

Metaplastic carcinoma of the breast: Clinicopathological features and treatment outcomes with long-term follow up

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Abstract. Metaplastic breast carcinoma is an uncommon subtype of invasive ductal carcinoma with a tendency towards poorer clinical outcomes. Following ethical approval, the current study reviewed the institutional records of ~2,500 women with breast cancer. A total of 14 cases of metaplastic breast cancer were reviewed for management and treatment outcomes. The results demonstrated that patients had median follow up of 30 months, a 5-year disease-free survival of 57.1% and 5-year overall survival of 57.1%. The majority of patients had at least T2 disease and all tumours were high grade. Additionally, most patients were triple negative and nodal metastases were uncommon. Metaplastic breast cancer is an aggressive variant of invasive breast cancer. Most patients can be treated with breast conservation and survival parameters tend to be worse than more common breast cancer subtypes.

Introduction

Metaplastic breast carcinoma (MpBC) is an uncommon breast cancer subtype that comprises less than 1% of all breast malignancies (1-5). MpBC was first described in 1973 by Huvos *et al* and was formally recognised as a distinct pathological subtype of breast cancer in 2000 (1,6). Histopathological subtyping of MpBC is complex, and may be characterised by differentiation of the invasive epithelium into a spectrum of squamous and mesenchymal elements and may be composed entirely of metaplastic elements or by a mixture of both metaplastic and carcinomatous regions (1,2,7). The 2012 WHO classification system of phenotypes of metaplastic breast carcinoma includes low grade adenosquamous carcinoma, fibromatosis-like

metaplastic carcinoma, squamous cell carcinoma, spindle cell carcinoma, and metaplastic carcinoma with mesenchymal differentiation (1).

Metaplastic breast carcinoma typically presents with high histological grade, and the majority exhibit triple negative receptor expression (1-5,8). In addition, MpBC tends to be diagnosed at a higher tumour stage than non-metaplastic invasive ductal carcinomas, with a greater mean tumour size reported by WHO, while simultaneously being less likely to have axillary nodal involvement (1-6,9-11). Distant metastases are frequently found in the absence of lymph node metastases in MpBC, most commonly in the brain and lungs (1,3,12,13).

The evidence for management in MpBC is largely reliant on the results of a small number of single institution case series, and MpBC tends to be managed similarly to that of the more common invasive ductal carcinomas (IDC). The aggressive, complex, and frequently unpredictable clinicopathological presentation of MpBC may argue for more aggressive management for local, regional, and distant control.

In this case series, we report on 14 patients with MpBC who were treated in our institution with curative intent. We discuss the clinical and histopathological features, treatment strategies, and clinical outcomes to date.

Subjects and methods

Ethical approval. Following North Coast NSW Human Research Ethics Committee approval (reference 2019/ETH12207; individual consent for this retrospective analysis was waived), the study was undertaken to review our institutional experience in the management of MpBC.

Subjects. A total of 14 patients with MpBC from our three integrated comprehensive cancer centres who received curative intent radiation therapy between January 2009 and January 2020 were included.

Methods. We reviewed age at diagnosis, gender, tumour laterality, tumour size, axillary nodal status, presence of lymphovascular invasion (LVI), histological grade, receptor status [estrogen receptor (ER); progesterone receptor (PR);

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human epidermal growth factor receptor 2 (HER-2)], immunohistochemistry (IHC), Ki-67 prognostic index, as well as MpBC subtype. We also reviewed the radiation therapy fractionation and radiation field, extent of surgery, and details of systemic therapy. We have previously published our treatment techniques and outcomes for patients with breast cancer (14-17). Tumour and nodal staging was based on findings at wide local excision or mastectomy, or in the case of neoadjuvant systemic therapy, based on radiological findings in addition to the pathological specimen.

Results

Patient data. A total of 14 female patients from 2009-2020 who were diagnosed with MpBC in the curative setting were included in this case series. The median age at diagnosis was 66 years. The median follow up time post-completion of radiation therapy was 30.1 months. In total, 12 of the 14 patients underwent staging with either one or all of body CT, whole body bone scan or positron emission tomography CT scan.

Clinicopathological features. Clinicopathological features of the patients are summarised in Table I. Based on the World Health Organisation classifications of tumours of the breast (1), the most common MpBC subtypes were pure spindle cell carcinoma or pure squamous cell carcinoma. The majority of tumours (42.9%) were T2, and the median tumour size was 34.5 mm. Thirteen patients (92.9%) were axillary node negative; one patient had 1 of 13 nodes positive at ALND. Lymphovascular invasion was identified in 3 of 14 patients (21.4%). All tumours were high grade (grade 3). The tumours in 13 of 14 patients were triple negative. For those in whom a Ki-67 proliferation index was reported, the score ranged between 25 and 90% (mean index score 50%).

Therapeutic regimens. All patients received radiation therapy; hypofractionation 40.05 Gray/15 fractions was the most common schedule. All patients who received radiation therapy in this study received intensity modulated radiation therapy (IMRT). Most patients were suitable for breast conservation surgery.

A total of 12 patients received chemotherapy and 2 either declined or were not offered chemotherapy. The most common chemotherapeutic regimens were adriamycin and taxol based, followed by taxol and cyclophosphamide regimens; one patient received the fluorouracil epirubicin cyclophosphamide-docetaxel (FEC-D) regimen. One patient received trastuzumab for HER-2 positive disease, and one patient letrozole for a mixed tumour with a triple positive IDC.

Clinical outcomes. Regarding follow up status, ten patients (71.4%) were alive and disease free at the time of publication. There were three patients (21.4%) who died from cancer progression, one patient has been lost to follow up. Of the three patients who died due to progressive disease, one of these presented with radiological T4 disease and underwent mastectomy and post mastectomy radiation therapy (PMRT); there was disease recurrence 4 months post-RT in the left chest wall scar site, and the patient subsequently underwent palliative RT to the sites of bony disease. This patient died

4 months afterwards. The second patient also had T4 disease and underwent radiation therapy to the breast and SCF after poor response to neoadjuvant chemotherapy, which was subsequently followed by mastectomy. The patient died 5 months later. The third of these patients experienced recurrence 32 months post-RT in the ipsilateral left chest wall, confirmed on histopathology, prior to developing distant disease.

The 5-year disease-free survival (DFS) was 57.1% and 5-year overall survival (OS) was 57.1%, as one patient who experienced local recurrence has unknown current clinical status. The 4 year DFS and OS were both 66.7%.

Discussion

Metaplastic breast cancer is an aggressive, uncommon variant of breast cancer that may have unpredictable clinical behaviour. Classification of various subtypes of MpBC is complex and there are often overlapping features seen on histopathology. Metaplastic carcinoma has been described as having lower response rates to systemic therapy, or frequently being chemoresistant (1-6,8,10,18-24).

Similar to other cases series, the majority of MpBC cases in this study presented with a tumour size of T2 or greater (3,5-9,25). There was a low incidence of axillary nodal metastases, which has been repeatedly reported since the earliest descriptions of the clinicopathological features of MpBC (3,5,10,11). The high incidence of distant metastases in the presence of low rates of nodal involvement has been extensively described, supporting the hypothesis that MpBC disseminates via the haematogenous route rather than via the lymphatic system (1,2,13,19,21,25-30). Although higher rates of mastectomy in MpBC relative to the more common invasive ductal carcinoma (IDC) have been reported in the literature (3,5,10,18-20), in our series a similar proportion of patients had breast conservation versus mastectomy.

Several reports have concluded that metaplastic carcinoma shares a similar basal phenotype to triple negative breast cancer (TNBC) and to the claudin-low molecular subtype (2,10,31-33). The WHO reports that greater than 90% of MpBC exhibit triple negative receptor expression (1) and this is supported by the other results of other retrospective studies (1,3,5). Our series included two patients with a HER-2 positive component.

Immunohistochemistry (IHC) for MpBC is critical not only for diagnosis and prognosis, but also for distinguishing between the various subtypes of MpBC. IHC for expression of high molecular weight cytokeratins (and basal markers) such as CK5/CK6, 34betaE12, AE1/AE3, E-Cadherin, CK14 and EGFR, are considered to be particularly important prognostic markers (2,7,34). Low molecular weight keratins are often negative (1). McCart Reed *et al* performed molecular analysis of 347 MpBC cases, and found that the majority of MpBC express EGFR, and EGFR overexpression was seen on molecular analysis to be associated with poor survival outcomes (7).

Although MpBC tends to be treated in a similar fashion to the more common breast carcinoma subtypes, disease-free survival and overall survival are significantly worse. It has been suggested that locoregional management may often not be optimised if based on the same tumour and nodal staging system as for the more common IDC (5,11,13,25,35,36).

Table I. Clinicopathological features of patients with MpBC (n=14).

Characteristic	N (%)
Histological subtype	
Adenosquamous	0 (0)
Fibromatosis-like	1 (7.1)
Pure spindle cell	3 (21.4)
Pure squamous cell carcinoma	3 (21.4)
Pure mesenchymal differentiation	2 (14.3)
Mixed	3 (21.4)
MpBC with no specific differentiating features	2 (14.3)
TNM Tumour Stage	
T1	3 (21.4)
T2	6 (42.9)
T3	3 (21.4)
T4	2 (14.3)
TNM Nodal Stage	
N0	13 (92.9)
N1	1 (7.1)
Surgery	
Wide Local Excision	8 (57.1)
Mastectomy	6 (42.9)
Sentinel Node Biopsy	9 (64.3)
Axillary Dissection	3 (21.4)
Radiation	
Primary Site	12 (85.7)
Nodal Irradiation	2 (14.3)
Tumour Cavity Boost	6 (42.9)
Hypofractionation	11 (78.6)
Conventional fractionation	3 (21.4)

MpBC, metaplastic breast carcinoma.

Five-year overall survival rates have been estimated to be between 49-69% (5,10,12-13,22,35,37-39).

The survival of MpBC patients reported in institutional studies is summarised in Table II. In general, MpBC patients experienced greater disease recurrence and poorer overall survival compared to both triple negative IDC and general IDC (10,12,13,37-39). Benson *et al* reported on 7 patients with MpBC from a single institution in India, in which all patients underwent mastectomy followed by PMRT and adjuvant chemotherapy (40). Three of seven patients were alive and well at last follow up at 5 years, one patient developed liver metastasis at 6 years post treatment, and three were lost to follow up.

WHO recognises a number of MpBC subtypes. The low-grade adenosquamous phenotype is typified by well-developed glandular and tubular formation, generally in an admixture with solid nests of squamous cells in a spindle celled background. Lymphocytes may often be seen in clusters (1,2). The fibromatosis-like phenotype is typically characterised by a prominent 'fibromatosis-like' stroma characterised by bland spindle cells in a collagenous background including some foci of dense eosinophilic keloidal

type collagen, and often with features of squamous differentiation including cytoplasmic keratinisation (1,2). In the squamous cell carcinoma variant, negative IHC staining for SCC of other primary origins is critical (2,41,42). SCC often consists of a cellular population of partly cystic cells with squamous differentiation, staining triple negative, adjacent to high grade invasive ductal cells, and therefore, is often a mixed phenotype. A conspicuous stromal reaction may often be described (1,2,41). For the spindle cell carcinoma variant, in addition to the presence of atypical spindle cell proliferation or proliferation of spindle cells, and areas of focal necrosis, a concurrent invasive ductal carcinoma or *in situ* component is commonly found to be diagnostic. Common myoepithelial markers such as p63, smooth muscle actin (SMA), C10, as well as calponin, may be diagnostic (1,2,42,43). Subtypes of mesenchymal differentiation, are often described as larger tumours (2,44). Many cases of mesenchymal differentiation present with one or more of chondroid, osseous, rhabdomyoid, or other elements, or mixed in with other differentiation (1,2). The term 'matrix producing carcinoma' has often been applied to MpBCs with mesenchymal elements (1). S100 may be used to confirm the presence of a matrix producing carcinoma (45).

A large proportion of MpBC display a mixture of elements, and ideally, each distinct element will be documented in the patient record. There are often conflicting reports about the relative aggression of the different subtypes of MpBC; specifically, with regards to their predilection for axillary nodal and distant involvement (6,13,19,35,46-49). Mixed pathologies may be more aggressive and have been associated with shorter DFS in some studies, and increasing numbers of morphologies in a mixed case may confer a survival disadvantage (7,38,39).

Several patients in this case series had unique presentations. One patient was diagnosed after histopathology from removal of a leaking implant capsule demonstrated MpBC, and was managed as occult disease. Given that it was not possible to see where the tumour was resected, this patient was not offered a breast boost. A second patient had low grade follicular lymphoma in a sentinel node that was CD20, CD21, and BCL2/BCL6 positive. A third patient had squamous cell carcinoma variant on WLE specimen and adenosquamous phenotype in the ALND specimen. Nodal involvement with different elements from the primary tumour in MpBC is not an uncommon finding (6,11,50). A fourth patient with fibromatosis-like variant, which while described as typically low grade, was grade 3 in this specimen (1,2).

It has been proposed that MpBC could be a particularly radiosensitive form of breast cancer (51). One patient in this study who presented with the mesenchymal differentiation phenotype had a 90 mm (T4) tumour extending into the pectoralis muscle, and radiological evidence of intramammary nodes. This patient underwent 2 cycles of neoadjuvant chemotherapy which was not well tolerated, and subsequently proceeded to radiation therapy with a fractionation of 48.06 Gy/18 fractions to the breast and 40.05 Gy/15 to the SCF. The pathological specimen from mastectomy showed only a single small focus of residual cancer next to adjacent scar tissue, enabling the mastectomy procedure to be fully clear of all margins (this patient, however, developed distant disease 6 months later). The American Society for Radiation Oncology (ASTRO) breast guidelines has proposed that the

Table II. Survival of patients with MpBC: Comparisons of institutional studies.

Author, year	Number of MpBC cases	5-year DFS/PFS/RFS/LRR	5-year OS in	(Refs.)
Jung <i>et al</i> , 2010	35	5-year DFS of 41.8 vs. 81.8% in the TNBC group and 87.3% in IDC overall	62.8 vs. 87.0% in the TNBC group, and 92.0% in IDC overall	(10)
Jin <i>et al</i> , 2018	26	5-year DFS of 53.8%	61.5%	(37)
Esbah <i>et al</i> , 2012	14	3-year PFS of 33%	56%	(12)
Fayaz <i>et al</i> , 2017	31	5-year PFS of 50%	69%	(39)
Cimino-Mathews <i>et al</i> , 2016	45	5-year RFS of 64%	69%	(38)
Leyrer <i>et al</i> , 2017	113	5-year LRR of 21%	69%	(13)

MpBC, metaplastic breast carcinoma; DFS, disease-free survival rate; PFS, progression-free survival rate; LRR, local-regional recurrence rate; RFS, recurrence free survival; OS, overall survival rate; IDC, invasive ductal carcinomas; TNBC, triple negative breast cancer.

radiobiological alpha: Beta ratio (a measure of cell sensitivity to changes in radiation fraction size) of metaplastic carcinoma is much higher than that of the more common IDC and that conventional fractionation could provide better control (44). In our series, 2 of 3 patients in total who received conventionally fractionated radiation remain alive (1 had WLE, 1 had mastectomy). Consideration of upfront radiation for larger lesions could therefore be an appropriate treatment strategy.

The recently published study by Moreno and colleagues from MD Anderson Cancer Center, which looked at 2,084 cases from the National Cancer Database from 2010-2014 and compared features of MpBC to both TNBC and other breast cancer subtypes, is the largest known study to date of MpBC (5). Patients with MpBC were observed to have worse OS at every clinical stage relative to both TNBC and other breast cancer subtypes. The investigators noted that on multivariate analysis, radiation therapy was a significant predictor for survival, with those who received radiation 30% less likely to die than those who did not receive radiation. The authors also noted that axillary nodal irradiation was slightly less used in MpBC compared to other breast cancer subtypes, with radiation utilised in 26.1% of MpBC cases targeting both breast/chest wall and regional nodes versus 33.7% in other breast cancer subtypes (not including TNBC). This is not unexpected, given that there is in general a lower predilection for nodal spread in MpBC relative to other breast cancer subtypes, as previously described. On multivariate analysis, treatment of regional nodes in addition to the breast or chest wall did not significantly influence outcomes in N0 or N⁺ disease. The conclusion of the authors was that it is reasonable to consider more extensive locoregional treatment in the form of axillary radiation therapy on a case by case basis.

Radiation therapy was delivered to half of the patients (54% of 113) in the study of Leyrer *et al*, who concluded on multivariate analysis that radiation therapy was the only factor correlating with reduced locoregional recurrence (13). There was a relative risk of 3.1 without radiation therapy, (CI, 1.13-9.88, P=0.027). Moreover, of the 47 patients who underwent radiation therapy, 40% received nodal irradiation. Of 36 patients who had breast conserving therapy who received

radiation therapy, only 1 case had local recurrence. Not having radiation therapy after resection was associated with an increased relative risk of 3.3 for LRR. Tseng and Martinez, analysing the SEER database of MpBC cases, concluded that radiation improved both DFS and OS for all patients undergoing treatment for MpBC (35). This was irrespective of the type of surgical procedure performed, with 36 and 26% decreases in death from any cause and breast-related mortality, respectively. Multivariate analyses demonstrated 38 and 34% decreases in death from any cause and breast-related mortality, respectively.

The use of PMRT in earlier stage MpBC is not fully elucidated, given the relatively rarity of the disease. There may be similarities with other series of outcomes in triple negative breast cancer. The study from 2011 by Wang *et al* randomised 681 Chinese women with Stage I-II disease who received mastectomy for TNBC to either adjuvant chemotherapy alone or chemotherapy in combination with PMRT, including nodal irradiation as indicated (27). The study demonstrated significant improvement in the group which received both chemotherapy and PMRT, with a 5-year RFS of 88.3% and OS of 90.4%, respectively, versus 78.7 and 74.6% in the chemotherapy alone group. Multiple case studies have suggested that the traditional indications for PMRT could be broadened in MpBC (5,21,34,35,40), while simultaneously acknowledging some limitations given the retrospective nature of these studies.

In this case series we have reviewed the clinicopathological outcomes of a small number of women who were treated for metaplastic breast cancer. We have reported on follow up, the unique findings on histopathology, and progress following multimodality management with a focus on radiation oncology outcomes. The use of extensive imaging in addition to standard mammography and ultrasound for staging appears to be particularly critical for metaplastic carcinoma, given its aggressive nature.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AG conceived and designed the current study. MH made a substantial contribution to the acquisition of data. AG, NJA, JW, JVA, PMD, ATL and TPS collected, assembled, analysed and interpreted the data and revised the manuscript critically for important intellectual content. AG and NJA confirmed the authenticity of all the data. All authors contributed to and approved the final manuscript.

Ethics approval and consent to participate

This retrospective review was approved by the North Coast NSW Human Research Ethics Committee (approval no. 2019/ETH12207). Consent for participation was not required.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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