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Original contribution

Cutaneous and mammary apocrine carcinomas have different immunoprofiles☆

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Summary Often the distinction of cutaneous apocrine carcinoma from metastatic mammary apocrine carcinoma to the skin can be a diagnostic dilemma because both tumors share similar histologic features and have overlapping immunohistochemical profile. We compared the expression of adipophilin, cytokeratin 5/6, p63, GATA3, mammaglobin, androgen receptor, estrogen receptor, progesterone receptor, and HER2 by immunohistochemistry in 14 cutaneous apocrine carcinomas (11 primary tumors, 3 metastases) and 26 primary apocrine carcinomas of the breast. Whereas focal adipophilin staining was seen in 36% (5/14) of cutaneous apocrine carcinoma, strong and diffuse adipophilin staining was seen in 88% (22/25) of mammary apocrine carcinoma (P = .0013). Differences in estrogen receptor and progesterone receptor expression were also statistically significant (P = .018 and .043). Androgen receptor was strongly positive in all cutaneous and mammary cases. Although there was no significant difference in the frequency of expression of cytokeratin 5/6, p63, HER2, GATA3, and mammaglobin in cutaneous apocrine carcinoma versus mammary apocrine carcinoma, strong and diffuse cytokeratin 5/6 and/or mammaglobin expression were seen only in cutaneous apocrine carcinoma. In conclusion, cutaneous apocrine carcinoma is likely adipophilin− ER+ PR+/− HER2− and can exhibit strong and diffuse cytokeratin 5/6 and/or mammaglobin expression. On the contrary, a mammary apocrine carcinoma is likely adipophilin+ ER− PR− and often exhibit 3+ HER2 with corresponding *HER2* gene amplification. A panel of adipophilin, ER, PR, HER2, cytokeratin 5/6, and mammaglobin may be helpful in distinguishing cutaneous apocrine carcinoma from mammary apocrine carcinoma.

1. Introduction

Apocrine cells are characterized by abundant eosinophilic or granular cytoplasm and a round vesicular nucleus with prominent and often multiple nucleoli. Apocrine carcinoma of the breast is defined as a carcinoma in which most of the tumor cells have apocrine morphology [1]. The reported incidence of pure mammary apocrine carcinoma ranges from less than 1% to 4% [2]. Japaze et al [3] have suggested that pure

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infiltrating apocrine carcinoma may be less aggressive than high-grade infiltrating ductal carcinomas and might respond differently to therapeutic agents. By immunohistochemistry, intraductal apocrine carcinoma and infiltrating apocrine carcinoma are frequently androgen receptor (AR) positive, estrogen receptor (ER) negative, and progesterone receptor (PR) negative [1,4–6].

Cutaneous apocrine carcinomas are rare and associated with poor prognosis. According to the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) registry from 1973 to 2006, the incidence of cutaneous apocrine adenocarcinoma ranged from 0.0049 to 0.0173/100 000 per year [7]. Median overall survival was 51.5 months, overall 5-year survival was 85.4%, and 5-year disease-specific survival was 88%. Overall survival was associated with surgical therapy, lymph node metastasis, and the presence of distant metastasis. Cutaneous apocrine carcinomas, similar to its mammary counterpart, show consistent strong AR expression [8,9].

Often the distinction of cutaneous apocrine carcinoma from metastatic mammary apocrine carcinoma to the skin represents a diagnostic dilemma because both tumors share similar histologic features and have overlapping immunohistochemical profile. Although surgical excision is the treatment of choice for cutaneous apocrine carcinoma, there is no uniform treatment guideline for those with metastatic disease. On the contrary, treatment options are available for metastatic mammary apocrine carcinoma [3]; thus, making the distinction of these 2 tumor types has treatment implications.

Although there have been studies investigating the role of immunohistochemistry including p63, cytokeratin (CK) 5/6, and mammaglobin in the distinction of cutaneous carcinoma versus metastatic breast carcinoma to skin [10,11], only rare cases of cutaneous apocrine carcinomas and no mammary apocrine carcinomas were included in these series. Because both cutaneous and mammary apocrine carcinomas are very rare tumors, there has been only one study comparing the immunoprofile of mammary versus cutaneous apocrine carcinomas [12]. We sought to investigate the sensitivity and specificity of 9 immunohistochemical markers (adipophilin, CK5/6, p63, GATA3, AR, ER, PR, mammaglobin, and HER2) in the distinction of cutaneous apocrine carcinoma from mammary apocrine carcinoma.

2. Materials and methods

The study was approved by the institutional review boards (IRBs) of Massachusetts General Hospital (IRB no. 2011-P-2489) and University of Texas Southwestern Medical Center (IRB no. STU 32011–117). Archival materials from 1989 to 2013 with a diagnosis of cutaneous apocrine carcinoma and mammary apocrine carcinomas were retrieved from the pathology databases. Fourteen cutaneous apocrine carcinomas and 26 mammary apocrine carcinomas with available archival materials were retrieved from the pathology files. The histologic sections of all cases were rereviewed, and the diagnoses were confirmed. Cutaneous and mammary carcinomas with predominant apocrine features and AR expression were included in the study [4,8,9]. Clinical information was extracted from the medical records. All patient data were deidentified.

2.1. Immunohistochemical analysis

Immunohistochemical studies were performed on 5-μm-thick sections of formalin-fixed, paraffin-embedded tissue in a Bond 3 automated immunostainer (Leica Microsystems, Bannockburn, IL) and primary antibodies against adipophilin (clone: AP125, 1:75; Fitzgerald Industries International, Acton, MA), CK5/6 (B4, 1:100; Dako, Carpinteria, CA), p63 (BC4A4, undiluted; Biocare Medical, Concord, MA), GATA3 (L50-823, 1:250; Biocare Medical), AR (AR441, 1:50; Dako), ER (6 F11, undiluted; Leica Microsystems), PR (16, undiluted; Leica Microsystems), mammaglobin (304-1A5, 1:400; Dako), and HER2/neu (4B5, 1:15; Ventana Medical System Inc., Tucson, AZ). Appropriate positive and negative controls were included. Positive staining of adipophilin, CK5/6, p63, GATA3, AR, ER, PR, and mammaglobin was scored as 4+ (76%-100% of the tumor cells), 3+ (51%-75%), 2+ (26%-50%), 1+ (6%-25%), and 0/negative (≤5%). Overexpression of HER2 was defined as positive membranous staining in more than 30% of the neoplastic cells. Partial and faint staining in less than 10% of tumor cells, weak to moderate complete membrane staining in more than 10% of the tumor cells, or intense or thick circumferential membrane staining in more than 30% of the tumor cells were scored as 1+ (negative), 2+ (equivocal), or 3+ (positive), respectively.

2.2. Fluorescence in situ hybridization

Unstained slides were cut at a 4-μm thickness. Dual-color fluorescent in situ hybridization was performed on sections cut from the same block with the *HER2* probe labeled with spectrum red and chromosome 17–specific centromere (D17Z1) probe labeled with spectrum green. Deparaffinization, in situ hybridization, and staining were performed using the PathVysion kit (Abbott-Vysis Lab, Abbott Park, IL), as per the manufacturer's protocols. Fluorescent signals in at least 60 nonoverlapping interphase nuclei with intact morphology were scored with a 100× objective, using a triple band-pass filter that permits simultaneous blue, green, and red colors. Only tumor cells from the site designated on the histologic slide by the pathologist were scored for the number of red (*HER2*) and green (chromosome 17) signals. A case was scored as amplified if the ratio of the number of fluorescent signals of *HER2* to chromosome 17 was greater than 2.2 [13].

2.3. Statistical analysis

The statistical association of adipophilin, CK5/6, p63, GATA3, AR, ER, PR, mammaglobin, and HER2