situated

lateral to small lesion measured 4 x 3.7 x 3.1 cm. Few enlarged lymph nodes with eccentric fatty hilum were noted in the left axilla, largest of these measured 2.2 x 1.0 cm and 1.4 x 1.1 cm. Core biopsy from larger lesion revealed invasive ductal carcinoma Grade III. Immuno-histochemical assessment revealed estrogen receptor (ER) negative (0%), progesterone receptor (PR) positive (80%) and Human Epidermal Growth Factor Receptor 2 (HER-2) 3+ positive. Fluorescent in situ hybridization (FISH) analysis on formalin fixed paraffin embedded tumor tissue blocks for HER-2 status revealed more than six signals per nucleus with HER-2/CEP-17 signal ratio of more than six confirming HER-2 positivity by FISH (Figure 1).

Her hematological, biochemical and echocardiography parameters were normal. Positron emission tomography (PET) revealed metabolically active lobulated heterogeneously enhancing soft tissue density mass with surrounding satellite nodule in the upper quadrant of left breast compatible with primary left breast malignancy. Increased FDG uptake was noted in lobulated heterogeneously enhancing soft tissue density mass measuring 6.2 x 4.0 x 6.2 cm with areas of necrosisin the upper quadrant of left breast. Metabolically active left axillary lymphnodes were suspicious for metastasis. She was treated with neo-adjuvant chemotherapy with docetaxel, carboplatin and trastuzumab for 6 cycles. PET done after 6 cycles of neoadjuvant chemotherapy revealed that previously seen primary left breast lesion, satellite nodules and left axillary lymph nodes have reduced in size and metabolic activity (Figure 2). Moreover, no evidence of active disease elsewhere in the body suggested good response to treatment. She underwent left modified radical mastectomy and axillary clearance a month later. Histopathology revealed invasive ductal carcinoma grade III of modified Bloom Richardson Classification. Tumor measures 5.8 x 5.3 x 3.0 cms. Lymphovascular invasion was seen and perineural invasion was not noted. Nipple and areolar complex were free of tumor and so were the surgical margins. Two out of twenty-two level I lymph nodes show metastatic carcinoma (2/22). All level II lymph nodes were free of carcinoma (0/11), suggesting pathological stage T3N1M0.

Six months postoperatively, she presented with complaints of headache for 20 days. PET revealed high grade active disease is seen in multiple metastatic left axillary, left supraclavicular, left cervical level IV and V, right cervical level IV lymphnodes and large nodal mass in anterior mediastinum/ prevascular region. Metabolically active lesion involving the right occipital lobe and smaller ring enhancing lesions in bilateral superior parietal lobes suggested metastases. Similarly, tiny pulmonary nodes in bilateral upper lobes, multiple hypermetabolic hepatic lesions, pancreatic lesions, right adrenal lesion, retrocaval node also suggested metastasis (Figure 3). Multiple skeletal metastatic lesions were seen with metabolically active lesion involving neck of left femur. Magnetic Resonance Imaging of brain revealed enhancing T2 heterogenously hyperintense lesion in the right occipito-parietal lobe with extensive perilesional edema, few foci of susceptibility weighted imaging hypointensities with effacement of adjacent sulci, occipital horn and body of right lateral ventricle and midline shift of 5 mm to the left side was suggestive of metastasis. Similar T2 heterogenously hyperintense peripheral enhancing lesions in bilateral parafalcine parietal cortices and left frontal lobe convexity cortical region, showing restricted diffusion, also suggestive of brain metastasis. Additionally, repeat FISH analyis revealed that patient's HER-2 status became negative (Figure 4).

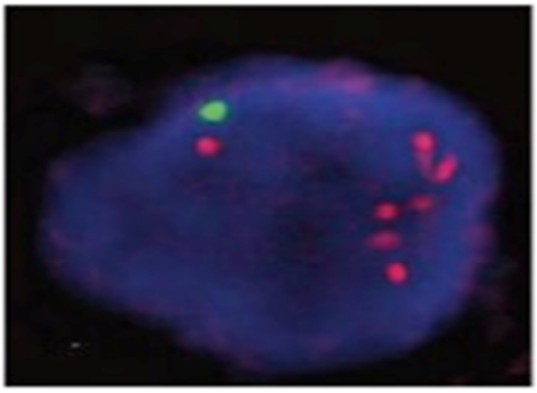

Figure 1: FISH analysis on formalin fixed paraffin embedded sections showing HER-2 signals (orange color) of more than six confirming HER-2 positivity.

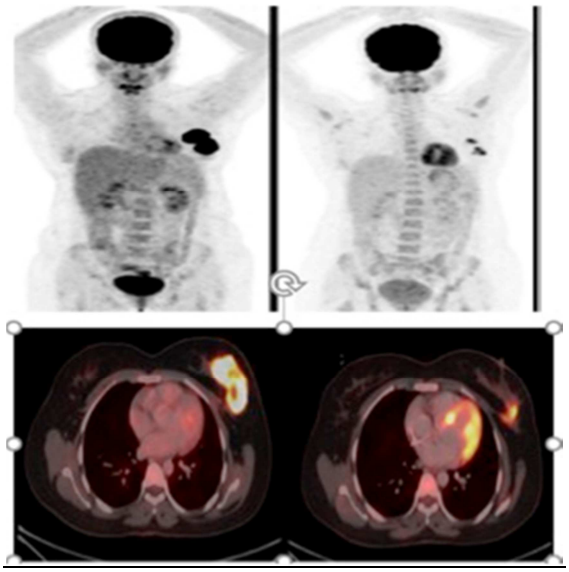

Figure 2: Positron emission tomography- Computed tomography scan comparsion after neo-adjuvant chemotherapy showing reduction in size and metabolic activity of right breast lesion.

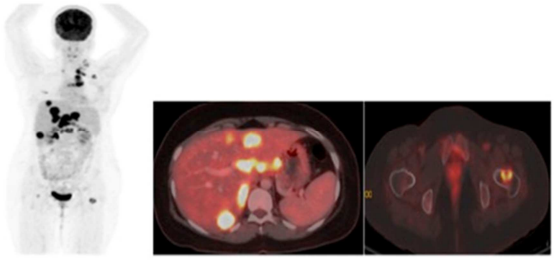

Figure 3: Positron emission tomography - Computed tomography scan showing multiple hypermetabolic hepatic lesions, pancreatic lesions, retrocaval nodes and left femur.

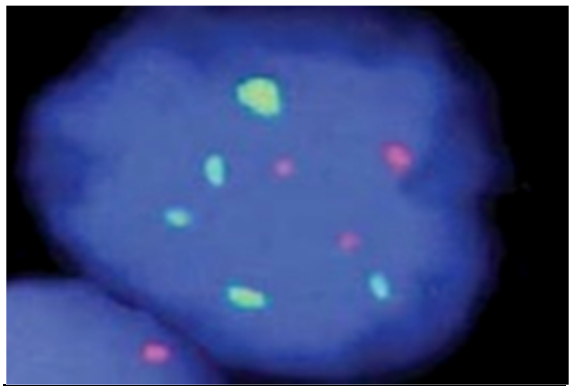

Figure 4: FISH analysis on formalin fixed paraffin embedded sections after surgery showing HER-2 signals (orange color) of less than six confirming HER-2 negativity.

DISCUSSION

The HER2 receptor belongs to the epidermal growth factor receptor (EGFR) family of receptors, which are critical in the activation of subcellular signal transduction pathways controlling epithelial cell growth and differentiation and possibly angiogenesis.[3] HER2 overexpression contends an unfavorable prognosis, particularly if patients are not treated with chemotherapy and HER2-directed agents. However, the added value of this information in clinical practice is questionable because outcomes are heavily influenced by the administration of therapy.[4] In women with breast cancer, the main benefit of HER2 testing is its predictive value for appropriate candidates who should receive HER2-directed agents.

The role of trastuzumab in HER-2 positive patients is well known. A 2012 meta-analysis, among almost 2000 patients with HER2-positive disease treated neoadjuvantly, the addition of trastuzumab to neoadjuvant chemotherpay increased the pathological complete response (pCR) rate from 23 to 40%.[5] pCR was associated with long-term outcome among patients with HER2-positive disease, irrespective of hormone receptor status (hazard ratio 0.39, 95% CI 0.31-0.50). In the phase II NeOAdjuvant Herceptin (NOAH) trial the addition of every-three-week trastuzumab to neoadjuvant anthracycline and taxane-based chemotherapy was associated with a pCR rate of 38% compared with 19% with chemotherapy alone.[6]

The 2013 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) update suggests repeat testing of patients with newly diagnosed breast cancer if histopathologic features are present suggesting HER2 discordance.[7] Investigators have previously studied HER2 expression in paired samples of pre and post treatment with trastuzumab. In a trial of 40 patients, Burstein et al reported that after 12 weeks of paclitaxel and tra0stuzumab, 26.1% of cases, all of whom were 3+ on immunohistochemistry prior to treatment, the HER2 status changed.[8] Similarly, in a study of 48 patients who were treated with 12 weeks of neoadjuvant trastuzumab and vinorelbine, Harris et al reported a HER2 conversion rate of 12% in 18 patients with enough residual tissue to repeat HER2 testing by immunohistochemistry.[9] Although the accuracy with which HER2 overexpression is detected by immunohistochemistry or FISH is comparable, still some issues may exist regarding the consistency with which the results of immunohistochemistry are reported. However, since we utilized FISH to determine HER2 gene amplification status before and after the treatment, we are confident that the loss of patient's HER2 status is not due to inconsistent testing. Most of the reports in the literature have reported modification in HER2 status from positive to negative post treatment, but a few studies have reported the change in the oppositve direction as well.[10] This change in HER2 status has been associated with worse relapse and overall survival of breast cancer patients.[11]

CONCLUSION

This case report highlights the importance of HER-2 in providing prognostic information. Our patient had a change in HER-2 status pre and post treatment, which has shown to affect relapse free survival in patients, as in our case. Therefore, future trials are recommended which can verify the clinical significance of pre and post neoadjuvant treatment HER2 status.

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