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Immunohistochemistry in the Recognition of "Basal-like" or "Basaloid" Breast Carcinoma

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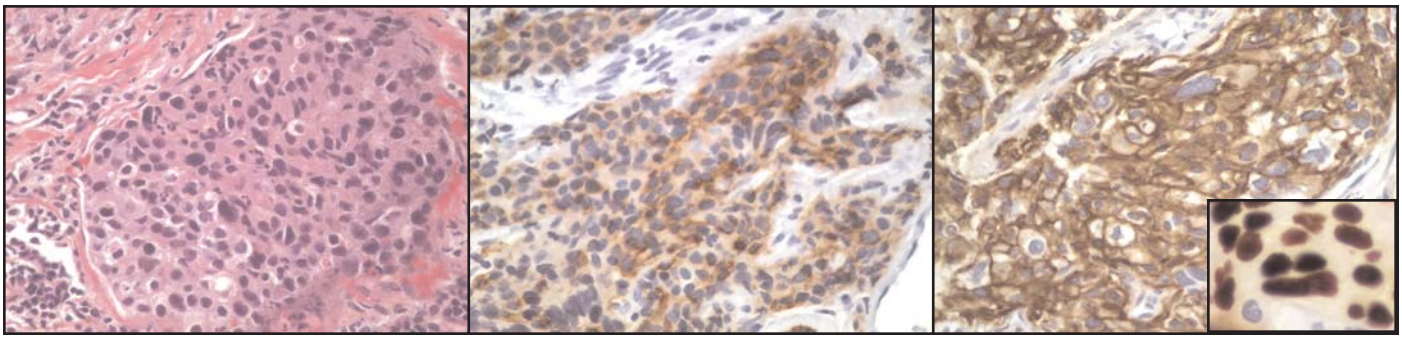
Over the past few months, we have had several inquiries regarding the use of immunohistochemistry for recognizing the so-called "basal-like" or "basaloid" variant of invasive breast carcinoma, something that was unfamiliar to me at the time. These inquiries have been driven by oncologists' requests for these studies (leading me to suspect that this type of breast carcinoma must have been a "hot topic" at a recent oncology meeting or in the recent oncology literature). This month, we will briefly review this variant of breast cancer, its clinical importance, and a practical approach to recognition of this recently described entity.

Breast carcinoma is very heterogeneous, with highly variable morphology, clinical behavior, and response to therapy. Some investigators have hypothesized that this heterogeneity may be related to the particular cell of origin or path of cell differentiation of the tumor cells in a particular case. It is well known that normal breast tissue contains two cell layers: an inner ductal or luminal population, and an outer basal or myoepithelial cell layer. By examining gene expression profiles using microarrays, Sorlie et al categorized breast carcinoma into five different groups, that were associated with different clinical courses. One of these groups was designated "basal-like" (because its gene expression profile was similar to normal breast basal cells), and represented 19% of tumors in the study group (of >300 cases). These "basal-like" breast carcinomas were typically negative for ER and PR, and also negative for HER-2 overexpression (or HER-2 gene amplification). They demonstrated significantly decreased relapse-free survival, reflecting poor prognosis. Furthermore, there was a strong association with the presence of BRCA1 mutations in the patients harboring these "basal-like" breast carcinomas.

Multiple immunohistochemical markers (that stain normal breast basal cells) have been used by different investigators to recognize basal-like differentiation, including cytokeratin 5 (or cytokeratin 5/6, which is diagnostically equivalent to cytokeratin 5), cytokeratin 14, cytokeratin 17, and EGFR. Multiple studies have demonstrated that as a group, breast cancers that express these markers have a worse prognosis. However, to my knowledge there is no universally agreed-upon criteria for recognition of these tumors using immunohistochemistry, and as a result those of us "in the trenches" who are trying to keep our oncologists happy may be at a loss to know where to draw the line between "basal-like" and "non-basal like" tumors.

Fortunately, an August 2004 paper published in Clinical Cancer Research by Nielsen et al provides easy to apply criteria that can assist us in recognizing the basal-like variant of breast carcinoma. Parenthetically, Dr. Allen Gown, one of the world's foremost immunohistochemists, was among the co-authors of this paper. The authors started with a group of 118 tumors that had been previously studied using gene expression profiling (using DNA microarrays to analyze expression for 8700 genes). This group included 21 cases that showed gene expression profiles of basal-like tumors. The authors found that by selecting breast cancer cases with negative immunostains for ER and HER-2 overexpression but positive immunostains



H&E section (left) from an ER negative, PR negative, HER-2 negative high grade breast cancer. Based on expression of CK5 (middle) and EGFR (right), it was interpreted as a basal-like breast cancer. The tumor also expressed p53 (right, inset).

for either cytokeratin 5/6 or EGFR (a.k.a. HER-1), they were able to identify 16 of the 21 basal-like tumors, giving a sensitivity for basal-like tumors of 76% and a specificity of 100%. When the authors applied these criteria to tissue microarrays from an additional group of 663 patients, 15% (102 patients) fell into the "basal-like" group. Follow up data on this group of immunohistochemically-defined basal-like tumors confirmed the worse prognosis of this group. The authors' criteria for interpreting the stains were as follows: ER positive = nuclear staining (weak or strong) in any invasive tumor cells. HER-2 positive = strong membrane staining on >20% of invasive tumor cells (equivalent to a 3+ Herceptest score; cases with a Herceptest score of 0, 1+, or 2+ are all considered "negative"). Cytokeratin 5 positive = any (weak or strong) cytoplasmic staining of invasive tumor cells. EGFR positive = any (weak or strong) cytoplasmic staining of invasive tumor cells.

Interestingly, all of these “basal-like” markers are also expressed by squamous tumors, and it would be interesting to see if these tumors express nuclear p63 (expressed in both myoepithelium and squamous tumors) as well as smooth muscle myosin (an excellent marker of breast basal cells).

In summary, basal-like breast cancer is a prognostically unfavorable subset of high grade breast carcinomas that are typically negative for ER, PR, and HER-2. They are estimated to account for 15-20% of breast cancers, and have a strong association with BRCA-1 mutations. Immunohistochemistry can be used to identify such cases with good sensitivity and excellent specificity, by selecting tumors that are negative for ER and HER-2, but positive for either cytokeratin 5 or EGFR. They also often express nuclear p53. All of the markers discussed in this review are available at PROPATH.

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References:

1. Sorlie T et al: Gene expression patterns of breast carcinoma distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 98:10869-10874, 2001.
2. Sorlie T et al: Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 98:8418-8423, 2003.
3. Nielsen TO et al: Immunohistochemical and clinical characterization of basal-like subtype of invasive breast carcinoma. Clinical Cancer Research 5367-5374, August 15, 2004.
4. Gusterson BA et al: Basal cytokeratins and their relationship to the cellular origin and functional classification of breast cancer (Review). Breast Cancer Research 7: 143-148, May 5, 2005.
5. Foulkes WD et al: Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. Journal of the National Cancer Institute 95 (19): 1482-1485, October 1, 2003.
6. Foulkes WD: Hypothesis: BRCA1 functions as a breast stem cell regulator. Journal of Medical Genetics 41: 1-5, 2004.
7. Jones C et al: CGH analysis of ductal carcinoma of the breast with basaloid / myoepithelial cell differentiation. British Journal of Cancer 85: 422-427, 2001.

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