Could Morphology Predict Breast Cancer Molecular Phenotype?: A Pilot Study

Ahmed Alomari, MD, Maria Orsaria MD, Alison Van Dyke, MD, Ph.D, and Sihem Khelifa, MD

Department of Pathology, Yale School of Medicine, New Haven, CT

ABSTRACT

Context: Pre- analytical errors are detrimental to breast cancer (BC) molecular studies. To overcome such effects, a set of BC was analyzed to identify morphological signatures related to molecular phenotypes. Such signatures should trigger the need to repeat molecular testing whenever unmatched morphology/phenotype is encountered.

Design: 77 BC needle core biopsies and corresponding final excisions were randomly retrieved from our archival data from 2009 to 2011. Morphological features including tumor type (ductal/lobular), nuclear grade, tumor necrosis, lymphocytic response, stromal sclerosis, retraction artifacts, and lympho-vascular invasion were analyzed. ER, PR, and HER2 immunochemistry slides were scored. Epidemiological data and Her2 FISH results were captured from our database system. Surgical excisions with tumor grade and stage, lympho-vascular invasion, lymph node status, and metastasis were reviewed.

Results: Out of 77 cases, 72 (94%) were ductal and 5 (6%) lobular. 47 (61%) ER+ and 30 (39%) ER-. 38 (49%) PR+ and 39 (51%) PR-. 39 (51%) cases were HER2+ (Average age 59 years) while 38 (49%) were HER2- (Average age 67 years). HER2+ cases were more likely to have nuclear grade3 ($p<0.0001$), retraction artifacts ($p=0.001$) and marked stromal sclerosis ($p=0.04$). A trend towards more necrosis in the HER2- cases was observed ($p=0.18$).

Conclusions: High nuclear grade, marked stromal sclerosis, and retraction artifacts could represent surrogate markers to HER2+ BC. Our results are in accordance to recent data relating extracellular matrix stiffness to tumor aggressive behavior and need to be confirmed on larger samples.

BACKGROUND

Accurate molecular phenotyping of BC not only is critical for appropriate therapeutic decision making but also has important prognostic implications. Amongst many factors, pre-analytical errors affect the results of molecular testing leading to falsely conveyed information and result in inappropriate management decisions. The morphology of BC is variable, and this applies to the epithelium and the stroma. Morphological characteristics of the epithelium, for instance, the nuclear grade have been shown to have prognostic importance. Many recent studies have emphasized the importance of the tumor extracellular matrix and its physical properties in tumor invasiveness and progression. It has also been shown that tumor can be suppressed by altering these physical properties. Accordingly, it is possible that, when combined, these epithelial and stromal characteristics can predict the molecular phenotype of the tumor.

AIMS

The aim of this study was to try to identify certain morphological features of BC that can correlate with the molecular phenotype. The development of such morphological signatures may trigger the need to repeat molecular testing whenever unmatched morphology/phenotype is encountered

METHODS

A retrospective search of the archival data of Yale New Haven Hospital from 2009 to 2011 was conducted for breast cancer cases. 77 cases with available core needle biopsy and the corresponding final excision were randomly chosen. These cases were reviewed by 2 pathologists and analyzed for morphological features. The biopsies were analyzed for tumor type (ductal/lobular), nuclear grade, tumor necrosis, lymphocytic response, stromal sclerosis, retraction artifacts, and lympho-vascular invasion. ER, PR, and HER2 immunochemistry slides were scored. Epidemiological data and Her2 FISH results were captured from our database system. Surgical excisions with tumor grade and stage, lympho-vascular invasion, lymph node status, and metastasis were reviewed. The Nottingham nuclear grading system was used for tumor grade. Necrosis was recorded as present or absent. Lymphocytic response was graded from 0-4 (none, mild, moderate and severe) and the pattern was scored as intratumoral or peripheral. Stromal sclerosis and retraction artifacts were also graded from 0 to 4 (none, mild, moderate and severe). Lympho-vascular invasion was assessed on H & E slides and in few cases by immunostains. It was recorded as present, absent or suspicious.

RESULTS

Out of these 77 cases, 72 (94%) were ductal and 5 (6%) were lobular. 47 (61%) cases were ER positive and 30 (39%) were ER negative. 38 (49%) cases were PR positive and 39 (51%) were PR negative. The cases were divided into 2 groups based on there HER2 status. 39 (51%) cases were HER2 positive (Luminal B and HER2 enriched intrinsic subtypes) while 38 (49%) cases were HER2- (luminal A subtype). The HER2+ patients were 8 years on average younger than the HER2- patients (59 vs. 67 years). The HER2+ cases were more likely to have grade 3 nuclei (85% vs. 37%; p <0.001). A statistically nonsignificant trend toward more necrosis was observed in the HER2- cases. 13 out of the 38 HER2- cases (34%) had necrosis while only 8 out of the 39 HER+ cases (21%) had necrosis (p=0.18). The presence of tumoral lymphocytic response was not significantly different between the two groups (51% in HER2+ cases vs. 42% in HER2- cases) (p-value?). Significant retraction artifacts (grade 2 and 3) were observed more commonly in HER2+ cases (54%) while only 18% of HER2- cases had significant retraction artifacts (p=0.001). Firm stroma with stromal sclerosis of grades 2 and 3 was also significantly associated with the HER2 positivity (90% in HER2+ vs. 70% in HER- cases; p=0.04. The presence or the suspicion for lympho-vascular invasion on the biopsy specimen was observed more commonly in HER2+ cases (70% vs. 32%; p=0.001), although this trend was not seen on the resection specimen (27% in HER2+ cases vs. 38% in HER2-). A statistically nonsignficant trend of high-er incidence of positive lymph node metastasis was observed in HER2+ cases (42% vs. 20%; p=0.06).

RESULTS

Table 1: HER2+ Breast Cancers are More Likely to Have Grade 3 Nuclei

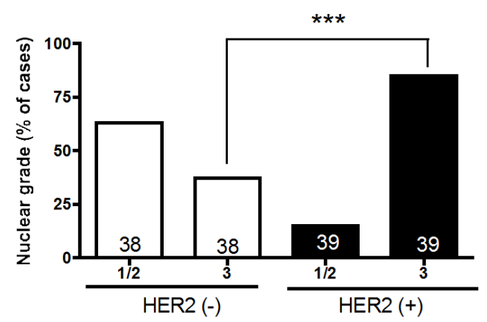


Table 2: HER2+ Breast Cancers are More Likely to Have Peritumoral Retraction Artifact

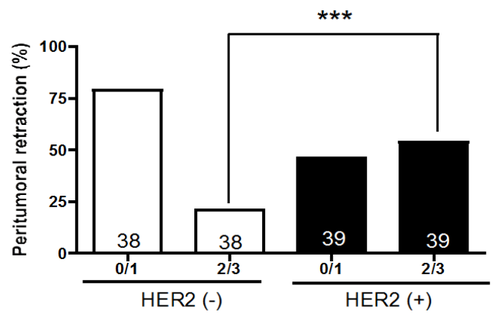
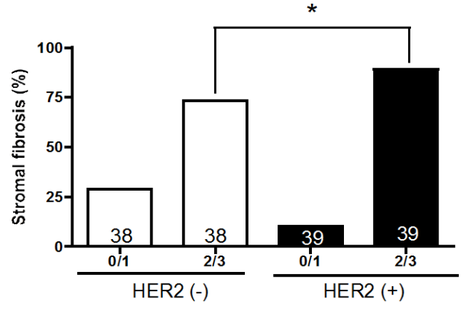


Table 3: HER2+ Breast Cancers are More Likely to Have Stromal Sclerosis



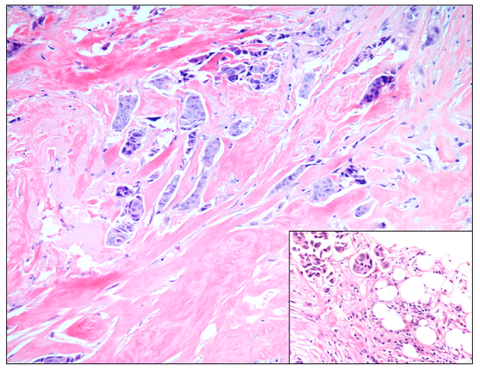


Figure 1: HER2+ breast cancers are more likely to have stromal sclerosis and retraction artifacts

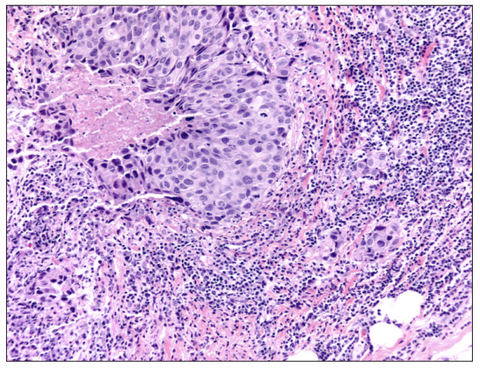


Figure 2. HER2- breast cancers have a tendency to present tumoral necrosis.

CONCLUSIONS

Based on this pilot study, we conclude that HER2+ Breast cancers are more likely to have higher nuclear grade, stromal fibrosis and retraction artifacts. This morphological signature, surrogate for HER2 overexpression, should help predicting the molecular phenotype of BC and should provide guidance of when to repeat molecular testing if in doubt. This study is also in accordance to recent data relating extracellular matrix stiffness to tumoral aggressive behavior therefore, we suggest to confirm our results on larger samples.

REFERENCES

1. G. Acs et al: The extent of retraction clefts correlates with lymphatic vessel density and VEGF-C expression and predicts nodal metastasis and poor prognosis in early-stage breast carcinoma. Mod Pathol. 2012 Feb;25(2):163-77.
2. KR. Levental et al: Matrix crosslinking forces tumor progression by enhancing integrin signaling. Cell. 2009 Nov 25.