

CASE REPORT

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Sebaceous gland metaplasia in intraductal papilloma of the breast

Received: 4 July 2000 / Accepted: 24 October 2000 / Published online: 3 February 2001
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Abstract We report here the first case of sebaceous gland metaplasia arising within an intraductal papilloma of the breast of a 70-year-old female. Several lobules and nests composed of clear cells closely resembling sebaceous glands of the skin were discovered within an intraductal papilloma of the breast. Squamous metaplasia was also noted in certain areas of the tumor. Immunohistochemically, the cells of the lobules and nests stained positively for monoclonal antibodies anti-cytokeratin 14 and epithelial membrane antigen. This study confirms a novel type of metaplasia of the breast.

Keywords Sebaceous glands · Metaplasia · Intraductal papilloma · Breast

Introduction

Several reports have demonstrated the presence of squamous metaplasia in the intraductal papilloma of the breast [2, 3, 9]. To our knowledge, no sebaceous gland metaplasia arising from within an intraductal papilloma of the breast have yet been reported. In this report, we describe the pathological and immunohistochemical features of a case of sebaceous gland metaplasia arising within an intraductal papilloma of the breast.

Case report

A 70-year-old Japanese woman complained of a bloody nipple discharge. An excisional biopsy was performed 6 months later,

and a mass measuring 4×3×3 mm in the lactiferous duct was found.

Materials and methods

The tissue obtained at surgery was fixed in 10% buffered formalin and embedded in paraffin. Routine histologic sections were stained with hematoxylin and eosin. Immunohistochemical staining with monoclonal cytokeratin 14 (Biogenex, San Ramon, Calif.), epithelial membrane antigen (EMA; Dako, Carpinteria, Calif.), and gross cystic disease fluid protein-15 (GCDFP-15; Novocastra, Newcastle upon Tyne, UK) was performed using the avidin-biotin complex-peroxidase method. Positive and negative control sections were stained appropriately. Alcian blue staining and periodic acid–Schiff (PAS) reaction were also performed.

Results

Histopathologic findings

Histology revealed a proliferation of the mammary ductal epithelium into the cystic duct lumina (Fig. 1). The cyst was lined by ductal epithelium and myoepithelium. In certain areas, papillary structures with well-developed fibrovascular stalks were seen. Two cell layers were readily identified: an outer layer of fusiform or spindle-shaped cells covering the stalks, and an inner layer of cuboidal or low columnar cells lining the duct lumina. In certain areas, partial fusion of the papillary fronds resulted in a solid growth pattern. Within the tumor tissue, there were a number of lobules and nests of clear cells similar to sebaceous glands of the skin. The cytoplasm of these cells appeared as a delicate network, with the nucleus being centrally located (Fig. 2). A few solid areas of the tumor, adjacent to or near the sebaceous gland area, consisted of squamous cells with brightly eosinophilic cytoplasm and evidence of intercellular bridges. The nuclei were round to oval and often had a single prominent nucleolus. In a few locations, keratohyaline granules were present (Fig. 3). No communication with the overlying epidermis or Montgomery's areolar tuber-

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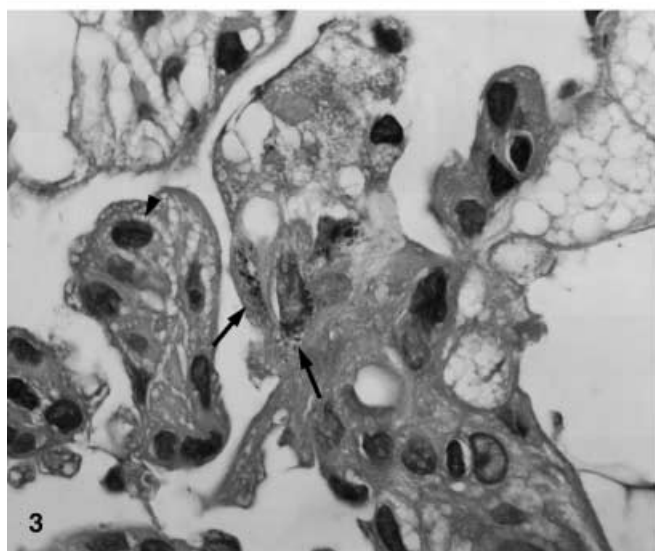
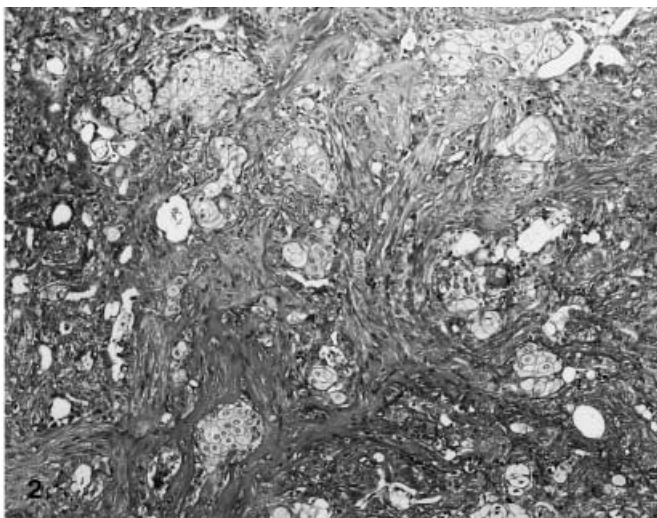
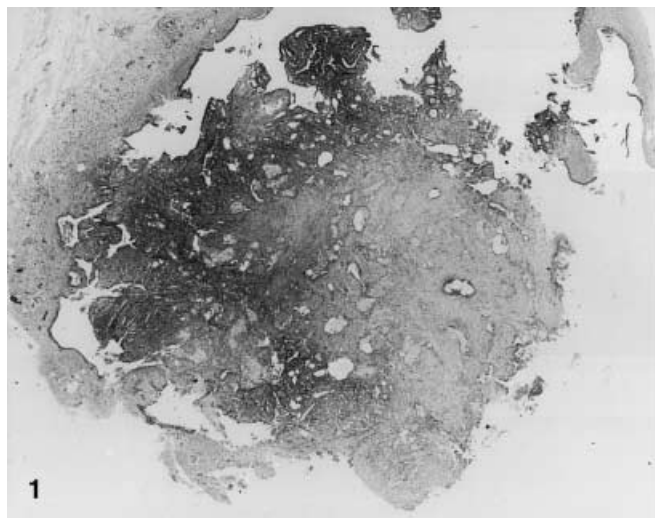


Fig. 1 Low-power magnification shows a dilated duct containing an intraductal papilloma (Hematoxylin and eosin, $\times 20$)

Fig. 2 A focal area of metaplastic sebaceous gland is present within the tumor. (Hematoxylin and eosin, $\times 100$)

Fig. 3 A focal area of squamous metaplasia within the tumor. Keratohyaline granules (*arrow*) and intercellular bridges (*arrow-head*) are seen. Sebaceous gland cells are also present. (Hematoxylin and eosin, $\times 1000$)

cle were detected. The clear cells were negative for Alcian blue staining and PAS reaction. The lesion was thus not of either a xanthelasma or mucous-secreting cell lineage.

Immunohistochemical findings

Results of the immunohistochemical staining of the control and tumor tissue are summarized in Table 1. Immunohistochemical staining for EMA demonstrated strong positivity in the apical region of the inner epithelial cells

of the cystic duct and the papilloma and in the sebaceous gland cells (Fig. 4A). Staining for cytokeratin 14 showed strong positivity in the outer myoepithelial cells of cystic duct and the papilloma (Fig. 4B) and in the squamous cells, sebaceous gland cells, and basal marginal cells of the sebaceous gland lobules and nests (Fig. 4C). The clear cells were negative for GCDFP-15 staining.

Discussion

It is generally believed that benign mammary lesions show a mixture of epithelial and myoepithelial cells. Immunohistochemical studies of the breast using EMA have demonstrated positivity along the luminal borders of the epithelial cells [3], while cytokeratin 14 staining has shown positively reactive myoepithelial cells [4]. In the present report, the use of EMA as an epithelial marker and of cytokeratin 14 to detect myoepithelial cells yielded identical results. These findings confirmed the lesion to be an intraductal papilloma.

Table 1 Immunohistochemical staining results *EMA* epithelial membrane antigen; *GCDFP-15* gross cystic disease fluid protein-15

	Cytokeratin 14	EMA	GCDFP-15
Sebaceous cells (skin)	+	+	—
Apocrine cells (skin)	—	+	+
Metaplastic sebaceous cells (mammary)	+	+	—
Metaplastic apocrine cells (mammary)	—	+	+
Epithelial cells (mammary)	—	+	+ ^a
Myoepithelial cells (mammary)	+	—	—

^aA few positive

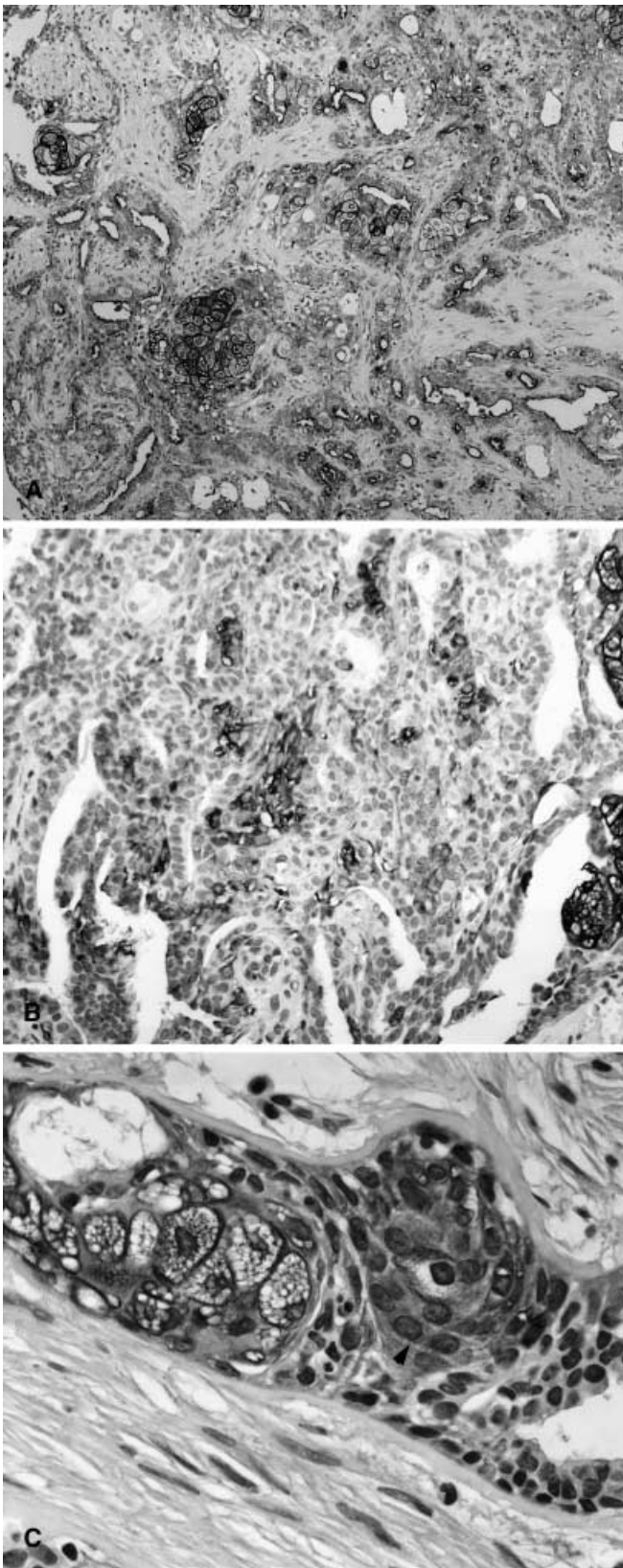


Fig. 4 **A** Sebaceous gland cells and the apical region of the inner epithelial cells are positive for epithelial membrane antigen (EMA). (Immunohistochemical staining, $\times 100$). **B** The outer myoepithelial cells are positive for cytokeratin 14 (Immunohistochemical staining, $\times 250$). **C** Sebaceous gland cells, basal marginal cells of the sebaceous gland lobules, and squamous cells are positive for cytokeratin 14. Arrowhead shows intercellular bridges. (Immunohistochemical staining, $\times 500$)

Squamous differentiation, as evidenced by the histologic findings and a strong reaction with cytokeratin 14, was noted in certain areas of the tumor. However, the origin of squamous cells remains controversial. Given that cytokeratin 14 is expressed in both metaplastic squamous epithelium and myoepithelial cells of the tumor, the present finding demonstrated that metaplastic squamous differentiation in the breast initially involved the myoepithelial cells [9].

We found that EMA and cytokeratin 14 were strongly reactive with metaplastic sebaceous gland cells, which is similar to findings of previous studies [5, 7]. The origin of the metaplastic sebaceous gland cells remains unclear. Cytokeratin 14 expression both in metaplastic squamous cells and sebaceous gland cells suggested an association between sebaceous gland metaplasia and squamous metaplasia of the intraductal papilloma of the breast. Therefore, sebaceous gland metaplasia of the intraductal papilloma may represent a variant of squamous metaplasia. Moreover, given that breast glands are modified skin glands, the metaplastic sebaceous gland cells may be from mammary stem cells with a pluripotentiality of differentiation.

In addition, clear foamy cells showing apocrine differentiation were usually found in the breast lesion. This change was described by Damiani and colleagues in their recent study [1]. However, the clear cells were negative for GCDFP-15 staining in this study and, thus, the possibility of apocrine differentiation of these cells could be ruled out.

To our knowledge, only five previous publications have mentioned sebaceous differentiation within a breast lesion, which were all found in primary breast carcinoma [6, 8, 10, 11, 12]. This study is the first report of sebaceous gland metaplasia arising within an intraductal papilloma, a benign lesion of the breast. This report confirms a new type of metaplasia of the breast, aside from apocrine and squamous metaplasia, both of which have been well demonstrated.

Acknowledgements The authors wish to thank Mr. J. Anbo, Mr. N. Yamada (Division of Pathology, Central Clinical Laboratory, Iwate Medical University), and Mr. S. Nakajima (Photo Center, Iwate Medical University), for their excellent technical support.

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