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BREAST CANCER (B OVERMOYER, SECTION EDITOR)

Metaplastic Breast Cancer: Clinical Overview and Molecular Aberrations for Potential Targeted Therapy

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Abstract Metaplastic breast cancer is a rare subtype of invasive mammary carcinoma, with an aggressive behavior and usually poor outcome. Responses to systemic chemotherapy are suboptimal compared to patients with standard invasive ductal carcinoma. Limited data are available in regards to best treatment modalities, including chemotherapy. This review gives an overview of metaplastic breast cancer and its clinical and pathologic characteristics, in addition to treatment strategies, clinical trials, and future directions.

Keywords Metaplastic breast cancer · Metaplastic carcinoma · Carcinosarcoma · Sarcomatoid carcinoma of the breast

Introduction

Metaplastic breast cancer [1, 2] (MpBC) is a rare subtype of breast cancer, accounting for less than 1 % of all breast malignancies. MpBC was officially recognized as a distinct histopathologic subtype by the World Health Organization in 2000; thus, historical information about demographics, patient presentations, tumor characteristics, treatments, and outcomes is limited and continuously evolved.

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MpBCs usually consist of various combinations of poorly differentiated carcinoma, mesenchymal (sarcomatous component with highly mitotic activity), and/or other epithelial (squamous) components [3]. Under the microscope, the demarcation between carcinomatous and sarcomatous components is usually distinct, although in the literature, "carcinosarcoma" has been used inconsistently to describe both the classic carcinosarcoma and the other metaplastic breast sarcomatoid carcinomas including adenocarcinoma with varying degrees of sarcomatoid metaplasia [4]. In addition, descriptive terms such as biphasic and monophasic sarcomatoid carcinomas have been used. Biphasic tumors are overtly carcinomatous with distinct sarcoma-like elements, while monophasic tumors show features similar to those of sarcomas with epithelial differentiation detected by immunohistochemical methods [5]. The World Health Organization (WHO) classifies metastatic breast cancer (MBC) into epithelial type and mixed type [6].

The majority of MpBC tumors are estrogen receptor (ER), progesterone receptor (PR), and HER2-negative, triple-negative breast cancer (TNBC) and usually carry a worse prognosis compared to non-metaplastic TNBC [7]. Additionally, available data support that MpBCs are usually more aggressive than pure invasive ductal or invasive lobular histologies [8], often presenting with larger T staging (T2, T3); however, lymph node involvement is less likely to be noted.

Clinical Features

The majority of patients present with a palpable breast lump or mass that has rapidly grown. Fine needle aspiration (FNA) is usually positive for malignancy in cases of MpBC, although both ductal and metaplastic elements are only present in just over half of the cases; thus, it is common for metaplastic tumors to be diagnosed after definitive surgery [9, 10]. On

mammography, MpBC appears as predominately circumscribed, noncalcified lesions and may be mistaken as benign findings. One salient feature that may distinguish MpBC is the occurrence of a circumscribed portion with a spiculated portion, which is seen in tumors that have a significant mixture of metaplastic and invasive carcinoma growth patterns [11]. However, in most times, MpBC presents with features similar to invasive ductal carcinomas or benign lesions [12•]. A study by Choi reported that the most common mammographic findings were oval shape (37 %), circumscribed margin (59 %), and high density (74 %). The most common sonographic findings were irregular shape (59.4 %), microlobulated margin (41 %), complex echogenicity (81 %), parallel orientation (97 %), and posterior acoustic enhancement (50 %). Axillary lymph node metastases were noted during 25 % of the sonographic examinations. On MRI, the most common findings of margin and shape were irregularity (57 and 52.4 %, respectively). High signal intensity was the most common finding on T2-weighted images (57 %) [13•].

There are some differences noted between patients presenting with MpBC compared to patients with typical infiltrating ductal carcinoma (IDC) [14, 15••, 16]. In the National Cancer Data Base, it was noted that patients with MpBC were older (61.1 vs. 59.7 years) and had a significantly increased proportion of African-Americans (14.1 vs. 10.2 %), fewer T1 tumors (29.5 vs. 65.2 %), more N0 tumors (78.1 vs. 65.7 %), more poorly differentiated tumors (67.8 vs. 38.8 %), and fewer ER-positive tumors (11.3 vs. 74 %) than the IDC. Due to the larger tumor size in MpBC, they were treated with breast-conserving surgery less frequently (38.5 vs. 55.8 %) and chemotherapy was used more often for patients with MpBC. Usually, patients with MpBC present with negative lymph nodes, in spite of larger tumor size, and have a higher percentage of triple negative tumors. In addition, MpBC tends to have more local recurrences (chest wall) and distant (often lung) metastasis. As a result of large tumor size at presentation, skin or chest wall fixation, nipple retraction, and ulceration are relatively frequent. Occasionally, they present as inflammatory cancer [17]. The prognosis of MpBC was poorer than that of invasive ductal carcinoma and triple-negative invasive ductal carcinomas; the 5-year overall survival rate was 54.5 % in MpBC versus 85.1 % in invasive ductal carcinoma and 73.3 % in triple-negative invasive ductal carcinomas ($P<0.001$) [15••]. Similar findings were noted for 5-year progression-free survival. It is also noted that the tumor size greater than 5 cm, lymph node involvement, and high Ki-67 greater than 14 % were significantly related to 5-year overall survival and progression-free survival, indicating a poor prognosis [15••]. In addition to the high likelihood of presentation with a more advanced stage, these tumors tend to have a higher percentage of local recurrence and distant metastasis, especially in the presence of squamous cell carcinoma in lymph node metastasis, skin involvement, and younger age [8].

Pathogenesis

The histogenesis and clonality of MpBC has been debated over the course of time. Classically, these tumors were felt to have two individualized components, epithelial and sarcomatous, and the "collision hypothesis" suggested that these two distinct cells of origin collided some time during oncogenesis. More recent modern data based on molecular diagnostics confirm that the components of MpBC share single lineage [18], thus prompting additional theories to the development of these tumors. One theory suggests that the initial oncogenic event occurs in a multipotent or myoepithelial cell as origin for these tumors [4, 19, 20] and is supported based upon components of MpBC demonstrating dual staining with epithelial and myoepithelial markers such as actin and S-100. A second hypothesis is that the oncogenic event "converts" normal breast cells into carcinomas with more primitive features that enhance epithelial-mesenchymal transition (EMT) [21].

Histology

A recent review by Schwartz et al. [22••] has nicely outlined the subtypes and classifications of MpBC by different groups. The most commonly used criteria are those of the WHO which classify MpBC into epithelial type and mixed type [6]. Epithelial MpBC includes squamous cell carcinoma in addition to adenocarcinoma with spindle cell differentiation and adenosquamous carcinoma. Mixed type includes carcinoma with chondroid metaplasia, carcinoma with osseous metaplasia, and carcinosarcoma. Tse et al. [3] classified MpBC into epithelial-only carcinoma, biphasic epithelial and sarcomatoid carcinoma, and monophasic spindle cell carcinoma. Other classifications such as by Wargotz and Norris classified MpBC into matrix-producing carcinoma, squamous cell carcinoma, spindle cell carcinoma, carcinosarcoma, and metaplastic carcinoma with osteoclastic giant cells [23–26]. Oberman classified MpBC into spindle cell carcinoma, invasive ductal carcinoma with extensive squamous metaplasia, and invasive carcinoma with pseudosarcomatous metaplasia [27].

Differential Diagnosis

Though MpBC is often noted to be an aggressive subtype of breast cancer, some MpBCs are low-grade fibromatosis-like metaplastic tumors which portend a good prognosis [28]. These tumors are composed of a bland proliferation of spindle

cells reminiscent of fibromatosis, but in contrast to fibromatosis, the spindle cells are immunoreactive for cytokeratin. Sometimes the spindle cells are accompanied by a small component (less than 5 %) of overt ductal or squamous carcinoma. These tumors are regarded as the most indolent form of metaplastic carcinoma and are capable of local recurrence, but distant metastasis is uncommon as in pure fibromatosis of the breast. Some reports of spindle cell carcinomas of the breast may include a proportion of low-grade fibromatosis-like tumors, which consequently portend a relatively favorable prognosis and may contribute to a few published clinical experiences, showing no difference in prognosis between MpBC and non-MpBC. Malignant phyllode tumors and pure breast sarcomas should also be distinguished from MpBC, as they are often managed using different approaches for surgical resection, radiation therapy, and systemic treatments.

Prognosis

The prognosis of MpBC was poorer than that of invasive ductal carcinoma and triple-negative invasive ductal carcinomas; the 5-year overall survival (OS) rate was 54.5 % in MpBC versus 85.1 % in invasive ductal carcinoma and 73.3 % in triple-negative invasive ductal carcinomas ($P<0.001$) [15••]. Similar findings were noted for 5-year progression-free survival (PFS). It is also noted that tumor size greater than 5 cm, lymph node involvement, and high Ki-67 greater than 14 % were significantly related to 5-year overall survival and progression-free survival, indicating a poor prognosis [15••]. In addition, more patients with MpBC present as stage IV disease (10.3 %) than IDC (0.9 %) [29]. As with other types of IDC, the outcomes are worse with more advanced stage, as patients with metastatic MpBC have an average OS of less than a year. These tumors tend to have a higher percentage of local recurrence and distant metastasis, especially in the presence of squamous cell carcinoma in lymph node metastasis, skin involvement, and younger age [8].

Treatment of Metaplastic Breast Cancer

Given the relative rarity of MpBC, there are no randomized clinical trials to guide therapy selection; however, multimodality treatment with chemotherapy, mastectomy, and radiation should be considered as appropriate for stage and clinical features at the time of breast cancer diagnosis and therapy should not be denied solely due to a diagnosis of MpBC [30, 31] (Table 1).

Table 1 Retrospective analyses of clinical characteristics and outcomes in metaplastic breast cancer

Author [Ref]	Number	Age (median)	T size ≥2 cm (%)	Axillary node positive (%)	ER+/PR+/HER2+ (%)	Received systemic chemotherapy (adjuvant or neoadjuvant) (%)	Surgery: mastectomy/BCS (%)	Received adjuvant radiation (%)	Stage IV at diagnosis (%)	Outcome DFS/OS
Pezzi [14]	892	61.1	70.5	21.9	11.3/10.4/NR	53.4	55.6/44/unknown 0.4	42.5	4.6	NR
Rayson [32]	27	59	85[a]	13	14.8/14.8/NR	33.3[a]	74/26[a]	22[a]	3.7	3-year DFS 40 %, 3-year OS 71 %. Median DFS 2.4 years, median OS 6.4 years
Hennessy [33]	100	48	71[a]	28[a]	6–8/9–10/2	82	51–66/29–34	30–54	6	5-year RFS 52 %, 5-year OS 64 %
Wargotz [34]	70	56	87[a]	26	9[a]/13[a]/NR	3[a]	93/4	16	0	5-year OS 49 %
Okada [8]	46	53	72	34	0/0/2[a]–4	48[a]	NR	NR	NR	33 % reoccur
Jung [35]	35	47.4	74.3	29[a]	5.7/8.6/8.6	88.6	48.6/51.4	71.4[a]	8.6	5-year DFS 41.8 %, 5-year OS 62.8 %
Lester [36]	47	59	66	21	6/9/0	83[a]	53/47	68[a]	4	5-year DFS 44 %
Luini [37]	37	56.6	70.3	27	0/0/NR	NR	51[a]/46[a]	NR	NR	5-year OS 50 %[a]
Beatty [38]	24	56	46[a]	29	4/4/0	75[a]	25/75	92	0	5-year DFS 84 %, 5-year OS 83 %

BCS breast-conserving surgery; *DFS* disease-free survival; *RFS* relapse free survival; *OS* overall survival; *ER* estrogen receptor; *PR* progesterone receptor

[a] Percentages calculated for purposes of comparison

Systemic Therapy Retrospective cohort comparisons have been conducted to determine the impact of historical therapeutic decisions with the largest of such reports generated by the researchers at the M.D. Anderson Cancer Center. These investigators evaluated patients diagnosed with sarcomatoid carcinoma and carcinosarcoma using both the M.D. Anderson database (n=100) and the Surveillance, Epidemiology and End-Results (SEER) database (n=313) [33]. In multivariate analysis, the initial stage of the tumor was strongly associated with outcome, whereas the use of adjuvant chemotherapy or radiation therapy was not, though admittedly this may be due to limitations in sample size as well as potentially diminished benefit from these therapeutic modalities. Treatment with neoadjuvant chemotherapy was also associated with a lower pCR rate compared to that previously reported for non-metaplastic TNBC (10 vs. 30–40 %). Among these 21 patients, 15 received anthracycline-containing breast cancer regimens, 5 anthracycline/taxane based, and 1 doxorubicin/ifosfamide (sarcoma-type chemotherapy). In a study by Esbah et al. [31], 14 patients were included, nine received adjuvant chemotherapy, three neoadjuvant, and one palliative chemotherapy. The most commonly used regimen in this study was anthracycline-based regimen, and about half of the patients received docetaxel as well. More than half of the patients developed local or distant recurrences during 5 years of follow-up, with the lung being one of the most common sites of metastasis. A study by Rayson et al. [32] included a total of 29 patients, of which 14 patients received chemotherapy, and their data suggested that "standard" regimens may be relatively ineffective for MBC. These findings would suggest that a subset of MpBCs derive potentially curative benefit from systemic chemotherapy but also support the chemorefractory behavior of these cancers and the need for development of regimens to overcome drug resistance. Given the relative chemorefractory nature of MpBCs, it is optimal to treat localized disease with neoadjuvant chemotherapy to allow monitoring of treatment response and discontinuation of inactive cytotoxic therapies in the event of tumor progression. In the metastatic setting, previous series with small numbers of patients have described a few partial responses of limited duration noted with doxorubicin-containing regimens [32, 39]. Patients with metastatic disease have a median survival around 8 months, and considering that standard systemic chemotherapy regimens appear to be less effective, patients with metastatic MpBC should strongly consider participation in clinical trials of innovative therapeutic regimens [32].

Local Therapy Defining best local treatment for MpBC is often difficult. In contrast to invasive ductal carcinoma, in which multiple randomized trials have shown that mastectomy and breast-conserving treatment (BCT) with radiation have similar overall survival [40, 41], most data in MpBC are from retrospective reviews which are associated with limitations such as unknown margin status at the time of surgical resection. Because many patients may present with a rapidly growing, large mass, modified radical mastectomy (MRM) is usually the most appropriate option for optimal surgical treatment, although BCT, lumpectomy, and local excision with wide margins should be considered for eligible patients [42•]. MRM was the main surgical procedure in most series [32, 39, 43]; however, several studies have shown that there is no difference in overall survival between mastectomy and BCT in patients who are candidates for breast-conserving surgery [42•, 44–46]. For example, in the MD Anderson retrospective experience, only T stage remained statistically significant for overall survival using multivariable analysis, while T stage and surgery type (mastectomy vs. breast-conserving surgery (BCS)) were significantly related to both recurrence-free survival and local recurrence-free survival [33]. These findings likely reflect the ability of surgical resection to cure a subset of patients with local recurrences as well as the high propensity for patients with MpBC to harbor undetectable distant metastatic disease at the time of initial diagnosis/surgical resection. In addition, the role of surgery to evaluate the axilla is very important, as axillary lymph nodes are noted to be involved in about 20–30 % of MpBC, and this is usually associated with a poorer prognosis. Most retrospective reviews document the results of complete axillary lymph node dissection, with a smaller number of patients undergoing sentinel lymph node biopsy. Though the data are lacking due to small patient numbers, there is no suggestion that patients who have negative sentinel lymph node biopsies have a worse prognosis than those who undergo complete axillary lymph node dissection with negative findings. As such, it is generally recommended for patients with clinically negative nodes to undergo sentinel lymph node biopsy. If disease is found in the sentinel nodes, patients should strongly consider ipsilateral complete axillary node dissection given the somewhat refractory nature of MpBC to standard chemotherapy and radiation.

The role of radiation therapy (RT) is less clear in the treatment of MpBC. A retrospective review of the SEER data by Tseng and Martinez [45] reviewed 1501 patients with MpBC diagnosed between 1988 and 2006. RT was given to 38.6 %. In the overall analysis, RT therapy provided an OS and disease-specific survival (DSS) benefit. When patients were stratified according to the type of surgery, RT provided an OS but not a DSS benefit to lumpectomy and mastectomy patients. As per the authors, these findings support the use of RT for patients with MBC following lumpectomy or mastectomy. In addition, a case series review of 18 patients with MBC, of which 72 % received RT, noted a significantly longer OS time among patients treated with adjuvant RT [47••].

In conclusion, on the basis of existing literature, and considering current standard treatments, it is reasonable to suggest local excision with wide margins in the form of mastectomy,

partial mastectomy, or wide local excision, followed by adjuvant radiation as clinically indicated to reduce the risk of local recurrence. As such, a multidisciplinary team approach would be considered ideal.

Future Directions and Novel Treatments

MpBC presents as stage IV in about 10 % of patients and up to 50 % of patients with localized disease and develops distant metastases. These patients usually have an ominous prognosis, with OS less than a year. MpBCs also present more commonly as a triple-negative disease with limited targeted therapy options. Differing transcript expression patterns have been identified between MpBCs and non-metaplastic, basal-like invasive ductal carcinomas [48]. For example, DNA repair pathways (TOP2A and BRCA1) were significantly downregulated in MpBCs compared to basal-like tumors. MpBCs (particularly those with spindle cell morphology) commonly showed downregulation of genes involved in cell-cell adhesion and upregulation of genes associated with extracellular matrix production [49]. Tumors with squamous and sarcomatoid metaplasia were also found to have upregulation of *TWIST1* and *SNAIL2*/*SLUG*, important controllers of EMT [50, 51]. Genomic signatures obtained from MpBCs also closely resembled an "EMT-core signature" derived by overexpressing EMT-inducing transcription factors in cell lines [52]. This inherent activation of EMT is presumed to be the reason MpBCs are associated with a higher rate of developing distant metastasis.

Hennessy et al. found that MpBCs with squamous and sarcomatoid metaplasia also closely resemble claudin-low tumors, a subtype of TNBC enriched in markers of EMT and notable for the absence of luminal differentiation markers [18, 53]. Furthermore, when a group of molecularly identified claudin-low tumors was histologically characterized, 10–20 % of them were identified as MpBCs [54]. MpBCs also have a high rate of genomic aberrations that may potentially result in activation of PI3K/mTOR/Akt pathway; notably, a high rate of mutation in *PIK3CA* (47 %) and occasional mutations in *PTEN* (5 %) was higher that would be expected in basal-like IDC (8 %) [18]. Reverse phase protein array (RPPA) confirmed elevations in the phosphorylation of phosphatidylinositol 3-kinase/Akt pathway proteins, further suggesting that inhibitors of the PI3K pathway may be a viable-targeted therapy option for the treatment of MpBCs [18].

Given these features, patients with metastatic disease ($n=5$) were evaluated at MD Anderson within the Center of Targeted Therapy and were treated with mTOR inhibitor (temsirolimus) in combination with liposomal doxorubicin and bevacizumab (DAT). Though the size of this cohort may inaccurately magnify the effects of the regimen, therapy with DAT resulted in a clinical benefit rate (CR+PR=SD≥ 6 months) of 60 %, including one complete response of greater than a 3-year duration (to date, the patient continues in remission on everolimus maintenance) [55]. Considering the high rate of PI3K/PTEN mutations and activation of the PI3K pathway in metaplastic tumors, and the response seen to the DAT regimen, it is possible that therapy targeting the PI3K/mTOR/Akt pathway may show promising activity in metaplastic cancers in larger randomized phase II trials.

Conclusion

MpBCs are a heterogeneous group of tumors with histologic variation that contain at least one area of epithelial carcinoma transitioning to a non-epithelial phenotype. These tumors appear to be more aggressive than IDC, tend to have a larger tumor size at presentation and less axillary lymph node involvement, and are most often triple negative. Though limited therapeutic outcome data exist for this group of patients, a multidisciplined approach is highly recommended and patients with localized disease who are candidates for systemic therapy should be treated using neoadjuvant chemotherapy to allow monitoring of treatment response and discontinuation of inactive cytotoxic therapies in the event of tumor progression. Local excision with "wide" margins (in form of mastectomy, wide local excision, or partial mastectomy) with axillary lymph node sampling (sentinel lymph node biopsy or axillary lymph node dissection) followed by radiation (if clinically indicated) is the recommended approach. Although data on responsiveness to cytotoxic chemotherapy are limited, the use of anthracycline-based neoadjuvant or adjuvant chemotherapy may be associated with improvements in patient outcomes and should be considered over non-anthracycline-containing regimens. In the metastatic setting, referring patients for participation in clinical trials with targeted agents, particularly regimens containing PI3K/Akt/mTOR inhibitors, should strongly be considered as the outcome with standard chemotherapy is dismal and these tumors have been associated with a relatively high rate of molecular aberrations that may activate the PI3K/Akt/mTOR pathway.

Compliance with Ethics Guidelines

Conflict of Interest Sausan Abouharb and Stacy Moulder declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Gogas J, Kouskos E, Markopoulos C, Mantas D, Antonopoulou Z, Kontzoglou K, et al. Carcinosarcoma of the breast: report of two cases. Eur J Gynaecol Oncol. 2003;24(1):93–5.
2. Aritas Y, Bedirli A, Karahan OI, Okten T, Sakrak O, Ince O. Carcinosarcoma of the breast: clinicopathologic and radiologic findings in an unusual case. Breast J. 2003;9(4):323–4. doi:10.1046/j.1524-4741.2003.09416.x.
3. Tse GM, Tan PH, Putti TC, Lui PC, Chaiwun B, Law BK. Metaplastic carcinoma of the breast: a clinicopathological review. J Clin Pathol. 2006;59(10):1079–83. doi:10.1136/jcp.2005.030536.
4. Wada H, Enomoto T, Tsujimoto M, Nomura T, Murata Y, Shroyer KR. Carcinosarcoma of the breast: molecular-biological study for analysis of histogenesis. Hum Pathol. 1998;29(11):1324–8.
5. Foschini MP, Dina RE, Eusebi V. Sarcomatoid neoplasms of the breast: proposed definitions for biphasic and monophasic sarcomatoid mammary carcinomas. Semin Diagn Pathol. 1993;10(2):128–36.
6. Bocker W. WHO classification of breast tumors and tumors of the female genital organs: pathology and genetics. Verh Dtsch Ges Pathol. 2002;86:116–9.
7. Bae SY, Lee SK, Koo MY, Hur SM, Choi MY, Cho DH, et al. The prognoses of metaplastic breast cancer patients compared to those of triple-negative breast cancer patients. Breast Cancer Res Treat. 2011;126(2):471–8. doi:10.1007/s10549-011-1359-8.
8. Okada N, Hasebe T, Iwasaki M, Tamura N, Akashi-Tanaka S, Hojo T, et al. Metaplastic carcinoma of the breast. Hum Pathol. 2010;41(7):960–70. doi:10.1016/j.humpath.2009.11.013.
9. Stanley MW, Tani EM, Skoog L. Metaplastic carcinoma of the breast: fine-needle aspiration cytology of seven cases. Diagn Cytopathol. 1989;5(1):22–8.
10. Gupta RK. Cytodiagnostic patterns of metaplastic breast carcinoma in aspiration samples: a study of 14 cases. Diagn Cytopathol. 1999;20(1):10–2. doi:10.1002/(SICI)1097-0339(199901)20:1<10::AID-DC3>3.0.CO;2-5.
11. Patterson SK, Tworek JA, Roubidoux MA, Helvie MA, Oberman HA. Metaplastic carcinoma of the breast: mammographic appearance with pathologic correlation. AJR Am J Roentgenol. 1997;169(3):709–12. doi:10.2214/ajr.169.3.9275883.
12.• Leddy R, Irshad A, Rumboldt T, Cluver A, Campbell A, Ackerman S. Review of metaplastic carcinoma of the breast: imaging findings and pathologic features. J Clin Imaging Sci. 2012;2:21. doi:10.4103/2156-7514.95435. *Pathologic and imaging findings that physicians should be aware of to recognize metaplastic breast cancer.*
13.• Choi BB, Shu KS. Metaplastic carcinoma of the breast: multimodality imaging and histopathologic assessment. Acta Radiol. 2012;53(1):5–11. doi:10.1258/ar.2011.110341. *Imaging and pathologic factors to be considered in the diagnosis of metaplastic breast cancer that should alert oncologists.*
14. Pezzi CM, Patel-Parekh L, Cole K, Franko J, Klimberg VS, Bland K. Characteristics and treatment of metaplastic breast cancer: analysis of 892 cases from the National Cancer Data Base. Ann Surg Oncol. 2007;14(1):166–73. doi:10.1245/s10434-006-9124-7.
15.•• Song Y, Liu X, Zhang G, Song H, Ren Y, He X, et al. Unique clinicopathological features of metaplastic breast carcinoma compared with invasive ductal carcinoma and poor prognostic indicators. World J Surg Oncol. 2013;11:129. doi:10.1186/1477-7819-11-129. *Comparison between clinicopathological features and outcomes of metaplastic breast carcinoma and invasive ductal carcinoma, showing a poorer outcome in metaplastic breast carcinoma.*
16. Lai HW, Tseng LM, Chang TW, Kuo YL, Hsieh CM, Chen ST, et al. The prognostic significance of metaplastic carcinoma of the breast (MCB)—a case controlled comparison study with infiltrating ductal carcinoma. Breast. 2013;22(5):968–73. doi:10.1016/j.breast.2013.05.010.
17. Kuo SH, Chen CL, Huang CS, Cheng AL. Metaplastic carcinoma of the breast: analysis of eight Asian patients with special emphasis on two unusual cases presenting with inflammatory-type breast cancer. Anticancer Res. 2000;20(3B):2219–22.
18. Hennessy BT, Gonzalez-Angulo AM, Stemke-Hale K, Gilcrease MZ, Krishnamurthy S, Lee JS, et al. Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics. Cancer Res. 2009;69(10):4116–24. doi:10.1158/0008-5472.CAN-08-3441.
19. Santiago Perez JT, Perez Vazquez MR, Rivera Valdespino Ade L, Gil Valdes D. Carcinosarcoma of the breast: a tumour with controversial histogenesis. Clin Transl Oncol. 2005;7(6):255–7.
20. Teixeira MR, Qvist H, Bohler PJ, Pandis N, Heim S. Cytogenetic analysis shows that carcinosarcomas of the breast are of monoclonal origin. Genes, Chromosomes Cancer. 1998;22(2):145–51.
21. Osako T, Horii R, Ogiya A, Iijima K, Iwase T, Akiyama F. Histogenesis of metaplastic breast carcinoma and axillary nodal metastases. Pathol Int. 2009;59(2):116–20. doi:10.1111/j.1440-1827.2008.02339.x.
22.•• Schwartz TL, Mogal H, Papageorgiou C, Veerapong J, Hsueh EC. Metaplastic breast cancer: histologic characteristics, prognostic factors and systemic treatment strategies. Exp Hematol Oncol. 2013;2(1):31. doi:10.1186/2162-3619-2-31. *A great updated overview of Metaplastic Breast Cancer.*
23. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. I. Matrix-producing carcinoma. Hum Pathol. 1989;20(7):628–35.
24. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. IV. Squamous cell carcinoma of ductal origin. Cancer. 1990;65(2):272–6.
25. Wargotz ES, Deos PH, Norris HJ. Metaplastic carcinomas of the breast. II. Spindle cell carcinoma. Hum Pathol. 1989;20(8):732–40.
26. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast: V. Metaplastic carcinoma with osteoclastic giant cells. Hum Pathol. 1990;21(11):1142–50.
27. Oberman HA. Metaplastic carcinoma of the breast. A clinicopathologic study of 29 patients. Am J Surg Pathol. 1987;11(12):918–29.
28. Gobbi H, Simpson JF, Borowsky A, Jensen RA, Page DL. Metaplastic breast tumors with a dominant fibromatosis-like phenotype have a high risk of local recurrence. Cancer. 1999;85(10):2170–82.
29. Park HS, Park S, Kim JH, Lee JH, Choi SY, Park BW, et al. Clinicopathologic features and outcomes of metaplastic breast carcinoma: comparison with invasive ductal carcinoma of the breast. Yonsei Med J. 2010;51(6):864–9. doi:10.3349/ymj.2010.51.6.864.
30. Sanguinetti A, Lucchini R, Santoprete S, Farabi R, Fioriti L, Bistoni G et al. Metaplastic carcinoma of the breast treatment, results and prognostic factors based on international literature. Ann Ital Chir. 2013; 84.
31. Esbah O, Turkoz FP, Turker I, Durnali A, Ekinci AS, Bal O, et al. Metaplastic breast carcinoma: case series and review of the literature. Asian Pac J Cancer Prev. 2012;13(9):4645–9.
32. Rayson D, Adjei AA, Suman VJ, Wold LE, Ingle JN. Metaplastic breast cancer: prognosis and response to systemic therapy. Ann Oncol. 1999;10(4):413–9.

33. Hennessy BT, Giordano S, Broglio K, Duan Z, Trent J, Buchholz TA, et al. Biphasic metaplastic sarcomatoid carcinoma of the breast. Ann Oncol. 2006;17(4):605–13. doi:10.1093/annonc/mdl006.
34. Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. III. Carcinosarcoma. Cancer. 1989;64(7):1490–9.
35. Jung SY, Kim HY, Nam BH, Min SY, Lee SJ, Park C, et al. Worse prognosis of metaplastic breast cancer patients than other patients with triple-negative breast cancer. Breast Cancer Res Treat. 2010;120(3):627–37. doi:10.1007/s10549-010-0780-8.
36. Lester TR, Hunt KK, Nayeemuddin KM, Bassett Jr RL, Gonzalez-Angulo AM, Feig BW, et al. Metaplastic sarcomatoid carcinoma of the breast appears more aggressive than other triple receptor-negative breast cancers. Breast Cancer Res Treat. 2012;131(1):41–8. doi:10.1007/s10549-011-1393-6.
37. Luini A, Aguilar M, Gatti G, Fasani R, Botteri E, Brito JA, et al. Metaplastic carcinoma of the breast, an unusual disease with worse prognosis: the experience of the European Institute of Oncology and review of the literature. Breast Cancer Res Treat. 2007;101(3):349–53. doi:10.1007/s10549-006-9301-1.
38. Beatty JD, Atwood M, Tickman R, Reiner M. Metaplastic breast cancer: clinical significance. Am J Surg. 2006;191(5):657–64. doi:10.1016/j.amjsurg.2006.01.038.
39. Al Sayed AD, El Weshi AN, Tulbah AM, Rahal MM, Ezzat AA. Metaplastic carcinoma of the breast clinical presentation, treatment results and prognostic factors. Acta Oncol. 2006;45(2):188–95. doi:10.1080/02841860500513235.
40. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227–32. doi:10.1056/NEJMoa020989.
41. Jacobson JA, Danforth DN, Cowan KH, D'Angelo T, Steinberg SM, Pierce L, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. New England J Med. 1995;332(14):907–11. doi:10.1056/NEJM199504063321402.
42.• Hu Q, Chen WX, Zhong SL, Li J, Luo Z, Tang JH, et al. Current progress in the treatment of metaplastic breast carcinoma. Asian Pac J Cancer Prev. 2013;14(11):6221–5. *Review of current multimodality treatment recommendations of metaplastic breast cancer.*
43. Chao TC, Wang CS, Chen SC, Chen MF. Metaplastic carcinomas of the breast. J Surg Oncol. 1999;71(4):220–5.
44. Dave G, Cosmatos H, Do T, Lodin K, Varshney D. Metaplastic carcinoma of the breast: a retrospective review. Int J Radiat Oncol Biol Phys. 2006;64(3):771–5. doi:10.1016/j.ijrobp.2005.08.024.
45. Tseng WH, Martinez SR. Metaplastic breast cancer: to radiate or not to radiate? Ann Surg Oncol. 2011;18(1):94–103. doi:10.1245/s10434-010-1198-6.
46. Gultekin M, Eren G, Babacan T, Yildiz F, Altundag K, Guler N, et al. Metaplastic breast carcinoma: a heterogeneous disease. Asian Pac J Cancer Prev. 2014;15(6):2851–6.
47.•• Nowara E, Drosik A, Samborska-Plewicka M, Nowara EM, Stanek-Widera A. Metaplastic breast carcinomas - analysis of prognostic factors in a case series. Contemp Oncol. 2014;18(2):116–9. doi:10.5114/wo.2014.41392. *Single institution case series with review of outcomes, treatment modalities, and pathologic findings.*
48. Weigelt B, Kreike B, Reis-Filho JS. Metaplastic breast carcinomas are basal-like breast cancers: a genomic profiling analysis. Breast Cancer Res Treat. 2009;117(2):273–80. doi:10.1007/s10549-008-0197-9.
49. Lien HC, Hsiao YH, Lin YS, Yao YT, Juan HF, Kuo WH, et al. Molecular signatures of metaplastic carcinoma of the breast by large-scale transcriptional profiling: identification of genes potentially related to epithelial-mesenchymal transition. Oncogene. 2007;26(57):7859–71. doi:10.1038/sj.onc.1210593.
50. Karreth F, Tuveson DA. Twist induces an epithelial-mesenchymal transition to facilitate tumor metastasis. Cancer Biol Ther. 2004;3(11):1058–9. doi:10.4161/cbt.3.11.1302.
51. Valsesia-Wittmann S, Magdeleine M, Dupasquier S, Garin E, Jallas AC, Combaret V, et al. Oncogenic cooperation between H-Twist and N-Myc overrides failsafe programs in cancer cells. Cancer Cell. 2004;6(6):625–30. doi:10.1016/j.ccr.2004.09.033.
52. Taube JH, Herschkowitz JI, Komurov K, Zhou AY, Gupta S, Yang J, et al. Core epithelial-to-mesenchymal transition interactome gene-expression signature is associated with claudin-low and metaplastic breast cancer subtypes. Proc Natl Acad Sci U S A. 2010;107(35):15449–54. doi:10.1073/pnas.1004900107.
53. Herschkowitz JI, Simin K, Weigman VJ, Mikaelian I, Usary J, Hu Z, et al. Identification of conserved gene expression features between murine mammary carcinoma models and human breast tumors. Genome Biol. 2007;8(5):R76. doi:10.1186/gb-2007-8-5-r76.
54. Prat A, Parker JS, Karginova O, Fan C, Livasy C, Herschkowitz JI et al. Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. Breast Cancer Res. 12(5):R68. doi: 10.1186/bcr2635.
55. Moulder S, Moroney J, Helgason T, Wheler J, Booser D, Albarracin C et al. Responses to liposomal doxorubicin, bevacizumab, and temsirolimus in metaplastic carcinoma of the breast: biologic rationale and implications for stem-cell research in breast cancer. J Clin Oncol. 29(19):e572-5. doi: 10.1200/JCO.2010.34.0604.