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Isolated CEP17 Copy Number Gain in Invasive Breast Cancer Results in a "Reverse" Amplification Status

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Dual-color silver-enhanced in situ hybridization (SISH) is a well-established method for determining the *HER2* gene amplification status in invasive breast cancers with equivocal "2+" HER2 protein expression. Dual-color SISH applies 2 different probes on a single tissue slide: a probe for the *HER2* gene and a centromere 17 (CEP17) probe. This technique allows the assessment of the mean *HER2* copy number (black dots) and the mean CEP17 copy number (red dots), as well as the calculation of the *HER2*/CEP17 ratio. An invasive breast carcinoma is considered to harbor a *HER2* gene amplification if the tumor nuclei show a mean *HER2* copy number gain of ≥4.0 (ie, on average ≥4.0 black dots per nucleus) and a mean *HER2*/CEP17 ratio of ≥2.0.[1] An invasive breast carcinoma with a mean *HER2* copy number of <4.0 and a mean *HER2*/CEP17 ratio of <2.0 is considered nonamplified.[1] All other possible scenarios require a correlation with the HER2 immunohistochemistry and, in case of equivocal 2+ HER2 protein expression, recounting of at least 20 nuclei in the area of invasive cancer with 2+ staining by an additional observer blinded for the previous results.[1]

In this article, we present a breast biopsy containing an invasive carcinoma of no special type with an equivocal 2+ immunohistochemical score (Figure 1). Dual-probe SISH revealed an increased CEP17 copy number in the absence of *HER2* gene amplification (Figure 2). After counting 20 nonoverlapping tumor nuclei, the mean CEP17 copy number amounted 7.00 copies per nucleus and the mean HER2 copy number amounted 2.80 copies per nucleus. This isolated CEP17 copy number gain gave the tumor a peculiar image of "reverse" amplification (Figure 2). It was not possible to perform additional array comparative genomic hybridization studies on this tumor; therefore, we cannot differentiate with certainty between a true polysomy 17 or an amplification of the (peri-) centromeric region of chromosome 17 in this lesion. A CEP17 copy number gain has long been attributed to a chromosome 17 polysomy, that is, the presence of multiple copies of the entire chromosome 17.[2] However, several studies have now shown that true polysomy 17 is a rather rare event in breast cancer.[3-6] An increased CEP17 copy number substantially more often represents a focal pericentromeric gain or so-called "co-amplification" of

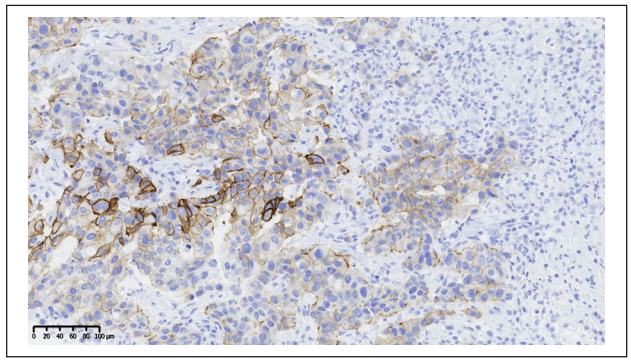

Figure 1. Immunohistochemical staining for HER2 shows weak to moderate complete membrane staining in >10% of the tumor cells within an invasive breast carcinoma of no special type, that is, an equivocal 2+ immunohistochemical HER2 score (original magnification 200×).

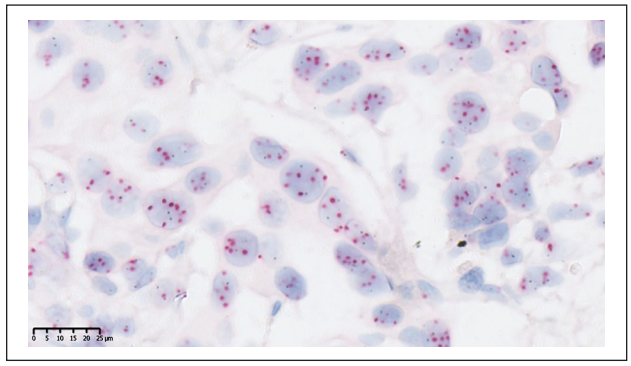

Figure 2. Silver-enhanced in situ hybridization (SISH) shows no increase of the HER2 copy number (black dots) in the breast cancer cells, accompanied by an increased CEP17 copy number (red dots), resulting in an image of "reverse" amplification (original magnification 800×).

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the centromeric region of chromosome 17.[3-6] Although the ASCO/CAP guidelines on HER2 testing do not provide a definition for CEP17 amplification,[1] most studies define CEP17 amplification as a mean CEP17 copy number of ≥3.0 copies.[4,7]

The prevalence of isolated CEP17 copy number amplification has not yet been extensively studied, and little is known about its clinical significance. Vanden Bempt et al did not observe an association between CEP17 copy number gain and tumor grade, hormone receptor status, or disease-free survival in a cohort of 266 breast cancer patients.[2] Similarly, a more recent report by Lee et al confirmed that CEP17 copy number gain was not associated with disease-free survival in a cohort of 945 invasive breast cancer patients.[7] However, subsequent subgroup analysis revealed that CEP17 amplification was associated with several adverse clinicopathological features, as well as reduced disease-free survival in patients with hormone receptor-positive HER2-negative (ie, luminal type) breast carcinoma.[7] Isolated CEP17 copy number increase might, therefore, be useful to identify a luminal HER2-negative patient subgroup with a poor prognosis, although this observation requires confirmation in independent patient populations.

Ethical Approval

This report is performed in accordance with the guidelines of the local ethics committee and the World Medical Association Declaration of Helsinki.

Informed Consent

In accordance with the guidelines of the local ethics committee, anonymous reporting of histopathological and molecular test findings does not require informed consent of the patients involved, provided that these results were obtained as part of the routine diagnostic procedures and no identifying patient details are reported.

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