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Report

Metaplastic breast carcinoma: clinical–pathologic characteristics and HER2/neu expression

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Summary

Background. Metaplastic breast carcinomas (MBC) are rare primary breast malignancies characterized by the co-existence of carcinoma with non-epithelial cellular elements. They can be classified as monophasic spindle cell (sarcomatoid) carcinoma, biphasic carcinosarcoma, adenocarcinoma with divergent stromal differentiation (osseous, chondroid and rarely rhabdoid) as well as adenosquamous and pure squamous cell carcinomas. There is a paucity of information on clinically relevant pathologic features and clinical outcomes for these rare tumors. The aim of this study was to review the pathologic features and clinical outcomes of all cases of MBC seen at a single institution between 1971 and 2000.

Methods. A computerized search of the Queen Elizabeth II Health Sciences Center (QEII HSC) surgical pathology files was performed for the years 1971–2000. Tumor blocks from identified cases were reviewed and immunohistochemistry was performed for estrogen and progesterone receptors (ER/PR), HER2/neu protein overexpression and cytokeratin profile. Clinical outcome information was obtained from hospital files and telephone contact with treating physicians.

Results. Twenty-six (26) cases were retrieved with only one case identified before 1990. All tumors were high grade with a median tumor size of 3.7 cm (range 1.4–9.5 cm). Thirteen cases had lymph node dissections available for evaluation, with 4 demonstrating nodal metastases. Five of 26 cases were ER positive within the adenocarcinomatous component, only two of which also expressed PR. Associated ductal carcinoma *in situ* (DCIS) was present in 11 cases. HER2/neu over-expression was seen in only one (1/26) adenosquamous carcinoma (3+ membranous staining of the malignant glandular component). At 23 months median follow-up, disease free survival (DFS) for the entire group was 53%.

Conclusions. Although a rare breast cancer subtype, MBC is of considerable interest due to its pathological heterogeneity and differences in clinical behavior compared to typical breast carcinomas. Increasing pathologic recognition of MBC as a discrete entity is suggested by the number of MBC diagnoses in the last decade compared to previous years. The poor DFS associated with MBC suggests that further research exploring mechanisms of carcinogenesis and identifying clinically relevant prognostic factors is needed to direct optimum clinical care. Importantly, MBC variants appear to rarely overexpress the HER2/neu oncoprotein.

Introduction

Metaplastic breast carcinomas (MBC) are a heterogeneous group of malignant lesions comprising $<1\%$ of all invasive breast cancers [1–3]. The unifying feature of these tumors is the presence of an epithelial or mesenchymal cell population admixed with adenocarcinoma. Pathologic classification of MBC remains problematic but the disease is generally divided into two main groups: (1) homogeneous spindle cell/sarcomatoid carcinoma, and (2) heterogeneous carcinosarcoma/carcinoma with sarcomatous differentiation (osseous, chondroid and rhabdoid). Pure epithelial malignant tumors with metaplasia, such as adenosquamous and pure squamous cell carcinoma are also considered as MBC subtypes [1–3].

MBC differs from typical adenocarcinomas in a number of pathologic and clinical variables. Nodal involvement has been shown to be less common compared to typical breast adenocarcinomas, with an incidence ranging from 6 to 26% [4–6]. The risk of developing metastatic disease however, is greater than expected based on historical comparisons to more common breast carcinoma variants. Recurrence rates for node-negative MBC have ranged from 35 to 62% within 2–5 years of initial diagnosis. This compares with a 17–20% risk of disease recurrence for invasive ductal carcinoma, NOS, of similar tumor size [7, 8]. It has also

been observed that some tumors classified as MBC behave in a manner similar to pure sarcomas with absence of regional lymph node involvement, aggressive vascular pattern of metastasis, and predilection for pulmonary involvement [9]. Hormone receptor expression in MBC is uncommon with reported estrogen/progesterone positivity in 0–17% of cases [4–6].

Due to the rarity of these tumors, clinical–pathologic characteristics remain to be fully defined. The incidence of HER2/neu over-expression is unknown and, therefore, the relevance of this therapeutically meaningful factor in MBC is unclear. The aim of our study was to review the pathologic characteristics, clinical outcomes and incidence of HER2/neu protein overexpression for all cases of MBC seen at a single institution between 1971 and 2000.

Methods

A search of the surgical pathology and pathology consultation computer files at the Queen Elizabeth II Health Sciences Centre (QEII HSC), the regional referral hospital, was performed and regional pathology laboratories were contacted for retrieval of tumor blocks. Mammary malignancies diagnosed as metaplastic, spindle cell, squamous and adenosquamous carcinomas as well as anaplastic carcinomas with osseous, chondroid and rhabdoid metaplasia, carcinosarcomas and primary sarcomas were sought. Only specimens that had surgical pathologic specimens of the primary tumor available for review were included (one case with only a core biopsy specimen was excluded).

The following features were assessed for all cases; histologic classification, tumor size, tumor grade (Nottingham Modified Bloom-Richardson grade) [10] presence of *in situ* component, vascular invasion, ER/PR status, HER2/neu status and cytokeratin profile. Nodal status was ascertained via review of the original pathology report.

Clinical outcomes were ascertained through reviews of hospital files and telephone contact with primary physicians. The distribution of progression-free survival (PFS) and overall survival (OS) was estimated using the Kaplan–Meier method.

Immunohistochemical staining

Staining was performed on 5-μm sections of routinely processed, formalin-fixed, paraffin-embedded surgical material. Paraffin sections were cut and mounted on silanized slides (Superfrost Plus: Fisher Scientific, Pittsburg PA, USA). Slides were stained using a labelled streptavidin–biotin detection method and automated immunostainer (Ventana Benchmark and Ventana Nexes, Tucson AZ, USA). Antibodies employed were as follows: Estrogen receptor primary antibody, clone 6F11, (Ventana, Tucson AZ, USA) pretreatment with cell conditioner 1 according to Ventana Benchmark protocol; Progesterone receptor primary antibody, clone 1A6 (Ventana, Tucson AZ), pretreatment with cell conditioner 1 according to Ventana Benchmark protocol; Tab250 monoclonal mouse anti-Her2 (Zymed Laboratories, San Francisco CA), dilution 1:100, no pretreatment with Ventana Nexes immunostainer; Polyclonal rabbit anti-human c-erbB2 oncoprotein DAKO A0185 (DAKO Mississauga, ON, Canada), used outside of the Herceptest, 1:400 dilution and microwave antigen retrieval with use of Ventana Nexes immunostainer; Anti-human epithelial membrane antigen, clone Mc5 (Ventana, Tucson AZ), no pretreatment, Ventana Nexes immunostainer; Anti-pan keratin antibody, AE1/AE3/PCK26 (Ventana, Tucson AZ), slides pretreated for 2 min with protease, Ventana Nexes; Anti-vimentin antibody, clone Vim3B4 (Ventana, Tucson AZ), slides pretreated with protease for 4 min, Ventana Nexes. Positive and negative controls were included with each assay. A positive HER2/neu immunohistochemical result was defined as moderate to strong complete membrane staining of at least10% of invasive tumor cells (3+) with both antibodies (DAKO A0185 and Tab250).

Results

Twenty-six (26) cases of MBC diagnosed between 1971 and 2000 were retrieved from the Atlantic Canada region. The earliest identified case was diagnosed in 1986, with the remainder diagnosed from 1990 onward. All patients were female with a median age at diagnosis of 65.5 years (range 33–87 years).

Five MBC subtypes were documented including; adenocarcinoma with spindle cell metaplasia, adenosquamous carcinoma, monophasic spindle cell carcinoma, metaplastic breast carcinoma with osteoclast giant cells and metaplastic breast carcinoma with chondroid differentiation. Clinical–pathologic features of the entire series are presented in Table 1.

There were 11 cases of adenocarcinoma with spindle cell metaplasia. These tumors were biphasic with foci of poorly differentiated, high grade, ductal carcinoma, NOS co-existing with malignant spindle cell foci. The spindle cell areas were either fibroblastic or exhibited a pattern consistent with malignant fibrous histiocytoma. In all cases the spindle cell component displayed weak to moderate staining with keratin markers (AE1/AE3 and/or EMA), supporting a diagnosis of MBC as opposed to primary breast sarcoma. The median tumor size for this subgroup was 5.5 cm (range 1.4–9.5 cm) with two of the five cases with lymph node dissections having nodal metastases. Four cases (4/11) had co-existing DCIS with 3 tumors (3/11) expressing estrogen receptors. All tumors were negative for HER2/neu protein over-expression

Adenosquamous carcinoma was diagnosed in 8 cases. These tumors typically displayed areas of squamous

Table 1. Results

Histological subtype	Age at diagnosis (median, yrs)	Tumor size (median, cms)	Nodal status (+/# of cases)	DCIS	ER and/or PR+	DFS
Adenocarcinoma with spindle cell metaplasia (n = 11)	61 (35–87)	5.5 (1.4–9.5)	2/5	4/11	3/11	45.5%
Adenosquamous carcinoma (n = 8)	63 (42–78)	4.5 (2.0–7.0)	2/5	5/8	2/8	62.5%
Spindle cell carcinoma (n = 4)	60 (33–87)	5.2 (3.3–7.0)	0/2	1/4	0/4	NC
MBC with osteoclast giant cells (n = 2)	52, 79	2.0	N/A	1/2	0/2	NC
MBC with chondroid differentiation (n = 1)	57	2.0	0/1	0/1	0/1	NC
Overall	65.5 (33–87)	3.7 (1.4–9.5)	4/13	11/26	5/26	

NC: Not calculated due to small patient numbers.
N/A: No cases with axillary lymph node dissections.

differentiation admixed with poorly differentiated ductal carcinoma with the glandular component comprising 5–95% of these lesions. Cases with extensive squamous differentiation often contained central cystic degeneration but no pure squamous cell carcinomas were seen. The median tumor size was 4.5 cm. (range 2.0–7.0 cm). Two cases (2/5) had lymph node metastases and 5 cases had associated DCIS. Two cases expressed estrogen receptors. The only case of HER2/neu protein over-expression was seen amongst this group of tumors with strong complete membranous staining of the glandular component only (Figure 1).

Four cases of malignant monophasic spindle cell tumors were diagnosed. Within this group, the infiltrating tumor was characterized by highly atypical spindled cells within fibrotic stroma. Each case demonstrated positive immunohistochemical staining with epithelial markers (AE1/AE3 and EMA, with one case being AE1/AE3 positive and EMA negative). These spindle cell neoplasms all had fibrosarcomatous morphology. The median tumor size was 4.8 cm (range 3.3–7.0 cm) with no specimens having nodal involvement (0/2). One of 4 cases had co-existing DCIS and all cases were ER/PR negative.

Two tumors had mixed malignant epithelial and mesenchymal differentiation with areas containing numerous osteoclast-like giant cells. The median tumor size was 2 cm, with one case having associated DCIS. Both cases were negative for ER/PR. One tumor had multiple foci of chondroid differentiation within a predominant carcinosarcomatous morphology. An *in situ* component was not seen. The tumor size was 2 cm and was negative for ER/PR and HER2/neu protein over-expression.

Overall DFS for the entire group for which information was available (19/26) was 53% at a median follow-up time of 23 months. Due to the small number of cases in each group, as well as incomplete information regarding nodal status for the entire series, meaningful comparisons across MBC subtypes were not possible. A comparison of DFS between cases with sarcomatous differentiation versus those with adenosquamous carcinoma revealed a numerically superior outcome for the latter patient population (DFS 45.5% versus 62.5%, respectively).

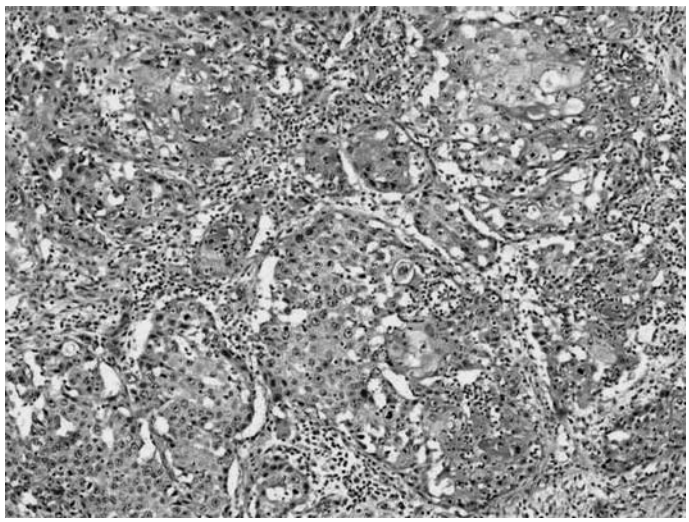

Figure 1. The image depicts the single case of metaplastic breast carcinoma in our series, which was positive HER2/neu protein over-expression. The tumor is an adenosquamous carcinoma; areas of squamous differentiation are shown.

Discussion

Metaplastic carcinoma of the breast is a rare, heterogeneous disease consisting of tumors with admixed epithelial and non-epithelial elements. The non-epithelial elements can consist of spindled stromal cells, bizarre stromal giant cells, cartilage, bone, and rarely skeletal muscle, in varying proportions [1–3, 11, 12]. Some classification schemes also include adenosquamous and pure squamous cell carcinomas as MBC subtypes based on the metaplastic epithelial component. [1, 2, 13].

Pathologic classification is challenging due to the diversity of histology pattern, rarity of the diagnosis and lack of consensus as to the most appropriate classification system for this group of tumors [1, 2]. MBC with a prominent spindle cell component contains atypical spindled cells with a fascicular or storiform arrangement. The degree of cytologic atypia however, can vary from markedly pleomorphic tumors resembling high-grade sarcomas to mild cellular atypia resembling benign fibrous lesions. The presence and amount of the associated ductal carcinomatous component can also vary. The monophasic spindle cell pattern of MBC may mimic other breast lesions including pure sarcoma, myoepithelial carcinoma, fibromatosis, nodular fasciitis, myofibroblastoma and granulation tissue [14]. Immunohistochemical evaluation with the use of a panel of anti-cytokeratin antibodies to demonstrate epithelial differentiation is essential in the diagnosis of MBC with a homogenous spindle cell population. The polyclonal wide spectrum screening keratin (Dako, Carpinteria CA) has been demonstrated to be more specific for MBC with spindle cell features than the AE1/AE3 antibody [15].

Low grade metaplastic breast tumors with a fibromatosis-like phenotype have been recently described, and also need to be considered in the differential diagnosis of low grade or benign appearing fibrous breast lesions. [16, 17]. As with high-grade forms of spindle cell MBC, demonstration of an epithelial phenotype is essential for the diagnosis.

The MBC cell of origin is thought most likely to be epithelial in nature with sarcomatous components representing areas of dedifferentiation or metaplasia. It has also been suggested that these lesions may arise from myoepithelial cells with divergent paths of tumor differentiation [18, 19]. Tumors with predominantly squamous differentiation most likely represent metaplasia of malignant ductal epithelial cells [13].

The only reported series of MBC to include more than 30 cases have been from Wargotz et al. (247 cases) [4, 5, 13, 20, 21] but the majority of published reports comprise 20 or fewer cases. They found the poorest 5 year overall survival rates for those diagnosed with carcinosarcoma and the best for those with matrix-producing carcinomas (5 year OS 49% and 68%, respectively), [4, 20]. Other studies have found tumor size but not MBC subtype to have prognostic importance [11].

Most previous series have found that MBC's are typically large at diagnosis [5, 6, 13, 20, 22, 23]. The median tumor size in our series was 3.7 cm for all subtypes (range, 1.4–9.5 cm), consistent with other reports. MBC is usually associated with a lower incidence of axillary nodal involvement than would be expected from similar sized typical breast adenocarcinomas. Previous reports have documented a 6–26% incidence of axillary nodal involvement [5, 6, 9, 13, 20]. Our series was limited by the small proportion of cases with nodal material available for review (13/26) but 31% of our cases were node positive (4/13), consistent with previous reports of nodal metastases in MBC. Advanced patient age, as well as significant locally advanced disease at diagnosis accounted for the majority of cases for which axillary lymph node dissection was not performed.

MBC has also been found to infrequently express hormone receptors with estrogen and or progesterone (ER/PR) positivity ranging from 0 to 17% in four series [4–6, 9]. Consistent with this finding, only five of the 26 cases (19%) in our series expressed ER. There were no ER negative/PR positive cases. ER expression was found in 3 of 11 cases of adenocarcinoma with spindle cell metaplasia and 2 of 8 adenosquamous carcinomas. All cases demonstrated nuclear staining within areas of ductal differentiation, and not in areas of spindle cell or squamous differentiation.

There is limited data regarding HER2/neu overexpression in MBC. To the author's knowledge, only one other study has investigated this prognostic/predictive factor in MBC. Bellino and colleagues studied 11 cases of MBC including variants with chondroid, spindle cell, and squamous metaplasia. HER2/neu overexpression, assessed by immunohistochemistry (CB11 clone, DAKO), was detected in 72% of spindle cell and squamous carcinomas and 33% of MBC with chondroid differentiation [24]. In contrast, only 1 of the 26 cases in our series (4%) over-expressed the HER2/neu oncoprotein. HER2/neu was over-expressed in one adenosquamous carcinoma with overexpression detected within the malignant ductal epithelium but not within the squamous component of the tumor (Figure 1). None of our cases demonstrated weak or equivocal (1+ or 2+) HER2/neu expression. The difference in the 2 results may be partly explained by the fact that 2 antibodies were employed in the current study and that only those cases demonstrating 3+ staining were counted as positive (Figure 2). The study by Bellino et al., in only using 1 antibody and not commenting on the degree of HER2/neu immunohistochemical staining required to consider a case positive, may have included cases that would likely be considered equivocal (2+) or negative (1+) according to current consensus guidelines [25].

Patients with metaplastic breast carcinomas tend to have poor outcomes with a high risk of recurrence following primary surgery. We were able to obtain clinical outcome information for 19 of 26 patients in our series. At a median follow-up of 23 months, disease-free survival (DFS) for those with information available was

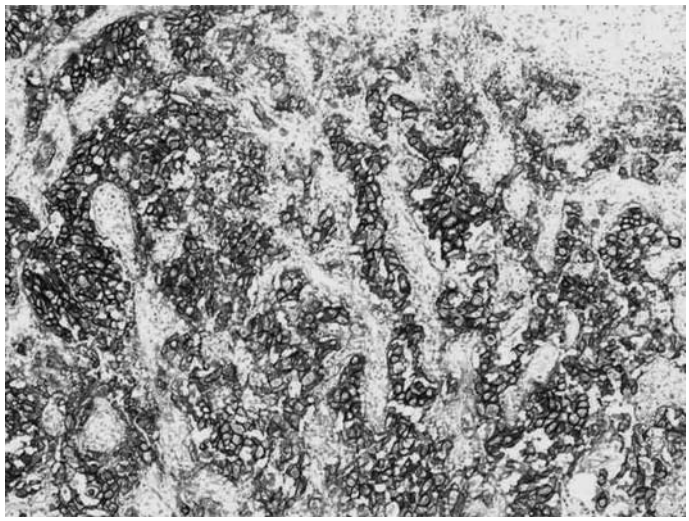

Figure 2. Immunohistochemical staining for HER2/neu protein of the adenosquamous carcinoma shown in Figure 1. There is strong 3+ membranous staining.

53%. Patients with adenosquamous cell carcinoma tended to have a better outcome than the other variants of MBC combined (DFS 62.5% versus 45.5%). Five other large series have found similar poor outcomes with reported DFS rates of 35–62% at median follow-up intervals of 2–5.4 years [4–6, 9, 20].

The systemic management of MBC has rarely been reported. The largest series reporting use of systemic therapy did not find any evidence of benefit for adjuvant chemotherapy, or significant response rates to systemic chemotherapy, or hormonal therapy for those with metastatic disease [9]. Eight patients in our series received adjuvant chemotherapy, with either the AC or CMF regimens. Due to the small number of patients receiving adjuvant therapy, it was not possible to examine differences in outcomes between those treated and those observed following surgery.

Of interest, is the fact that although the time interval for inclusion in our series spanned 1971–2000, the first case was diagnosed in 1986 with the remainder being recognized after 1990. This may suggest incomplete tumor description and/or missclassification within both the cancer registry and central pathology computer system in earlier years. Alternatively, this finding may also suggest increased recognition of MBC as a distinct breast tumor subtype on the basis of improved diagnostic accuracy or a true rise in incidence.

Our study, like those before it, is limited by the small number of cases retrieved due to the relative rarity of MBC. As well, our data on nodal status is limited by the small proportion of cases with available lymph node material available for review. Despite these limitations, a number of conclusions are of interest: (i) overexpression of HER2/neu was rare (4%); (ii) MBC variants were frequently ER and PR negative; (iii) at a median follow-up of 23 months, DFS was only 53%; (iv) there was evidence of increased recognition and diagnosis of MBC after 1990.

Our findings, if replicated, may have important implications for this uncommon disease and suggests that trastuzumab may not play a significant role in disease management [25, 26]. The confirmation of the rarity of hormone receptor expression and the previously reported lack of evidence of benefit from adjuvant chemotherapy suggests that optimal systemic management of MBC remains to be defined. Our data emphasizes the need to explore novel prognostic and therapeutic targets for this disease, especially if there continues to be increased recognition and/or incidence of MBC as suggested by our data.

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