Metaplastic breast carcinoma producing prominent basal lamina with neuroendocrine differentiation: A case report

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Received December 30, 2022; Accepted February 21, 2023

DOI: 10.3892/mco.2023.2632

Abstract. Metaplastic breast carcinoma (MBC) is a heterogeneous group of invasive breast carcinomas (IBCs) characterized by the differentiation of the neoplastic epithelium toward squamous cells and/or mesenchymal-appearing elements. The present study describes the case of a 42-year-old woman who underwent a mastectomy and sentinel lymph node biopsy for two tumors in their left breast. One of the resected tumors was diagnosed as MBC with neuroendocrine (NE) differentiation and the other was diagnosed as IBC of no special type. The MBC tumor contained a matrix composed of basal lamina with a focal area of myxoid matrix and squamoid differentiation. To the best of our knowledge, the present study is the first report of MBC producing prominent basal lamina. The patient has remained alive and well for >10 years without recurrence, and has been treated with oral and injected anticancer drugs.

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Abbreviations: CA15-3, carbohydrate antigen 15-3; CEA, carcinoembryonic antigen; BCSS, breast cancer-specific survival; DFI, disease-free interval; EGFR, epidermal growth factor receptor; ER, estrogen receptor; GATA-3, GATA binding protein 3; HER-2, human epidermal growth factor receptor-2; IBC, invasive breast carcinoma; MBC, metaplastic breast carcinoma; MPC, matrix-producing carcinoma; mTOR, mammalian target of rapamycin; NE, neuroendocrine; NET, neuroendocrine tumor; OS, overall survival; PAS, periodic-acid Schiff; PD-L1, programmed death ligand 1; PgR, progesterone receptor; PI3K, phosphatidylinositol-3 kinase; SQ, squamous cell carcinoma

Key words: metaplastic breast carcinoma, basement membrane, neuroendocrine, chemotherapy

Introduction

Because carcinoma of the breast arises from the mammary glandular epithelium, it usually exhibits the features of adenocarcinoma. However, in <5% of breast carcinomas, some or all of the neoplastic cells acquire a nonglandular morphology and growth pattern by a process known as metaplasia (1). Metaplastic breast carcinoma (MBC) is a heterogeneous group of invasive breast carcinomas (IBCs) characterized by the differentiation of the neoplastic epithelium toward squamous cells and/or mesenchymal-looking elements (2). The clinical features of metaplastic carcinoma are similar to those of ER-negative IBC of no special type; however, metaplastic carcinomas are more likely to present at an advanced stage (2). MBCs are reported to have lower response rates to conventional adjuvant chemotherapy (2) and a worse clinical outcome compared to non-MBC carcinomas (3). We describe the pathological and immunohistochemical features of a patient with a rare MBC that produced prominent basal lamina with neuroendocrine (NE) differentiation, and we explain the course of its treatment.

Case Report

A 42-year-old Japanese woman with a history of hyperlipidemia was referred to Sodegaura Satsukidai Hospital (Sodegaura, Japan) in January 2010 with the chief complaint of a left breast tumor. The physical examination revealed no abnormalities except for a palpable elastic firm tumor in her left breast. There was no abnormal data including tumor markers such as CEA, CA15-3, and HER2 on laboratory findings. In the area that showed focal asymmetric density by mammography, two separate hypo-echoic masses with irregular surfaces

were revealed by mammary ultrasonography (Fig. 1A). The two tumors detected by MRI with contrast medium were a 14x14-mm internally heterogeneous ring-enhanced tumor under the nipple and a 16x15-mm internally homogenous enhanced tumor in the approximate center of the left breast, without lymph node swelling (Fig. 1B). Both tumors had spiculated margins and an irregular shape. An analysis of the shape of the time/signal intensity curves of the tumors revealed a washout curve in both tumors, and malignant tumors were thus suspected.

After fine-needle aspiration biopsy results confirmed the presence of IBC, we performed a mastectomy along with a sentinel lymph node biopsy for both tumors.

The patient's postoperative course was uneventful. She was discharged on the 10th postoperative day. Beginning at 1 month post-surgery, she received six cycles of CMF (cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 500 mg/m^2). Thereafter, she received four cycles of weekly paclitaxel (80 mg/m^2). She also took a daily oral dose of tegafur/gimeracil/oteracil potassium (300 mg/day) for 2 years. Although >10 years have passed since the patient's surgery, she is alive without recurrence.

On gross examination, the heterogeneous tumor was 12x11 mm, and the homogenous tumor was 17x15 mm (Fig. 1C). Microscopy ruled out lymph node metastasis, and the smaller heterogeneous tumor revealed the following unusual pathological characteristics. The shape of the tumor cells with hyperchromatic nuclei was polygonal, and the tumor cells' cytoplasm was eosinophilic. The tumor had eosinophilic matrix with no apparent osteocytes or osteoblasts (Figs. 2A and 3A). No obvious chondromatous matrix was observed. The eosinophilic matrix was hyalinized focally (Fig. 2A). In some areas, the tumor cells had myxoid matrix (Fig. 2D). Some tumor cells with dense eosinophilic cytoplasm, which had intercellular bridges without keratinization, seemed to have squamoid differentiation (Fig. 2E). In other areas, the tumor cells showed organoid nesting with rosette formation, and the tumor cells at the periphery of the nest were arranged in a palisading pattern (Fig. 2F). Necrosis was present in the center of the nest. These findings suggested NE morphology, but eosinophilic stroma was also observed.

The eosinophilic hyalinized matrix was positive for periodic-acid Schiff (PAS) stain (Fig. 3C), Alcian blue stain, and Masson's trichrome stain. Elastic and collagen fibers were stained with elastic Van Gieson's stain (Figs. 2B and 3B). Congo Red staining was negative, and the matrix did not show SATB2 immunostaining. The matrix was positive for laminin (Fig. 2C) and type IV collagen (Fig. 3D) but negative for CAM5.2 (Fig. 3E) and vimentin.

Table I summarizes the immunohistochemistry results of the tumor cells. The tumor cells with eosinophilic matrix exhibited diffuse immunoexpressions of CAM5.2 (Fig. 3E), CK 34 beta E12, S100, and SOX10 (Fig. 3F). CK 5/6, vimentin, CD56, alpha smooth muscle actin, and CD10 were focally positive. GATA binding protein 3 (GATA-3) was negative. The carcinoma with myxoid matrix showed CAM5.2, CK 34 beta E12, SOX10, and CD56-positive staining and focally positive staining of CK5/6, vimentin, and S100. The carcinoma with squamoid differentiation revealed immunoexpressions of CAM5.2, CK 34 beta E12, CK 5/6, S100, SOX10, and CD56; CK 5/6 was strongly positive and vimentin and CD10 were focally positive. However, p63 and desmocollin 3, which are markers for squamous cell carcinoma (SQ), were negative.

The tumor cells with NE morphology showed diffuse and strong CD56 staining whereas synaptophysin and chromogranin were negative. The tumor cells with NE morphology were also positive for CAM5.2, CK 34 beta E12, and SOX10, and negative for CK 5/6 and vimentin. We diagnosed this component as carcinoma with NE differentiation; carcinoma with squamoid differentiation was excluded because CK5/6 was negative. Inflammatory cells including plasma cells and lymphocytes proliferated in the stroma.

The matrix of this case was thought to be basement lamina, because the laminin and type IV collagen were positive. Squamoid differentiation was suspected based on the presence of intercellular bridges, but SQ was excluded based on the negative p63 and desmocollin 3 immunostaining. In light of these results, we diagnosed this tumor as MBC producing prominent basal lamina with NE differentiation. The following percentages were determined: basal lamina-producing carcinoma, 45%; carcinoma with myxoid matrix, 5%; carcinoma with squamoid differentiation, 20%; and carcinoma with NE differentiation, 30%.

The larger, homogeneous tumor showed tubular formation and scirrhous carcinoma and contained myxoid matrix, but it did not contain eosinophilic hyalinized matrix. The tumor cells were positive for CAM5.2, CK 34 beta E 12, and CK 5/6 but negative for laminin, type IV collagen, alpha smooth muscle actin, and vimentin. S100, CD10, and CD56 were focally positive. GATA-3 was positive. We diagnosed this tumor as IBC of no special type.

Both tumors showed negative estrogen receptor (ER) and human epidermal growth factor-2 (HER2) immunostaining and were negative for progesterone receptor (PgR) with the exception of the basal lamina-producing carcinoma, which exhibited focal immunoexpression of PgR. The histological grade of both tumors was grade 3. Because the smaller tumor produced basal lamina and was GATA-3-negative but the larger tumor did not produce basal lamina and was GATA-3-positive, we speculated that the patient had multiple simultaneous ipsilateral primary carcinomas. The UICC (Union for International Cancer Control) TNM classification was stage Ia (T1cN0M0).

Discussion

The tumor cells of this patient's case were polygonal-shaped, and there was an eosinophilic substance around the tumor cells. Because SATB2 [which is specific for osteoblastic differentiation (4)] was negative, osseous differentiation was excluded. The negative Congo Red staining result excluded the possibility of amyloid deposition. The patient's breast carcinoma was confirmed to produce laminin and type IV collagen around tumor cell nests and around each tumor cell.

The intercellular accumulation of an enormous amount of basal lamina material has been reported in adenoid cystic carcinomas (5), pleomorphic adenomas (6), myoepithelial carcinomas (7), ovarian clear cell carcinomas (8), hepatoid yolk sac tumors (9), and skin tumors (10). The tumor cells showed myoepithelial characteristics and produced redundant base-

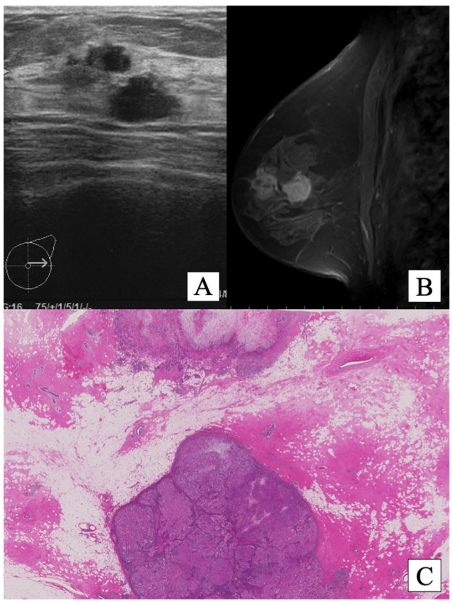

Figure 1. (A) The two separate hypo-echoic masses with irregular surfaces as revealed by ultrasonography. (B) MRI with contrast medium revealed an internally heterogeneous tumor and an internally homogenous tumor. (C) There were two separate nodules. The size of one nodule was 12x11 mm (lower tumor), and the size of the other was 17x15 mm (upper tumor). Magnification: x0.9.

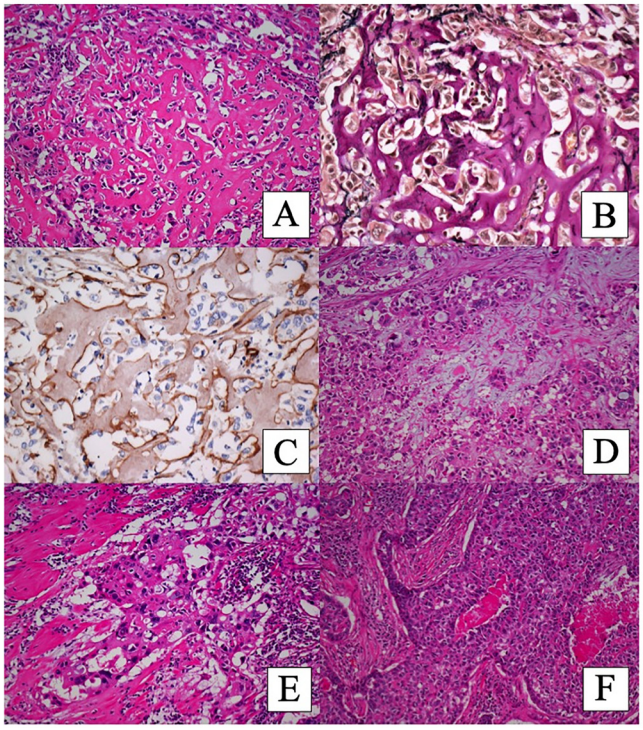

Figure 2. (A) The smaller, heterogeneous tumor had eosinophilic, thickly woven fiber-like stroma. Although there were no apparent osteocytes or osteoblasts, the stroma looked like osseous matrix (x10). (B) Elastic and collagen fibers proliferated in the stroma (Van Gieson's stain, x20). (C) The eosinophilic hyalinized matrix was positive for laminin, showing that the tumor cells produced prominent basal lamina (x20). (D) The tumor cells had myxoid stroma. No obvious chondromatous matrix was observed (x10). (E) Carcinoma with squamoid differentiation. Intercellular bridges were identified; keratinization was not observed (x10). (F) Carcinoma with neuroendocrine differentiation. The tumor cells showed organoid nesting, and the tumor cells at the periphery of the nest were arranged in a palisading pattern. There was necrosis in the center of the nests (x10).

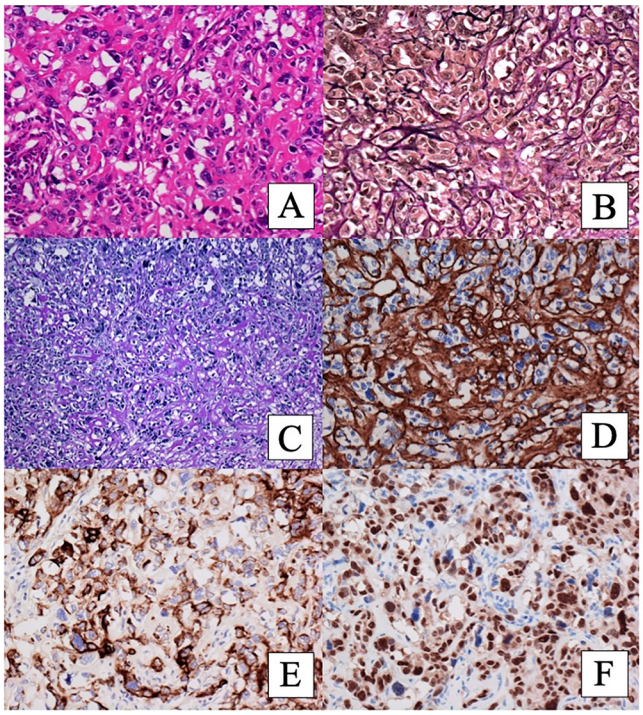

Figure 3. (A) The tumor had eosinophilic cytoplasm, and eosinophilic, thick hyalinized matrix was suspected to exist around the tumor cells (x20). (B) Elastic fibers proliferated in the stroma, but the proliferation of collagen fibers was minimal (Van Gieson's stain, x20). (C) Periodic-acid Schiff stain was positive in the stroma (x10). (D) The eosinophilic hyalinized matrix was positive for type IV collagen, showing that the tumor cells produced prominent basal lamina (x20). (E) The cytoplasm of the tumor cells showed staining for CAM5.2 but the eosinophilic hyalinized stroma was negative for CAM5.2, clearly indicating that the tumor had hyalinized matrix (x20). (F) The nuclei of tumor cells revealed strong immunoexpression of SOX10, showing that the tumor cells had myoepithelial differentiation (x20).

ment membrane (5-7). The myoepithelial cells of the normal human breast gland contribute to the formation of basement membrane, and the myogenic differentiation of these cells is responsible for the contractile phenotype (11). Extracellular material is responsible for maintaining the proper polarity of the epithelial cells (12). Tumor-derived myoepithelial cells are negative for laminin and deficient in the ability to confer polarity to luminal epithelial cells (13). We have found no English-language reports of breast carcinoma that mention myoepithelial differentiation and redundant basement membrane in the same patient. The present report thus appears to be the first description in the English literature of breast carcinoma that produced redundant basal lamina material. There are also no comparative morphology or immunohistochemistry studies of this topic.

The World Health Organization (WHO) classification published in 2003 defined malignant myoepithelioma (myoepithelial carcinoma) as an infiltrating tumor composed of myoepithelial cells with identifiable mitotic activity (14). The immunohistochemistry of the tumor cells of the present patient's case showed myoepithelial differentiation such as expressions of CD10, SOX10, and S100. Two different tumor-related matrices are noted in myoepithelial carcinoma in a salivary gland: myxoid and hyalinized. Our patient's tumor had both myxoid and hyalinized tumor-related matrices.

Table I. The immunohistochemistry results of the two tumors.

	Tumor 1				
Antibodies	Basal lamina	Myxoid	Squamoid	NE	Tumor 2
CAM 5.2	+	+	+	+	+
CK 34 beta E12	+	+	+	+	+
CK 5/6	Focal	Focal	+	-	+
p63	-	-	-	-	-
Desmocolin 3	-	-	-	-	-
Vimentin	Focal	Focal	Focal	-	-
S100	+	Focal	+	-	Focal
SOX10	+	+	+	+	+
CD10	Focal	-	Focal	-	Focal
SMA	Focal	-	-	-	-
CD56	Focal	+	+	+	Focal
Synaptophysin	-	-	-	-	-
Chromogranin A	-	-	-	-	-
GATA3	-	-	-	-	+
ER	-	-	-	-	-
PgR	Focal	-	-	-	-
HER2	-	-	-	-	-
Type IV collagen	+	+	+	+	-
Laminin	+	+	+	+	-

Basal lamina, carcinoma with prominent basal lamina; ER, estrogen receptor; HER2, human epidermal growth factor-2; Myxoid, carcinoma with myxoid stroma; NE, carcinoma with neuroendocrine differentiation; PgR, progesterone receptor; SMA, alpha smooth muscle actin; Squamoid, carcinoma with squamoid differentiation.

These findings suggested that the tumor was myoepithelial carcinoma. The formation of type IV collagen-positive basal lamina around tumor cells was reported in a patient with myoepithelial carcinoma of a salivary gland (7); however, myoepithelial carcinoma of the breast is merged with MBC in the recently published WHO classification of breast tumors (2).

Historically, the term matrix-producing carcinoma (MPC) was applied to a subgroup of MBCs defined as invasive breast carcinoma with a direct transition of carcinoma to a cartilaginous or osseous matrix without the presence of intervening spindle cells (2). Such tumors are now classified as MBC with heterologous mesenchymal components (including chondroid, osseous, rhabdomyoid, and even neuroglial differentiation) in the recently published WHO classification of breast tumors (2). MBC with heterologous mesenchymal differentiation was suspected in the present patient, but its morphology differed from that of chondroid differentiation, and the negative SATB2 immunostaining excluded the possibility of osseous differentiation.

MBCs are a heterogeneous group of IBCs characterized by differentiation of the neoplastic epithelium toward squamous cells and/or mesenchymal-appearing elements, including but not restricted to spindle, chondroid, and osseous cells (2). An MBC can be monophasic with only one metaplastic component or biphasic with two or more components. The tumor in the present case was a biphasic MBC with squamoid differentiation of the tumor cells and redundant basal lamina material around the tumor nests and around each tumor cell. This case showed both the triple-negative (ER, PgR, HER-2) immunophenotype that has been reported in the vast majority of MBCs (15) and the negative GATA-3 expression that has been described in MBC (16).

MBC patients with a high proportion of triple-negative breast carcinoma have shown lower overall survival (OS) than non-MBC patients (3). For MBC patients, the use of radiation therapy and chemotherapy is associated with improved OS (17). The MBC subtype (i.e., MPC, squamous, mixed squamous/spindle, and spindle carcinoma) was reported to be an independent prognostic variable associated with breast-cancer-specific survival (BCSS) and the disease-free interval (DFI) (18). Notably, MPC was reported to have a better prognosis than other subtypes of MBC. Among the subtypes of MBC, both the mixed squamous/spindle type and the spindle type, which have aggressive biological behavior, were associated with worse prognosis (18). Future advances in molecular biology and molecular genetics may elucidate these differences in the prognosis of MBC subtypes.

Neuroendocrine carcinoma is an invasive carcinoma characterized by high-grade NE morphology and a diffuse immunoreactivity for NE markers. Because carcinoma with NE differentiation is one of components of this tumor, we did not diagnose this case as neuroendocrine carcinoma, but IBC with NE differentiation (19,20). There is no specific therapy targeting NE differentiation, and all IBCs with NE

differentiation are treated similarly to other IBCs (21). Patients with neuroendocrine tumors (NETs) of the breast treated with endocrine therapy and radiotherapy had longer OS than those who did not receive treatment, whereas patients who were treated with chemotherapy had lower OS than those who were not, because of the non-defined regimen and the poor response itself (22).

After our patient's surgery, we chose to treat using only chemotherapy with a regimen that had been reported to be effective at that time (17). For >10 years, the patient has lived without recurrence and is considered to have had a high quality of life due to the long-term treatment with anticancer drugs for this rare tumor. Chemotherapy agents such as taxane, liposomal doxorubicin, and molecular-targeted therapy drugs against PI3K, mTOR, and EGFR are reported to provide a favorable response to MBC (3).

The prognoses of advanced MBCs are expected to improve further with the continued advances in modalities such as radiotherapy, immunotherapy (including immunotherapy using immune-checkpoint inhibitors such as programmed death ligand 1 [PD-L1]), and new pharmacotherapies including gene therapy drugs and anticancer drugs. The present case revealed that MBCs can show stromal hyalinization that consists of basement membrane materials, including laminin and type IV collagen. MBCs show differentiation of the neoplastic epithelium towards squamous cells and/or mesenchymal-looking elements. Our patient's case also indicates that MBCs can show differentiation towards myoepithelial cells and NE cells. A further accumulation of case reports will enable analyses of more data of patients with these tumors.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

All authors (YF, KH, TW, HA, SK, MO, YN, AF and HY) contributed to the conception and design of the present case report. Material preparation and data collection was performed by YF, KH, TW and HA. Pathological diagnosis was performed by KH, SK, MO and YN. YF and KH confirm the authenticity of all the raw data. The first draft of the manuscript was written by YF and KH. All authors commented on drafts of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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