Matrix-producing Carcinoma as an Aggressive Triple-negative Breast Cancer: Clinicopathological Features and Response to Neoadjuvant Chemotherapy

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Abstract. *Background: Breast matrix-producing carcinomas (MPCs) are rare, and usually triple-negative (TNBC; i.e. oestrogen receptor-, progesterone receptor-, and human epidermal growth factor receptor 2-negative). This study evaluated the clinical features, immunohistochemical profiles, and pathological response to neoadjuvant chemotherapy (NAC) of patients with MPCs. Patients and Methods: Five MPCs were identified among 247 patients with TNBC receiving anthracycline- and taxane-based NAC. Pathological response was assessed using surgical specimens. Results: All tumours were histological grade 3 according to pre-treatment core biopsies. Mean Ki-67 and p53 positivity were 65% and 90%, respectively. All tumours were TNBC, and epidermal growth factor receptor-, cytokeratin 5/6-, and vimentin-positive. Grade 3 (pathological complete response) was achieved in 0% (0/5) and 32% (77/242) of those with MPCs and with TNBCs of no specific histological type, respectively, and grade 1a (poor response) in 80% (4/5) and 13% (31/242), respectively. Conclusion: MPCs are basal-type TNBCs expressing epithelial-mesenchymal transition markers, with a poor response to standard NAC. Further studies are needed to improve the treatment of this rare but aggressive tumour.*

Matrix-producing carcinoma (MPC) of the breast is a rare and specialized histological type of metaplastic carcinoma (1). MPC is defined as an invasive breast carcinoma with

direct transition to a cartilaginous or osseous matrix with no intervening spindle-cell component. MPCs resemble triple-negative breast cancer (TNBC), defined as oestrogen receptor (ER)-, progesterone receptor (PR)-, and human epidermal growth factor receptor 2 (HER2)-negative (2-4). This tumour should, thus be, initially treated with chemotherapy. Although effective standardized regimens have been established for TNBC of no special histological type (NST TNBC), the efficacy of these treatments for minor histological types are unknown because of their rareness. We report five MPCs treated with neoadjuvant chemotherapy (NAC) followed by surgery, and evaluate the clinical features, immunohistochemical expression profiles, and pathological response to NAC compared with NST TNBC.

Patients and Methods

Patients and treatment. Five cases of MPC were identified among 247 patients with TNBC who received NAC at Yokohama City University Medical Centre (Yokohama, Japan) between 2007 and 2015. Prior to surgery, patients received NAC consisting of sequential chemotherapy with FEC (fluorouracil 500 mg/m², epirubicin 100 mg/m², cyclophosphamide 500 mg/m², q3w) or EC (epirubicin 100 mg/m², cyclophosphamide 500 mg/m², q3w) and docetaxel (75 mg/m², q3w). One patient diagnosed with a T4 tumour received sequential EC, docetaxel, and TC (docetaxel 75 mg/m², cyclophosphamide 600 mg/m², q3w). All patients with stage II or III TNBC breast cancer were eligible for NAC. Patients with stage IV TNBC were eligible if NAC followed by surgery was needed for local control. All patients were staged according to the World Health Organization (WHO) classification (5).

Tissue preparation and immunohistochemistry. Core needle biopsy specimens from patient's pre-chemotherapy were fixed in 20% (w/v) phosphate-buffered formalin and embedded in paraffin. Hematoxylin and eosin-stained sections were prepared using routine histological techniques and graded according to the WHO

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Table I. Antibodies used in this study. Antigen retrieval was achieved by autoclaving tissue sections in 0.1 mmol/l citrate buffer, pH 6.0 for 40 min at 95°C.

Antigen	Antibody type	Clone	Source
Ki-67	Monoclonal	MIB-1	Dako, Glostrup, Denmark
ER	Monoclonal	SP1	Roche Diagnostics, Basel, Switzerland
PR	Monoclonal	1E2	Roche Diagnostics
HER2	Polyclonal	–	Dako, Glostrup, Denmark
p53	Monoclonal	DO-7	Dako, Glostrup, Denmark
EGFR	Monoclonal	3C6	Roche Diagnostics, Basel, Switzerland
CK5/6	Monoclonal	D5/16 B4	Dako, Glostrup, Denmark
Vimentin	Monoclonal	V9	Dako, Glostrup, Denmark
ALDH1	Monoclonal	ALDH1A1	Abcam, Cambridge, England

ER: Oestrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; EGFR: human epidermal growth factor receptor; CK: cytokeratin; ALDH1: aldehyde dehydrogenase 1.

classification (5). Immunohistochemical staining was performed using a Dako-Autostainer (Dako, Kyoto, Japan), with the primary antibodies listed in Table I. Positive cytokeratin (CK)5/6 and epidermal growth factor receptor (EGFR) expression were indicated by weak or strong carcinoma cell staining in the cytoplasm and membrane. Tumours staining positively for CK5/6 or EGFR were considered as basal subtype, while double-negatively stained tumours were defined as non-basal (6). Aldehyde dehydrogenase 1 (ALDH1) expression was classified as positive when >1% of tumour cells showed clear cytoplasmic staining (7-9).

Evaluation of pathological response. Slides were assessed by two pathologists at our Institution in a blinded manner. Pathological response to chemotherapy was assessed using the grading system (grades 3, 2b, 2a, 1b, 1a, and 0) according to Japanese Breast Cancer Society criteria (10). The grades were defined as follows: Grade 3: necrosis or disappearance of all invasive tumour cells (*i.e.* pathological complete response; pCR) (11); grade 2b: marked disappearance of invasive cancer cells and only focal residual clusters detected; grade 2a: marked change in $\geq 66\%$ of cancer cells; grade 1b: marked change in $\geq 33\%$ but $< 66\%$ of cancer cells; grade 1a: change in cancer cells regardless of the area, or marked changes in $< 33\%$ of cancer cells; and grade 0: almost no change in cancer cells after treatment. Grades 0 and 1a were considered extremely poor pathological responses.

Results

The clinicopathological features and treatments of the five patients with MPC are summarized in Table II. All patients were women (mean age=53 years). The average tumour size was 5.5 cm. Magnetic resonance imaging (MRI) or computed tomography (CT) showed an enhanced ring-like appearance (Figure 1). Three patients (60%) had positive axillary lymph nodes. The mean Ki-67 and p53 positivity was 65% and 90%, respectively. All tumours were TNBCs which were positive for EGFR or CK5/6, and for the epithelial–mesenchymal transition (EMT) marker vimentin (12, 13). All tumours were negative for the breast cancer

stem cell marker ALDH1 (9, 14). Representative immunohistochemical images are shown in Figure 2. All patients were treated with NAC followed by surgery, and the percentages of each pathological response grade in the MPC and NST TNBC cases are shown in Figure 3. No patients with MPC achieved pCR (grade 3), and 60% (3/5) of patients showed an extremely poor tumour response (grade 1a), compared with only 13% (31/242) of patients with NST TNBC. Regarding the prognosis of patients with MPC after NAC and surgery, three (60%) died of metastatic disease within 4 years and two (40%) with small or node-negative tumours remained alive after 5 years.

Discussion

MPC is a rare tumour with few reported studies, which included a small number of cases (15). We only identified five MPC cases (2.0%) among 247 patients with TNBC treated with NAC between 2007 and 2015. The prevalence of MPC cases among all patients with operable breast cancer was only 0.3% at our Institution. Kusafuka *et al.* and Okuyama *et al.* reported prevalence of MPCs among all invasive breast cancer cases of 0.2% and 0.05%, respectively (16, 17). Given that metaplastic carcinomas are rare, MPCs comprise <1% of all invasive breast carcinomas. Downs-Kelly *et al.* reported 32 cases of MPC (2), all of whom were female (mean age 50 years), similarly to the current cases. However, they reported a median primary tumour size of 3.0 cm compared with 5.5 cm in our study. The median tumour size for 1,325 patients with NST TNBC treated at our Institution between 1997 and 2015 was 2.0 cm, indicating that MPCs tend to be larger than NST TNBCs.

Some radiological findings of MPCs have been reported (16). Imaging diagnosis using contrast-enhanced CT or MRI revealed irregularly shaped tumours with peripheral ring-shaped contrast enhancement, as in the current cases. This

Table II. Clinicopathological features and treatment response of patients with matrix-producing carcinoma.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	53	65	50	43	57
Tumor size (cm)	8.6×6.0×5.0	3.2×2.7×2.5	1.5×1.3×1.0	3.7×3.5×3.5	10×10×5.0
Site	Lt EBD	Rt BDE	Lt C	Rt C	Lt ABCDE
Lymph node status	+	+	–	–	+
Clinical stage	T3N1M0	T2N2M0	T2N0M0	T2N0M0	T4N2M1
Histological grade	3	3	3	3	3
Ki-67 (%)	69	74	65	50	45
p53 (%)	81	100	100	90	90
ER	–	–	–	–	–
PR	–	–	–	–	–
HER2	–	–	–	–	–
EGFR	+	+	+	+	+
CK5/6	+	+	+	–	–
Vimentin	+	+	+	+	+
ALDH1	–	–	–	–	–
NAC regimen	FEC-DOC	EC-DOC	FEC-DOC	FEC-DOC	EC-DOC-TC
Operation	Bt + Ax	Bt + SNB	Bp + SNB	Bt + Ax	Bt + Ax
Pathological response	1a	1a	2a	1a	1a
Follow-up (months)	DOD(46)	DOD(43)	NED (73)	NED (66)	DOD (16)

Site: Tumour location according to Breast Cancer ICD-10 Code; Lt: left; Rt: right; A: upper-inner quadrant; B: lower-inner quadrant; C: upper-outer quadrant; D: lower-outer quadrant; E: central portion; –: negative for marker; +: positive for marker; ER: oestrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; EGFR: epidermal growth factor receptor; CK5/6: cytokeratin 5/6; ALDH1: aldehyde dehydrogenase 1; NAC: neoadjuvant chemotherapy; FEC: 500 mg/m² fluorouracil, 100 mg/m² epirubicin, 500 mg/m² cyclophosphamide; DOC: 75 mg/m² docetaxel; EC: 100 mg/m² epirubicin, 500 mg/m² cyclophosphamide; TC: 75 mg/m² docetaxel, 600 mg/m² cyclophosphamide; Bt: total mastectomy; Bp: partial mastectomy; Ax: axillary lymph node dissection; SNB: sentinel node biopsy; DOD: died of disease; NED: no evidence of disease.

was likely caused by a ring of carcinoma cells at the tumour periphery and a matrix component in the centre of the tumour. We therefore considered the possibility of an MPC diagnosis when such images were obtained. The current study found a high rate (60%) of axillary lymph node metastasis at diagnosis; conversely, Downs-Kelly *et al.* and Shui *et al.* showed lower rates of 22% and 7.7%, respectively (2, 4). Further analyses of large numbers of age-/tumour grade-matched patients with NST TNBC are needed.

Most metaplastic breast carcinomas are TNBCs (1, 2, 18), including all MPCs of the current study; it is notable that no cases of MPC were detected in any of our patients with non-TNBC. Furthermore, all the MPCs demonstrated high proliferative activity, indicated by high histological grade, high Ki-67 index, and high level of p53 expression. The mean Ki-67 index of the MPCs (45%) was higher than that of NST TNBCs (36%), suggesting that MPCs are a biologically aggressive subgroup of TNBC. Notably, all MPCs in this study expressed EGFR, in 3/5 cases concomitantly with CK5/6, which are markers of basal subtype. Few studies have examined the relationship between basal subtype and MPCs. Shui *et al.* reported that eight out of 10 patients with MPC were positive for CK5/6 or EGFR (4). These results suggest that MPC should clinically be regarded as a basal subtype of TNBC.

In regard to EMT and mutation of breast cancer susceptibility gene 1 (BRCA1), the basal subtype was recently shown to largely overlap with TNBC (12, 19). EMT is associated with increased aggressiveness and invasive and metastatic potential of breast cancer, and is characterized by up-regulation of the key EMT marker, vimentin (12, 20). Okuyama *et al.* found that specimens from eight patients with MPC were all positive for vimentin, as in our cases (17). Furthermore, vimentin has been reported to be a poor prognostic factor, especially in TNBC (13). All MPCs in the present study were basal subtype TNBC with positive vimentin expression.

MPCs are thought to be part of the TNBC spectrum, and to be biologically aggressive with an EMT-like molecular make-up. Genetically, the claudin-low subtype is characterized by enrichment of EMT markers, and largely overlaps with the genetic features of metaplastic breast cancer (21, 22). MPCs may thus be regulated similarly to claudin-low subtype breast cancer. This perspective may further our understanding of the biological features of MPCs and thus aid the development of novel anticancer-targeted therapies for this rare tumour type.

BRCA1 mutations cause hereditary breast cancer and have been associated with up to 15% of TNBCs, while TNBCs in turn account for 70% of breast tumours arising in *BRCA1* mutation carriers (23). TNBC with *BRCA1* mutation is

Figure 1. Primary matrix-producing carcinoma. Peripheral ring-shaped contrast enhancement is apparent in all cases. Cases 1 and 5, enhanced computed tomography; Cases 2-4, T1-weighted enhanced magnetic resonance imaging.

strongly associated with basal subtype TNBC, mostly showing higher histological grade, higher Ki-67 index, and more *p53* mutations, compared with tumours from age-matched patients with sporadic breast cancer (19, 24). These characteristics were compatible with those of the current MPC cases, although none of these had any particular family history of breast cancer, and their *BRCA1* status was not investigated. Further studies are needed to clarify the relationship between MPCs and *BRCA1* mutations.

MPC is a rare disease with little published information to guide therapeutic choices. MPCs are negative for ER, PR, and HER2, and thus no targeted therapies are currently available, making conventional chemotherapy the backbone of systemic treatment for MPCs as well as for NST TNBC. NAC is associated with high pathological response rates in NST TNBC, but metaplastic carcinomas are usually chemoresistant (25, 26). However, information required to evaluate the impact of NAC on pathological response of MPCs is currently lacking. No patients in this study achieved a grade 3 (pCR) response to NAC, and most patients with MPC showed poor pathological responses (assessed as grade 1a tumours) compared with those with NST TNBC. Dose-dense perioperative chemotherapy (DDCT) has recently been used in a clinical setting to improve the prognosis of patients with high-risk TNBC (27), and DDCT may thus be a possible effective treatment option for MPC.

Recent studies showed that chemoresistance in metaplastic carcinomas, potentially claudin-low or basal subtype tumours, might stem from their EMT-like molecular make-up, down-

regulation of DNA damage response pathways (22, 28), and enrichment of stem cell-like markers. Patients with TNBC with poor pathological responses to NAC have poorer clinical outcomes, and new treatments for MPC should thus be based on their specific expression profiles. The recently refined version of the TNBC molecular classification defined four main subtypes: Basal 1, basal 2, mesenchymal, and luminal androgen receptor subtypes, with unique ontologies and differential responses to therapy (29). They reported that basal 2 subtype, characterized by the expression of EGFR and TP63 similarly to the MPCs in the current study, responded to antimitotic agents such as platinum salts and poly ADP ribose polymerase (PARP) inhibitors. PARP inhibitors have been used to treat basal subtype breast tumours (30), especially poorly differentiated tumours with EMT features and defects in homologous recombination DNA repair (31). Furthermore, a recent large study showed that PARP inhibitors provided significant benefits over standard therapy in patients with metastatic TNBC and *BRCA1/2* mutation (32). These new agents might be promising targeted treatments for MPC. Regarding chemoresistance and the association with stem cell-like markers, the relationship between MPCs and ALDH1 remains unclear. Few published studies have reported on the expression of cancer stem cell markers in specific histological types of breast cancer, and in contrast to our results, these studies showed enrichment of markers such as ALDH1 in metaplastic breast carcinomas, including MPCs (14, 33). Further translational and clinical studies with large numbers of cases are therefore needed.

Figure 2. Representative immunohistochemical images. A: Positivity for Ki-67 was observed in ~75% of tumour cell nuclei. B: Positive p53 staining was observed in ~100% of tumour cell nuclei. C: Positive vimentin staining was observed in the cytoplasm of cancer cells, but not in the matrix component. D: Positive epidermal growth factor receptor staining was observed in the cytoplasm/membrane of carcinoma cells. E: Cytokeratin 5/6 staining was observed in the cytoplasm/membrane of carcinoma cells. Scale bars, 50 μ m; inset, 25 μ m.

MPC is an extremely rare disease. Patients with MPC present with TNBC, larger tumour size, higher lymph node involvement, higher grade, *p53* mutations, a higher Ki-67 index, and frequent expression of vimentin and basal markers. They also show a markedly poor pathological response to conventional NAC regimens compared to patients with NST TNBC, suggesting that MPCs comprise a novel chemoresistant subgroup of TNBC. Based on the unique biological features of MPCs, new chemotherapeutic regimens including agents such as DDCT, platinum salts, and PARP inhibitors may be required to treat this rare, but aggressive subtype of TNBC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

Authors' Contributions

Conception and design: KS; Acquisition of data: KS, AY, DS; Analysis and interpretation of data: KS, TI; Drafting the article: KS; Critically revising the article for important intellectual content: TI, SS, KN, TC; Final approval of the version to be published: IE; All Authors read and approved the final article.

Figure 3. Distribution of pathological response grades in patients with matrix-producing carcinoma (MPC) and with triple-negative breast cancer of no special histological type (NST TNBC) treated with neoadjuvant chemotherapy at our Institution.

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