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Case Report

Primary breast acinic cell carcinoma and concurrent carcinoma arising from microglandular adenosis

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Abstract: Primary acinic cell carcinoma (ACC) of breast is a rare salivary gland-like tumor. It shows diffuse infiltrative growth pattern with small acinar or glandular structures, and sometimes with microglandular background. As the overlapping morphological features of mammary ACC and microglandular carcinoma, whether the two lesions form part oriented from same histological spectrum was still a question. Herein, we presented an extremely rare case of breast primary ACC and concurrent carcinoma arising from microglandular adenosis (MGACA) in a 41-year-old woman, indicating the close relationship between them. We also found claudin-low expression in MGACA in this case which was not reported before in literatures.

Keywords: Breast, acinic cell carcinoma, microglandular adenosis, claudin-low

Introduction

Primary acinic cell carcinoma (ACC) of breast is a rare salivary gland-like tumor, firstly reported by Roncaroli et al in 1996 [1]. Its histological pattern was diffuse infiltrative growth with small acinar or glandular structures, sometimes with microglandular background.

As the overlapping morphological features of mammary ACC and microglandular carcinoma, whether the two lesions form part from same histological spectrum was still a question. We herein present an extremely rare case of co-occurrence of breast primary ACC and carcinoma arising from microglandular adenosis (MGACA). To our best knowledge, this is the third case describing this phenomenon presented in English literatures [2, 3]. We also found claudin-low expression in MGACA in this case which was not reported before.

Case presentation

The patient was a 41-year-old woman, presented with a non-tender, hard and movable node in her right breast. She had a 20 years history of hepatitis B and 5 years history of hyperthyroidism, but family history of breast cancer or other cancers were unremarkable.

Immunohistochemical analysis was performed on 4-μm-thick sections utilizing standard protocols on a Ventana Benchmark XT autostainer.

Mammographic imaging showed a small oval radiopaque mass in the upper outer quadrant of the right breast. An ultrasound guided core needle biopsy (CNB) was performed, histology showed invasive carcinoma, arranged in solid, nests and cords (**Figure 1A**), along with focal central necrosis (**Figure 1B**) and accompanied with some areas of glandular structures. The glandular structures were well formed, with open lumina which containing eosinophilic materials (**Figure 1C**); and the lumen cells exhibiting some coarse eosinophilic granules (**Figure 1D**). Both tumor cells were ER negative, PR negative, HER2/neu negative (triple-negative), and myoepithelial markers negative, but S-100 positive on immunohistochemistry (**Figure 1E**, **1F**). Glandular structures were strong positive for lysozyme, but the invasive carcinoma was negative for it (**Figure 1G**, **1H**). Ki-67 positive were seen in 10% and 40% of

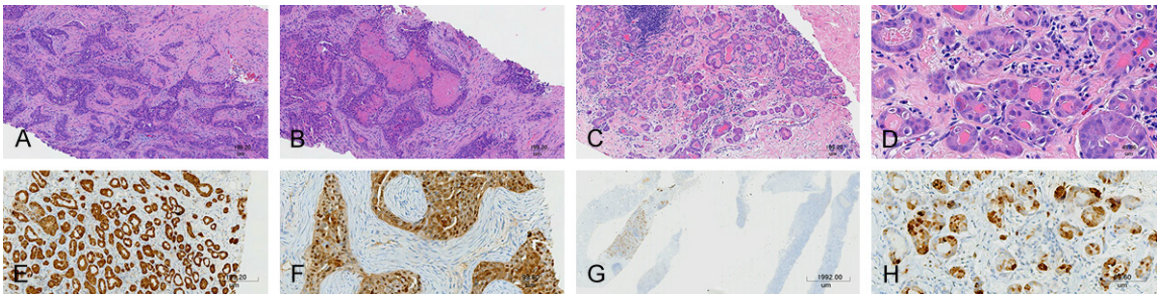

Figure 1. CNB specimen. Hematoxylin and eosin staining (HE) (A-D), immunohistochemistry (IHC) (E-H). (A) The invasive carcinoma was arranged in solid nests and cords. (B) The invasive carcinoma cells with focal central necrosis. (C) The glandular structures were well formed, with open lumina which containing eosinophilic materials. (D) The lumen cells exhibiting some coarse eosinophilic granules. (E and F) Both tumor cells were S-100 positive. (G and H) Glandular structures were strong positive for lysozyme, but the invasive carcinoma was negative for it.

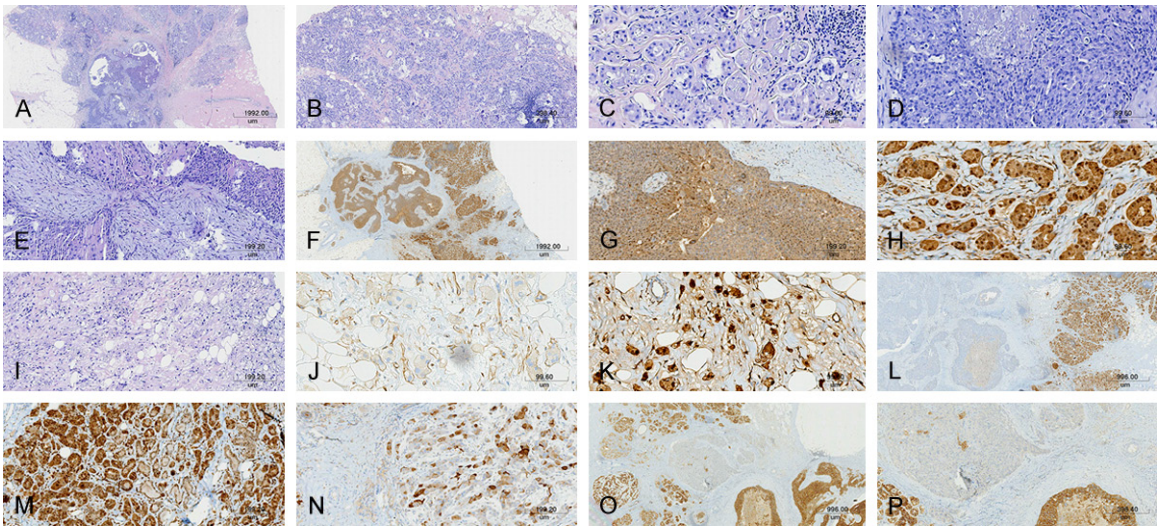

Figure 2. Segmental mastectomy specimen. HE staining (A-E, I), IHC (F-H, J-P). (A) The tumor showed two morphologically distinct cell populations on microscopy. (B) One cell-population was characterized by acinar, glandular and microglandular structures, distributed in the fibrofatty stromal. (C) The cytoplasm was often vacuolated with moderate, pale or weakly eosinophilic stain. (D) The other cell-population was variable size clusters of tumor cells arranged in solid nests and cords with poorly differentiated carcinoma cells. (E) Scattered cells exhibited eosinophilic cytoplasm and apoptotic nuclear, indicating chemotherapy change. (F-H) Both of the cell-population was diffuse positive for S-100. (I) Among the first cell-population, there are some microglandular structure areas. (J) The MGA area contained collagen IV positive clear basement membrane. (K) The MGA components were strong positive for S-100. (L and M) The ACC area was strong positive for lysozyme. (N) The ACC area was positive for GCDFP-15. (O and P) The second population cells with the same focal negative for Claudin1, 3, 4, 7.

cells of glandular and invasive carcinoma respectively.

Segmental mastectomy surgery was performed after four-cycle neoadjuvant chemotherapy with TC (paclitaxel and cyclophosphamide). The tumor was measured 1.2 × 1.0 cm, it showed two morphologically distinct cell populations on microscopy (**Figure 2A**). One cell-population was characterized by acinar, glandular and microglandular structures, distributed in the fibrofatty stromal (**Figure 2B**); cytoplasm was often vacuolated with moderate, pale or weakly eosinophilic stained (**Figure 2C**). In some glandular structures of this cell-population, nuclear atypia was obvious, and some lumens of the glands contained dense colloid-like eosinophilic materials noted in the CNB specimen described above. The other cell-population was variable size clusters of tumor cells arranged in solid nests and cords. Poorly differentiated carcinoma cells exhibited with high-grade nuclei,

abundant mitotic figures, and apoptotic changes (**Figure 2D**). Scattered cells exhibited eosinophilic cytoplasm and apoptotic nuclear, indicating chemotherapy change (**Figure 2E**).

Both of the cell-population were triple-negative for ER, PR, Her-2/neu and negative for myoepithelial markers, epidermal growth factor receptor (EGFR) and GATA-binding protein-3 (GATA-3), but diffuse positive for S-100 (**Figure 2F-H**).

Among the first cell-population, some microglandular structure areas (**Figure 2I**) strong positive for S-100 (**Figure 2K**), contained collagen IV positive clear basement membrane (**Figure 2J**); but the other areas lack of it. As for the morphologic and immunohistochemistry features, diagnose of microglandular adenosis (MGA) was made. The latter area, which negative for myoepithelial markers and basement membrane markers, was strong positive for lysozyme (**Figure 2L**, **2M**) and GCDFP-15 (**Figure 2N**), and part of it expressed with glandular structure, was diagnosed with ACC. Ki-67 positive cells were seen in less than 1% or about 20% of the tumor cells in these two areas. There were no distinctions of claudin1, 3, 4, 7 expression between the two components, which were either high or low expression.

The second population cells were diffuse positive for CK5/6 and S-100, with the same focal negative for Claudin1, 3, 4, 7 (**Figure 2O**, **2P**). The whole population was negative for collagen, lysozyme (**Figure 2I**) and GCDFP-15; ki-67 positive was seen in 40% cells. Because the presence of MGA, we inferred this population as MGACA, probably is a basal-like cell type with focal claudin-low expression.

Total of four-cycle adjuvant chemotherapy with TC regimen was given after surgery, the patient was disease-free from last follow-up at 13th month.

Discussion

ACC is characterized by acinic cells presenting zymogen-type secretory granules in cytoplasma. However; the spectrum of architectural and cytological features in ACC of the salivary gland is much broader. Architectural growth patterns are divided into solid, microcystic, papillary-cystic, and follicular. The cellular features are identified as acinar, intercalated ductal, vacuolated, clear, and non-specific glandular.

Peintinger et al [4] described the different points of MGA, pointing out that ACC of the breast has a microglandular growth pattern, luminal eosinophilic colloid-like secretory materials, and diffuse and intense positive immunoreactivity for the S-100 protein. These features are similar to MGA. However, ACC shows immunoreactivity for EMA, lysozyme, amylase, and α-1-antichymotrypsin, while the glands in MGA are surrounded by a basal lamina, the neoplastic glands of ACC do not possess a basal lamina.

In this case, the ACC components were identified as glandular, acinar and microglandular pattern, tumor cells were immunoreactive with anti-lysozyme, and contained electron-dense cytoplasmic globules, demonstrating the diagnosis. Furthermore, focally, the demonstration of basement membrane material peripherally around microglandular structures, incompatible with a pure acinic cell carcinoma, indicated MGA. Morphologically, the striking MGA gradually merged into ACC.

We also found another population of tumor cells in this case, which were arranged in solid, nests, cords of variable size. Poorly differentiated carcinoma cells exhibited with high-grade nuclei, abundant mitotic figures, and apoptotic cells. According to literatures [4, 5], ACC showed a diffuse infiltrative pattern with microglandular structures mixed with solid nests in some cases. Roncaroli et al [1] and Chang et al [5] found the central comedo-like necrosis in the solid tumor cell nests which cytologically and immunohistochemically closely similar to typical acinar cells. Pure ACC required triple-negative stain of both glandular and solid tumor cell populations, but strongly positive stain to lysozyme, α-1-antitrypsin, and EMA [5]. In this case, this population of tumor cells were triple-negative, negative to lysozyme, but strong positive to S-100, diffuse positive to CK5/6 and focal negative to Claudin1, 3, 4, 7, indicating it was a basal-like subtype breast cancer with focal claudin-low expression. Because of the presence of MGA, these features enable us reminiscent of MGACA.

No special type (NST) breast cancer is the most common type of MGACA, rare cases include

adenoid cystic carcinoma, carcinoma with secretory differentiation, squamous metaplasia, chondromyxoid metaplasia or basaloid features and matrix-producing carcinoma (MPC) etc. MPC is a rare subtype of metaplastic carcinoma, occurring in association with MGA [6, 7].

Through the combined analysis of murine mammary carcinoma models and human BCs, a new intrinsic subtype was described in 2007 [8]. The claudin-low subtype (CL), a unique feature of these tumors is lack of cell-cell adherens and tight junction genes, such as E-cadherin and claudins. Claudin-low tumors exhibit several characteristic features, including low expression of adherens and tight junction proteins, low level of luminal/epithelial differentiation, stem cell-like features, and a high frequency of metaplastic differentiation [9]. The presence of metaplastic carcinoma in MGACA made it associated with claudin-low breast cancers. In this case, focal claudin-low expression confirmed the relationship between them.

MGACA has dual luminal (CK8/18 expression) and basal-like (EGFR expression and triple negative) features, suggesting that MGACA does not fit well under any of the categories of the currently proposed molecular classification of the breast carcinoma [10]. In our experience, whether claudin-low type is suitable needs to be proven.

According to literatures, the relationships between ACC, MGA and MGA-associated lesions remain unclear [11]. Two related studies [2, 3] reported 2 cases of ACC arising in MGA, suggested a close relationship between the two lesions. R Kahn et al [2] reported a mammary carcinoma with features of both apparent acinic cell differentiation and microglandular carcinoma; they supposed these two morphologic entities may constitute part of a continuous spectrum. In Falleti et al's report, transition from areas of typical MGA into atypical area and imperceptibly merge into carcinoma is well evidenced by immunohistochemistry, suggesting that ACC might origin from MGA [3]. Huo et al reported two cases with coarse granules, exhibiting acinic cell features and MGA growth pattern coexisting, also suggesting a possible link between the two features [12]. Previous reports shown the pathogenesis of ACC is related to MGA [2, 4, 13, 14], but it is suspected by authors who presented 20 cases of carcinoma arising in MGA did not identify any acinic cell differentiation, despite the presence of overlapping immunohistochemical features [15]. Nevertheless, some of the morphological, immunohistochemical and ultrastructural features of these lesions are different, so a histogenetic link remains to be proven.

Damiani et al [13] reported two breast tumors and one salivary ACC which showed focally positive with GCDFP15, a marker of apocrine differentiation. Although expression of apocrine differentiation is not a feature of salivary gland ACC, but the mRNA of prolactin-inducible protein shares the same aminoacidic sequence of GCDFP15, has been found in normal acinar cells of salivary glands [16]. In one of L. Huo et al's two cases, the positive ER staining in the granular cells was against apocrine differentiation, therefore, they concluded that the cells with the coarse granules had morphological and immunohistochemical features distinct from apocrine cells [12]. In this case, although GCDFP15 was diffuse positive in the ACC, as for the dissimilarity of the morphology features, we also don't think ACC is associated with apocrine features.

In general, co-occurrence of ACC and MGACA is extremely rare even the relationship between them maybe tightness. We firstly described claudin-low components in MGACA, whether claudin-low type is suitable for describing MGACA is still needs to be proven.

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Disclosure of conflict of interest

None.

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