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A Case of Carcinoma with Apocrine Differentiation of the Breast; Cytopathological Analysis and A Consideration to The Pathogenesis

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ABSTRACT

We report a rare case of invasive carcinoma with apocrine differentiation (apocrine carcinoma) in 86-year-old female presenting a breast lump. The tumor had a characteristic steroid receptor profile being estrogen (ER)-negative, progesterone (PR)-negative and androgen (AR)-positive, and classical apocrine morphology in at least 90% of the tumor. Cytopathological analysis of this neoplasm using fine needle aspiration cytology and core needle biopsy clarified characteristic morphology of the apocrine carcinoma, and immunohistochemical profiles made clear differential diagnosis of the apocrine carcinoma from resemble lesions with eosinophilic granular cells such as carcinoma with oncocytic pattern, granular cell tumors and histiocytic proliferation.

Pathogenesis of carcinoma with apocrine differentiation is unknown. Occurrence of apocrine cells in the neoplasm of the breast has been regarded as through metaplastic processes. In this case, the tumor was constituted by uniform cells with apocrine morphology. Importantly, co-existence of other tumor types or lesions like apocrine ductal carcinoma in situ (DCIS) was not present. The evidence implies that histogenesis of the apocrine carcinoma in the present case was through the rout directly developed from some native cells originated in fetal breast tissue or through the rout directly transformed cells from some normal adult cells in the mammary gland.

INTRODUCTION

Invasive apocrine carcinoma was first documented by Krompecher in 1916 [1]. Carcinoma with apocrine differentiation is a rare subtype, constituting about 1% of all breast carcinomas [2]. The 2019 edition of the WHO Classification of Breast Tumors utilizes the term “carcinoma with apocrine differentiation” to describe tumors with specific morphology by large cells with abundant eosinophilic granular cytoplasm and enlarged nucleoli resembling apocrine sweat glands [3]. Furthermore, apocrine morphology in > 90% of tumor cells is determined as an essential criteria, and estrogen (ER)-negative, progesterone (PR)-negative and androgen (AR)-positive steroid receptor profile is also regulated as a desirable diagnostic criteria [3]. Patients with this tumor type tend to be older than those with invasive ductal carcinomas [4]. Most carcinomas with apocrine differentiation are known

to occur sporadic. However, some carcinomas in patients with germ line phosphatase and tensine homolog (PTEN) mutation (Cowden syndrome) are suggested to have apocrine morphology [5].

Architecturally, most examples of carcinoma with apocrine carcinoma resemble breast carcinoma of no special type (NST), with a predominant solid growth pattern. Carcinomas with apocrine differentiation express gross cystic disease fluid protein (GCDFP)-15 [6], an antigen also found in apocrine metaplasia. For the apocrine carcinoma, AR is consistently expressed in the carcinoma cells [7]. AR activation is known to associate with human epidermal growth factor receptor (HER)2 overexpression and /or erb-b2 receptor tyrosine kinase 2 (ERBB2) amplification in 30-60% of cases [8]. Furthermore, glutamyl-tRNA amidotransferase subunit (GATA)3 is expressed in 90% of carcinomas with apocrine morphology [9].

A variety of benign apocrine lesions include apocrine metaplasia in cystic change, apocrine change in sclerosing adenosis and atypical apocrine hyperplasia. As for malignant apocrine lesions, apocrine ductal carcinoma in situ (DCIS), encapsulated apocrine papillary carcinoma and apocrine lobular carcinoma in situ are known [10,11]. These lesions are also suggested to concern apocrine metaplasia [12-14]. Presumably, some of them are related to the development of apocrine carcinoma. Pathogenesis of the carcinoma with apocrine differentiation is not known. Cytopathological analysis of apocrine carcinoma and related lesions must be important for understanding of pathogenesis of apocrine carcinoma. However, such studies have been limitedly done [15-17].

CASE PRESENTATION

86-year-old woman was referred to the Department of Endocrine Surgery of Ogaki Tokushukai hospital for a lump in her left breast. Her medical history was unremarkable. As a family history, her mother died of breast cancer. The patient noticed a mass in her left breast 1.5 years ago. On the examination of our hospital, an elastic hard tumor with poor mobility 42 mm in diameter was recognized in the upper inner quadrant of the left breast. Mammography test showed irregular, high dens mass 42mm in size with obscured margins. Ultrasonography images proved irregular, hypoechoic mass 42.5 x 33.2 x 20.3mm in size with indistinct margins (Figure A1). Computed Tomography (CT) examination proved, a well-circumscribed oval lesion in her left breast (Figure A2). Fine needle aspiration cytology (FNAC) (mammotome needle biopsy under ultrasound guidance) from the breast mass yielded moderately cellular smears composed of loosely cohesive clusters of large, polygonal cells with abundant, basophilic and granular cytoplasm on Papanicolau stain. The nucleus was centrally placed, vesicular, moderately pleomorphic and displayed prominent nucleoli with irregular nuclear borders. The cells in clusters showed distinct cell margins with nuclear overlapping. Few binucleate forms were also present (Figure A3). Subsequently, core needle biopsy (CNB) (echo-guided mammotome biopsy) was done. Microscopic examination showed ill circumscribed tumor mass composed of cells arranged in nests or sheets. They were round to oval polygonal cells, with abundant granular eosinophilic cytoplasm and round to oval nucleus with variably prominent nucleoli (Figure A4). These evidences by FNAC and CNB clearly clarified that all the tumor cells were of apocrine type with non-apocrine ductal cells. The tumor cells were infiltrating the surrounding fibrofatty tissue.

Immunohistochemically, GCDFP-15 was positively expressed in the tumor (Figure B1). The tumor cells had a characteristic steroid receptor profile that was ER-negative, PGR-negative and AR-positive (Figure B2). HER2 was weakly positive. GATA3 was expressed in 90% of carcinoma cells (Figure B3). Furthermore, the tumor cells were positive for cytokeratin (E-cadherin) (Figure B4). Expression of S-100 and CD68 was negative.

Lumpectomy of the tumor was performed 1.5 months later after the CNB. Size of tumor was identical to that by the ultrasonography image. Histology of the tumor nodule was same as the that of the biopsy. Morphology and immunohistochemical profile of the tumor cells resected by the lumpectomy was also similar to that of the biopsy. The nuclei were enlarged and round to oval, with marked or moderate atypia and prominent nucleoli. The predominant growth pattern was solid. The mitotic activity was moderate. Average score of the raveling indices of ki-67 was approximately 10%. Consequently, the carcinoma was regarded as grade 2 type. Lymph node metastases of the carcinoma was confirmed in 3 lymph nodes out of the 21 left axillary lymph nodes.

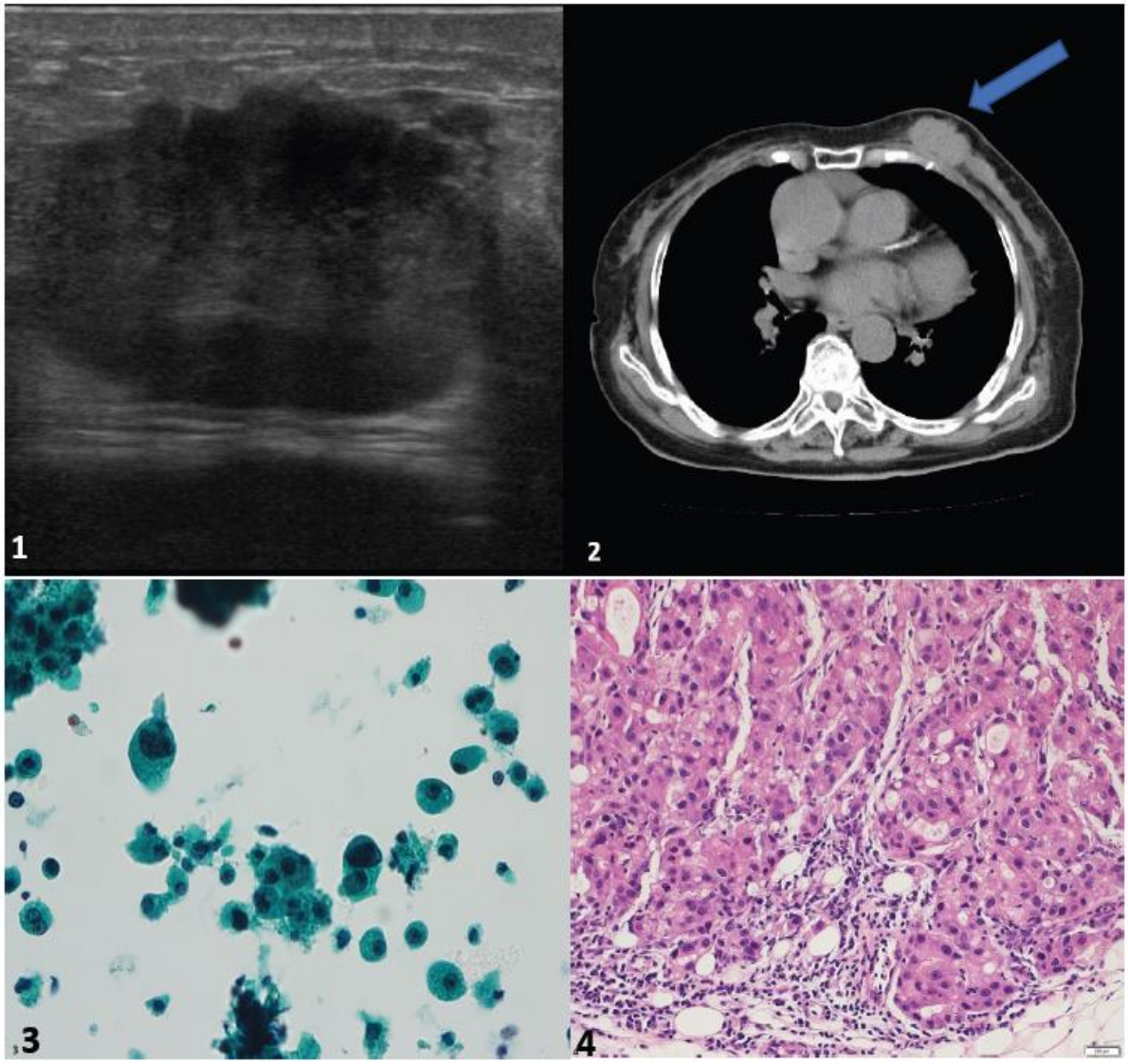

Figure A1: Ultrasonography image of tumor. Hypoechoic mass 42.5 x 33.2 x 20.3mm in size with indistinct margins is seen.

Figure A2: Enhanced CT shows a circumscribed mass in her left breast (arrow).

Figure A3: FNAC from the breast mass. Clusters of large, polygonal cells having nuclei with prominent nucleoli and abundant basophilic and granular cytoplasm are seen.

Figure A4: Histology of carcinoma with apocrine differentiation. The cells have abundant granular eosinophilic or vacuolated cytoplasm.

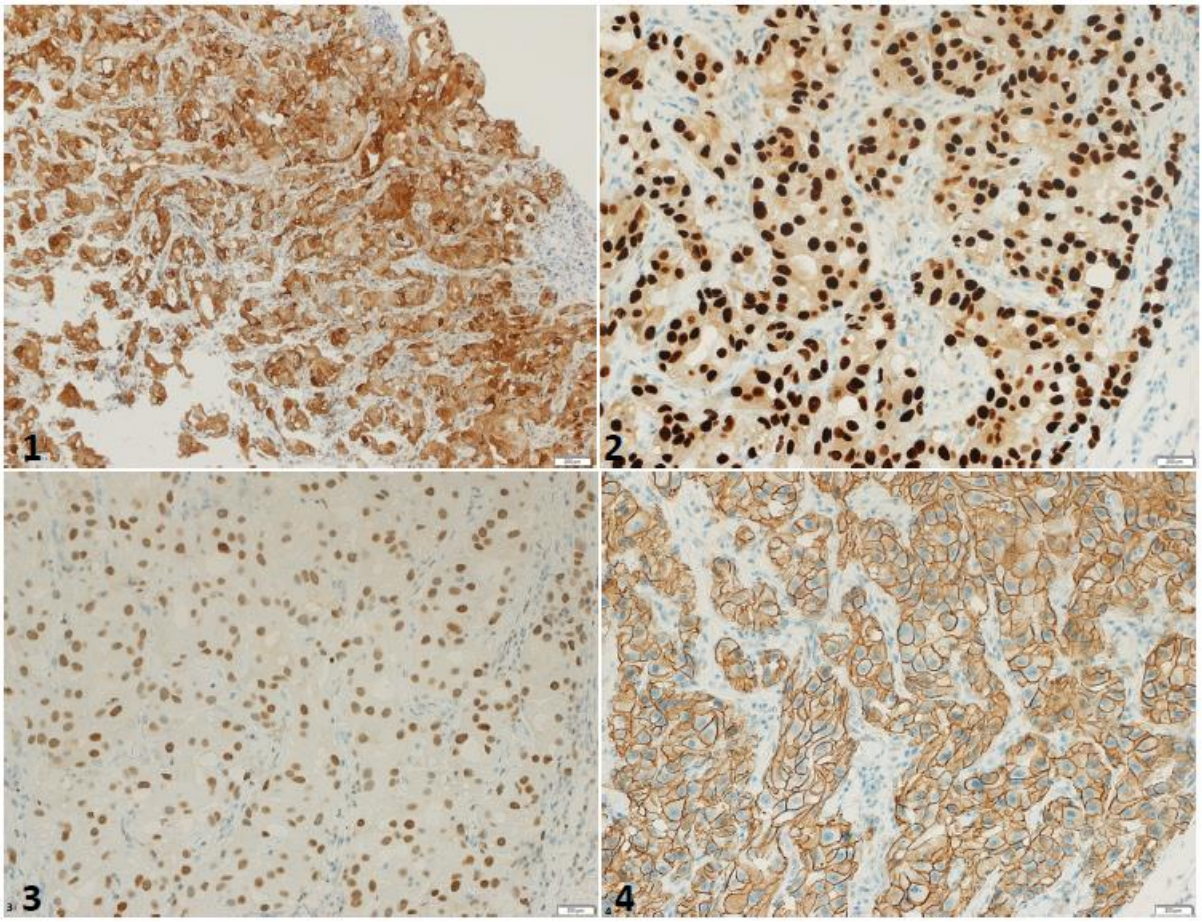

Figure B1: Immunohistochemistry for GCDFP-15 showing positive cytoplasmic staining.

Figure B2: Immunohistochemistry for AR showing strong positive nuclear staining.

Figure B3: Immunohistochemistry for GATA3 showing positive nuclear staining.

Figure B4: Immunohistochemistry for E-cadherin showing positive cell membrane staining.

DISCUSSION

The diagnosis of apocrine carcinoma on FNAC at all times poses problems on account of its cytomorphological mimicker's like apocrine metaplasia, apocrine adenosis, apocrine DCIS and apocrine carcinoma. At any rate, cytopathological features of the present case of apocrine carcinoma was fundamentally identical to the previous reports [15-17]. The diagnosis on FNAC was substantiated by subsequent CNB. Immunohistochemical profile of the present case was also identical to that was indicated in the current WHO classification [3]. Differential diagnosis of the present apocrine carcinoma from the resemble lesions of breast carcinoma with oncocytic pattern, granular cell tumors and histiocytic proliferation, all of which have eosinophilic granular cells, was made by morphology of cytoplasm and nucleus, and immunohistochemical profile of cytokeratin (AE1/AE3) (+), GCDFP-15 (+), ER (-), PR(-) AR(+), S-100(-), CD68(-) and GATA3(+). Furthermore, positive response of E-cadherin denied possibility of the invasive lobular carcinoma with apocrine differentiation.

An apocrine epithelium is frequently observed in the breast lesions, but the biological significance and the mechanism by which this particular cellular feature is produced remain obscure. The occurrence of apocrine cells

in the breast has been regarded to concern the metaplastic process [12-14]. Apocrine epithelium of the breast is assumed to reflect a metaplastic alteration in epithelial structures of the terminal duct-lobular units and has been intensely studied for a possible relationship to cystic disease of the breast and breast carcinoma [18]. Nonetheless, the relationship of apocrine metaplasia to the breast cancer is unclear, and the histogenesis of the carcinoma with apocrine differentiation is not known.

However, considering the previous references [11,18,19], following pathways may be appropriate for the pathogenesis; (1) developing through metaplastic process, (2) developing from some native apocrine cells [18]; (3), developing from both routes. Regarding metaplastic pathways, some benign apocrine lesions like apocrine metaplasia in cystic change, apocrine adenosis and atypical apocrine hyperplasia as well as malignant lesions such as apocrine DCIS and encapsulated apocrine papillary carcinoma have been assumed to be indirect or direct precursor lesions for the apocrine carcinoma. Meanwhile, there have been many studies examining the possible relationship of apocrine differentiation, especially apocrine cysts, to breast carcinoma, however, the data remain inconclusive. Furthermore, several authors have investigated breasts with and without carcinoma and found no significant differences in the frequency of apocrine epithelium [20-23].

Jones et al. [19] performed molecular cytogenetic comparison in benign apocrine hyperplasia with apocrine DCIS and invasive apocrine carcinoma. The most common alterations in apocrine hyperplasia were gains of 2q,13q and 1p and losses of 1p,17q, 22q, 2p, 10q, and 16q. Apocrine DCIS and invasive carcinomas showed gains of 1q, 2q, 1p, and losses of 1p, 22q, 17q and 16q as their most common DNA copy number changes. The data suggest that some apocrine hyperplasia is a putative nonobligate precursor of apocrine carcinoma.

Viacava et al. [18] analyzed 10 autopsy specimens of female breasts from fetuses between 28 and 40 weeks of gestational age and tissue from 6 normal breasts, obtained after breast reduction in nulliparous young women between 22 and 28 years of age. They concluded that apocrine epithelium of the breast is a normal process of differentiation rather than metaplasia.

The term “pure apocrine carcinoma” has been used to define tumors characterized by ER and PR receptor negative status, and apocrine morphology in at least 90% of the tumors. Nevertheless, cells like apocrine DCIS with intermediate or high nuclear grade features may co-exist in apocrine carcinoma like that DCIS co-exists in NST [10]. In the present case, co-existence of other tumor types including apocrine DCIS or other lesions were not noticed. The evidence implies that histogenesis of the apocrine carcinoma in the present case was through the rout directly developed from the native apocrine cells originated in fetal breast tissue or through the rout directly transformed cells from some normal adult mammary gland tissue [18].

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