CLINICAL VIGNETTE

Importance of Complete Testing of Multicentric Breast Cancers

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Case Report

A 73-year-old woman discovered a mass in her right breast. Mammogram confirmed the presence of a 1.7 centimeter (cm) mass in the 6 o'clock position as well an additional 2.5 cm mass at 2 o'clock. Core biopsies of both lesions were consistent with a moderately differentiated infiltrating ductal carcinoma; ER was >90% and PR>90% and HER2neu negative by FISH on the 2 o'clock lesion; these tests were not performed on the 6 o'clock cancer. Physical examination revealed palpable axillary lymphadenopathy and PET scan for staging purposes revealed an SUV of 11.2 and 12.2 in the breast masses as well as multiple PET-avid axillary, supraclavicular, and mediastinal enlarged nodes.

Because of the presence of metastatic disease additional ER, PR and HER2 status were requested on the additional breast lesion. Immunohistochemistry revealed ER and PR were similarly >90% but HER2 was 2+ by IHC and amplified with a ratio of 4.7 by FISH.

She was treated with docetaxel, trastuzumab and pertuzumab (THP) for 6 cycles and had resolution of her palpable lymphadenopathy in addition to her mediastinal nodes. Since chemotherapy, she has been continued on dual targeted therapy with trastuzumab and pertuzumab and anastrazole was added. Three and one half years later, she remains in complete remission on maintenance trastuzumab, pertuzumab and anastrazole.

Discussion

The detection of multiple simultaneous foci of breast cancer has been described for decades.[1] Simultaneous ipsilateral invasive breast cancers can be described as both multicentric and multifocal. Multifocal (MF) breast cancers are defined when there is more than one distinct tumor within the *same* quadrant of the breast while multicentric cancers develop in *different* quadrants of the breast.[2,3] The real incidence of multiple simultaneous cancers is unknown and seems to vary widely from 13-75% depending upon many factors.[4,5] Due to the increased utilization and advances in preoperative imaging, the incidence of MF/MC breast carcinoma is rising.[6] The prognostic significance of MC/MF disease is not clear at this time. Although multiple foci of cancer correlates with a higher disease burden, current evidence recommends staging according to the largest single invasive focus. The current American Joint Committee on Cancer (AJCC) guidelines for synchronous multiple ipsilateral breast cancer recommend that the 'T' stage to be based upon the diameter of the largest tumor focus with multiplicity ('m') in parentheses.[7] The College of American Pathologist (CAP) guidelines suggest testing and reporting biological parameters (ER,PR,ki-67,HER2) on the largest tumor focus when multiple simultaneous carcinomas are identified whereas additional tumor foci are only reported and assessed when they differ morphologically from the larger tumor.[8]

Whether the development of multiple synchronous cancers in the same breast can be explained by the spreading of a single primary tumor or, alternatively due to multiple carcinomas arising simultaneously is a matter of debate. Because the management of breast cancer relies on not only the stage of breast cancer at diagnosis but also on the molecular phenotype; knowing hormone receptor and her-2 status of individual tumor foci in multiple synchronous cancers can have clinical implications. In a study from a single institution, Chou et al. found discordant HER2 results in 8/172 (5%) ipsilateral synchronous breast cancer. Similarly, Choi and colleagues found HER2 discordance in 6% of their 110 cases when evaluating simultaneous invasive cancers. Discordant HER2 status was significantly associated with ER discordance but not correlated with difference in grade, histology, or PR status.[9,10] Buggi et al. analyzed 113 cases of multifocal carcinomas with histological features. Mismatches among tumor foci were present up to 18% of cases. Such discrepancies led to the alteration of adjuvant therapy in 12% of the cases.[11] Boros et al. also examined 155 multiple breast carcinomas and 463 foci were examined. In their subset, they found mismatches in up to 29% of cases. Nineteen patients (12%) may have been deprived of adequate oncological therapy if only the largest tumor were assessed.[12]

Conclusion

Our case demonstrates the importance of recognizing the potential heterogeneity in HER2 status among foci of multicentric/multifocal breast carcinomas. In this scenario, following the CAP guidelines and not testing the second focus due to identical grade and subtype of breast cancer would have led us to omit HER2 directed therapy and potentially contributed to a worse outcome.

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