Benign Myoepithelial Tumors of the Breast Have Immunophenotypic Characteristics Similar to Metaplastic Matrix-Producing and Spindle Cell Carcinomas

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Key Words: Breast; Myoepithelial cells; Adenomyoepithelioma; Metaplastic carcinoma

DOI: 10.1309/G6CTR8MDTFUW19XV

Abstract

We immunohistochemically compared benign myoepithelial tumors (adenomyoepitheliomas [AMEs]) and metaplastic matrix-producing (MMP-CA) and spindle cell (MSC-CA) carcinomas of the breast to identify helpful diagnostic markers. Normal myoepithelial cells (MECs) consistently expressed cytokeratin, α-smooth muscle actin (SMA), myosin, S-100, CD10, and maspin. They were variably positive for vimentin and negative for epithelial membrane antigen (EMA), steroid receptors, p53, and HER-2/neu. MECs in AMEs less frequently expressed CD10 (4/8 [50%]) and myosin (6/8 [75%]) but frequently acquired characteristics of luminal cells, such as expression of EMA (5/8 [63%]) and steroid receptors (5/8 [63%]). No abnormal p53 or HER-2/neu expression was seen in AMEs. MMP-CA and MSC-CA were similar to AMEs in cytokeratin, vimentin, S-100, maspin, and HER-2/neu expression. MMP-CAs expressed less α-SMA (2/8 [25%]) and myosin (2/7 [29%]) and lacked estrogen receptor (0/9 [0%]). MSC-CAs were consistently CD10+ (4/4 [100%]) yet failed to express myosin (0/3 [0%]). p53 overexpression was seen frequently in MMP-CAs (4/8 [50%]) and MSC-CAs (1/3 [33%]).

Benign myoepithelial mammary tumors differ immunophenotypically from normal MECs; a panel of immunohistochemical markers may be required to establish their myoepithelial origin. A similarly altered myoepithelial phenotype also is characteristic of metaplastic mammary carcinomas. The abnormal expression of oncogenes or antioncogenes, such as p53, may be more useful for distinguishing between those entities than the expression of the classic myoepithelial markers.

True myoepithelial tumors rarely are diagnosed in the breast. However, hyperplasia of the myoepithelial cells (MECs) often accompanies glandular hyperplasia (eg, sclerosing adenosis, papillomatosis) and can resemble benign myoepithelial neoplasms, ie, adenomyoepitheliomas (AMEs). A noninvasive growth pattern and a variable mixture of MECs and glandular elements characterizes AMEs.1 The spindle shape of proliferating MECs and their ability to produce extracellular matrix may yield a histologic appearance that closely approximates that of metaplastic carcinomas (spindle cell and matrix-producing variants). Several earlier studies have demonstrated that metaplastic breast carcinomas may have immunohistochemical and ultrastructural characteristics consistent with myoepithelial differentiation,2,3 yet the issue of similarity between AME and metaplastic carcinoma has not been examined thoroughly. With the increased application of small-needle biopsies for the diagnosis of breast lesions, it is important to further explore the aforementioned similarities and to find significant differences. We compared the immunophenotypic characteristics and oncogene expression of normal breast MECs, benign myoepithelial breast tumors, and metaplastic breast carcinomas.

Materials and Methods

Tissues

We studied 8 AMEs (in women; age range, 29-67 years), 1 mixed tumor (in a woman, 75 years old), and 12 metaplastic breast carcinomas with chondroid and/or spindle cell differentiation (in women; age range, 32-83 years). Diagnostic criteria...
for these entities have been published.4-6 The AMEs showed an admixture of proliferating spindle MECs and few epithelial-lined duct-like structures. In 2 cases, the AMEs were mostly solid, composed of polygonal or plasmacytoid cells containing few compressed epithelial-lined spaces. The mixed tumor (pleomorphic adenoma) showed an admixture of myoepithelial and epithelial cells in clusters or duct-like structures dispersed in a chondroid matrix. Spindle cell carcinomas were composed predominantly of elongated, cytokeratin-positive cells often showing a storiform growth pattern. Metaplastic matrix-producing carcinomas contained areas of chondroid differentiation admixed with areas of regular ductal carcinoma. One of the carcinomas showed a mixture of spindle cell and chondroid areas.

Immunohistochemical Analysis

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded sections by using an automatic immunostainer (DAKO, Carpinteria, CA) and a streptavidin-biotin-peroxidase complex technique (LSAB2 system, DAKO). Heat-induced epitope retrieval was performed in a Handy Steamer Plus (Black and Decker, Shelton, CT) in citrate buffer, pH 6.0 (DAKO) or EDTA (for maspin) for 20 minutes. The following primary antibodies were used: anti–estrogen receptor (ER; clone 1D5; dilution 1:400; DAKO), anti–progesterone receptor (PR; clone 1A6; dilution 1:80; DAKO), anti–androgen receptor (AR; clone AR441; dilution 1:100; DAKO), anti–cytokeratin AE1/3 (clone AE1/AE3; dilution 1:80; Signet, Dedham, MA), anti–HER-2/neu (rabbit polyclonal; dilution 1:1,600; Ventana, Tucson, AZ), antivimentin (clone VIM3B4; dilution 1:400; DAKO), anti-p53 (clone DO-7; dilution 1:400; DAKO), antimaspin (clone G167-70; dilution 1:3,200; Pharmingen, San Diego, CA), anti-CD10 (clone 56C6; dilution 1:80; Neomarkers, Fremont, CA), anti–epithelial membrane antigen (EMA; clone E29; dilution 1:1,600; DAKO), anti–α-smooth muscle actin (SMA; clone 1A4; dilution 1:200; DAKO), and anti–smooth muscle myosin heavy chain (clone SMMS-1; dilution 1:400; DAKO). Negative controls were obtained by omitting the primary antibodies. Benign breast parenchyma adjacent to the tumor served as an internal positive control.

Double Immunohistochemical Analysis

For selected cases, double immunohistochemical staining was performed using the combinations of anti-SMA and anti-ER or anti-SMA and anti-EMA and the DAKO EnVision Doublestain System. The first and second primary antibodies were omitted independently in control sections. In addition, consecutive sections were stained individually with each of the antibodies.

Scoring

The results of immunostaining were graded on a 4-point scale (0-3) incorporating the intensity of staining and the percentage positive cells as follows: 0, no staining; 1+, weak, speckled staining that did not entirely cover the appropriate cellular compartment or uniform staining of the appropriate compartment seen in fewer than 10% of cells; 2+, complete but moderate staining of the appropriate compartment in more than 10% of cells; 3+, complete and strong staining in the appropriate cellular compartment seen in more than 10% of cells. ER, PR, AR, HER-2/neu, and p53 immunostains were considered positive for scores greater than 1. The remaining immunostains were designated as positive for scores greater than 0.

Results

Normal MECs

Normal MECs consistently expressed cytokeratin (AE1/3), SMA, myosin, S-100, CD10, maspin, and vimentin. They were negative for EMA, steroid receptors (ER, PR, and AR), p53, and HER-2/neu. Normal luminal cells did not express SMA, myosin, CD10, vimentin, or p53, yet they were strongly positive for EMA, AE1/3, and steroid receptors. Occasionally, weak expression of S-100, maspin, and HER-2/neu was observed for luminal cells.

Benign Myoepithelial Tumors

Results of immunostaining for the spindle cell component of benign myoepithelial tumors are summarized in 5Table 1[]. The myoepithelial component of AMEs invariably showed immunoreactivity for cytokeratin, maspin, and vimentin. In contrast, normal MECs did not express these markers. Double immunohistochemical analysis showed that, contrary to normal MECs, luminal (EMA and steroid receptors) and myoepithelial markers (SMA, myosin, or CD10) were expressed in the same cells. In addition, consecutive sections were stained individually with each of the antibodies.

Metaplastic Carcinomas

The results of immunostaining for metaplastic carcinomas are given in 5Table 2[]. Similar to the benign myoepithelial...
breast lesions, metaplastic carcinomas were positive for cytokeratin (AE1/3), vimentin, maspin, and S-100 and negative for HER-2/neu. Matrix-producing carcinomas frequently were positive for EMA. Double immunohistochemical analysis revealed that a population of tumor cells coexpressed EMA and α-SMA (Image 2). Compared with AMEs, spindle cell carcinomas were more often CD10+ and negative for myosin, while the concurrent absence of both SMA and myosin was more frequently observed in matrix-producing carcinomas (Figure 1). p53 was overexpressed in 4 (50%) of 8 metaplastic matrix-producing carcinomas and 1 (33%) of 3 metaplastic spindle cell carcinomas (Figure 1). Both types of metaplastic carcinomas were consistently negative for steroid receptors.

**Discussion**

Our results showed that benign myoepithelial breast lesions have an altered phenotype compared with normal MECs. This most often was manifested by the complete loss of CD10 expression in 5 (56%) of 9 cases and by the reduction in the intensity of expression of SMA and myosin. Furthermore, benign myoepithelial tumors unexpectedly expressed EMA and α-SMA (Image 2). Compared with AMEs, spindle cell carcinomas were more often CD10+ and negative for myosin, while the concurrent absence of both SMA and myosin was more frequently observed in matrix-producing carcinomas (Figure 1). p53 was overexpressed in 4 (50%) of 8 metaplastic matrix-producing carcinomas and 1 (33%) of 3 metaplastic spindle cell carcinomas (Figure 1). Both types of metaplastic carcinomas were consistently negative for steroid receptors.

**Table 1**

<table>
<thead>
<tr>
<th>Case No./ Age (y)</th>
<th>AE1/3</th>
<th>Vimentin</th>
<th>SMA</th>
<th>Myosin</th>
<th>Maspin</th>
<th>CD10</th>
<th>S-100</th>
<th>EMA</th>
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AR, androgen receptor; EMA, epithelial membrane antigen; ER, estrogen receptor; ND, not determined owing to loss of diagnostic material; PR, progesterone receptor; SMA, smooth muscle actin.

* See the “Scoring” section in “Materials and Methods” for an explanation of the scoring system.

expression in benign myoepithelial lesions may contribute to neoplastic growth properties of myoepithelial tumors.

The myoepithelial component of AMEs often showed reduced levels of expression of SMA and occasionally absent myosin expression. Muscle markers were detected in the majority of previously studied cases of AME13-17 and mixed tumors.18-21 Sileikiene et al15 noted loss of actin immunoreactivity in only 1 of 15 AMEs. The myoepithelial component of adenomyoepitheliomas (AME), metaplastic spindle cell carcinomas (MSC-CA), and metaplastic matrix-producing carcinomas (MMP-CA).
reported decreased α-SMA expression in continuously passaged MECs. No case in our series showed complete absence of both SMA and myosin.

Some of the benign myoepithelial breast lesions coexpressed epithelial and myoepithelial markers in the spindle-polygonal cell component. These features may indicate an origin from a bipotent progenitor cell. Stingl et al described a bipotent progenitor population in normal human mammary gland tissue with a capacity of generating cells with a luminal or myoepithelial phenotype. The same authors have shown that a small population of cells with a luminal or myoepithelial phenotype (EMA+/CD10+) appears after 72 hours of growth in vitro. The presence of steroid hormone receptors in some of the benign myoepithelial lesions included in our study further supports this notion. ER-positive AMEs and mixed tumors of the breast have been reported. Those studies, however, could not confirm that neoplastic MECs expressed ER since biochemical assays were used. In 2 more recent immunohistochemical studies, ER was found in the ductal-epithelioid component of AMEs and mixed tumors, whereas the myoepithelial component was negative for ER. This is in contrast with our results and may be secondary to technical differences, including the absence of antigen retrieval, which may yield underestimation of weakly positive cells.

Metaplastic carcinomas of the breast were positive for cytokeratin, vimentin, S-100, and maspin, similar to normal MECs and benign myoepithelial lesions. Other authors found vimentin and S-100 expression in these tumors, and our study confirmed such observations. However, it is important to recognize that vimentin expression has been observed frequently (33%-86% of cases) in carcinomas of the breast, in the absence of metaplastic features. While 100% of matrix-producing carcinomas have been reported to express S-100, spindle cell carcinomas and carcinomas have exhibited weaker or, sometimes, absent S-100 immunoreactivity.

Cytokeratin expression in metaplastic breast carcinomas is variable. Matrix-producing carcinomas reveal near absolute immunoreactivity for cytokeratin, while spindle cell carcinomas typically show reduced or absent cytokeratin expression. In our series, we detected cytokeratin in all carcinomas studied. The previously reported cytokeratin negativity may reflect more sarcomatous features of those tumors, the focal nature of cytokeratin expression, or both. Further technical issues such as storage of archival material, different antibodies, and antigen-retrieval procedures could contribute to the differences.

In contrast with previous studies of nonmetaplastic carcinomas in which maspin immunoreactivity was found in only 25% of invasive ductal carcinomas, not otherwise specified type, and 20% of tubular carcinomas, we detected maspin in all tested metaplastic carcinomas. Maspin is a serine protease inhibitor, which is produced predominantly by breast MECs. It has been reported to inhibit invasion and motility of mammary carcinoma cells in vitro and tumor growth and metastasis in vivo. It also has been shown to have an antiangiogenic effect. The biological significance of maspin reactivity in metaplastic carcinomas is not clear. The strong maspin expression in matrix-producing breast carcinomas...
Double immunostaining for epithelial membrane antigen (EMA; brown) and α-smooth muscle actin (SMA; red) in normal breast (A), the spindle-polygonal cell component of adenomyoepitheliomas (B), and metaplastic matrix-producing carcinomas (C). Note that EMA and α-SMA often are expressed in the same cells (original magnification ×1,000).

Table 2
Immunohistochemical Profile of Metaplastic Breast Carcinomas*

<table>
<thead>
<tr>
<th>Case No./Age (y)</th>
<th>AE1/3</th>
<th>Vimentin</th>
<th>SMA</th>
<th>Myosin</th>
<th>Maspin</th>
<th>CD10</th>
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<th>EMA</th>
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AR, androgen receptor; EMA, epithelial membrane antigen; ER, estrogen receptor; ND, not determined owing to loss of diagnostic material; PR, progesterone receptor; SMA, smooth muscle actin.

*See the “Scoring” section in “Materials and Methods” for an explanation of the scoring system.
†The tumor of this patient showed spindle cell and matrix-producing features.
may, at least in part, contribute to the reported more favorable prognosis compared with conventional carcinoma.40

Contrary to the results for benign myoepithelial lesions, metaplastic carcinomas rarely expressed SMA or myosin, and there was only 1 case with simultaneous, weak expression of these antigens. There was a trend for higher expression of SMA in spindle cell carcinomas than in matrix-producing tumors. Variable expression of muscle markers has been reported.2,3,27-29,32,33 Wargotz and Norris2 reported focal or diffuse actin immunoreactivity in 38% (5/13) of matrix-producing breast carcinomas and intermediate or diffuse immunoreactivity in 77% (30/39) of carcinomas. Gobbi et al27 found SMA expression in 22% (2/9) of metaplastic carcinomas with spindle cells and muscle specific actin expression in 80% (8/10) of the tumors. Sneige et al32 noted that the majority of low-grade spindle cell carcinomas (19/24) were positive for SMA, while no expression of myosin was detected.

We observed increased EMA expression in carcinomas with chondroid matrix and decreased expression in metaplastic carcinomas with spindle cells. Wargotz and Norris5,3 reported variable EMA expression in almost all (92%) matrix-producing carcinomas included in their studies and variable EMA immunoreactivity in only 21% of carcinomas. In addition, other have similarly reported absence of EMA in spindle cell carcinomas.26,29 Gobbi et al27 reported weak EMA positivity in rare spindle cells and few epithelial cells in 4 of 8 metaplastic breast carcinomas with a “fibromatosis-like” component.

Metaplastic carcinomas in our study overexpressed p53 in 5 of 11 cases, which can help distinguish them from benign myoepithelial proliferations. Similarly Chhieng et al30 observed p53 immunoreactivity in almost all (92%) matrix-producing carcinomas included in their studies and variable EMA immunoreactivity in nearly all (80%) of carcinomas. In addition, others have similarly reported absence of EMA in spindle cell carcinomas.26,29 Gobbi et al27 reported weak EMA positivity in rare spindle cells and few epithelial cells in 4 of 8 metaplastic breast carcinomas with a “fibromatosis-like” component.

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We did not find HER-2/neu expression in benign myoepithelial lesions or metaplastic breast carcinomas, which shows that HER-2/neu cannot be used to differentiate those entities. Similarly Chhieng et al30 and Sneige et al33 showed that metaplastic matrix-producing and spindle cell carcinomas of the breast were HER-2/neu negative.

Benign myoepithelial tumors of the breast and metaplastic breast carcinomas demonstrate immunohistochemical profiles that are similar but not identical to those seen in MECs. This conclusion also is strongly supported by recently published preliminary results of complementary DNA microarray analysis that compared expression patterns of metaplastic carcinomas and benign myoepithelial tumors.41 Because of this similar immunophenotype, the distinction between entities may be difficult, especially on a small biopsy specimen. Evaluation of classic myoepithelial markers has limited value in distinguishing benign from malignant tumors. Overexpression of p53 supports a diagnosis of metaplastic carcinoma; however, it is observed in fewer than 50% of the cases. Further studies are needed to reveal the oncogene abnormalities in the remaining portion of metaplastic carcinomas.

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