REVIEW ARTICLE

METAPLASTIC BREAST CANCER: PATHOLOGICAL SUBTYPES, CLINICAL PRESENTATION, IMAGING CHARACTERISTICS, IMMUNOHISTOCHEMISTRY, TREATMENT AND PROGNOSIS

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DOI: 10.5455/ijmsph.2014.090720141 Received Date: 15.06.2014 Accepted Date: 09.07.2014

ABSTRACT
Metaplastic breast cancer is a rare subtype of breast cancer that is histologically heterogeneous, being composed of both sarcomatous and epithelial components. It presents as rapidly growing palpable masses. Incidence of nodal metastasis is low, as compared to intraductal carcinoma, but it has a high metastatic potential and more chances of local recurrence. Many different pathological classifications are available, the most popular being "Wargotz and Norris classification". Imaging features mimic those of intraductal carcinoma. Immunohistochemically, these tumors show a basal/myoepithelial phenotype with positivity for cytokeratins, AE1/AE3, smooth muscle actin, p63, alpha B-crystallin, etc. These tumors show no or very low positivity for hormone receptors or HER-2 over expression. Therefore, they are often called triple negative carcinomas. They are aggressive tumors with suboptimal response to standard chemotherapy regimens. Overall prognosis of the patients with metaplastic breast cancer is worse than the patients with intraductal breast carcinoma. Further research is needed for formulating targeted therapies for this aggressive tumor.
Key Words: Metaplastic Breast Cancer; Intraductal Cancer; Tumor Size

Introduction

Metaplastic breast cancer (MpBC) is a rare, histologically diverse breast cancer which represents less than 1% of breast cancers.[1,2] It consists of a heterogeneous group of malignant neoplasms containing both glandular and non – glandular components with mixed epithelial and mesenchymal differentiation.[3] The sarcomatous elements include cartilage, bone, myxoid changes and spindle cell component.[4] WHO classifies Metaplastic breast cancer into epithelial and mixed type with further differentiation into subtypes.[5] The more popular Wargotz and Norris classification differentiates Metaplastic breast cancers into 5 subtypes: spindle-cell, squamous cell, carcinosarcoma, matrix-producing and MpBC with osteoclastic giant cells.[6-8]

Although pathogenesis and cell of origin of metaplastic breast cancer (MpBC) is still not completely clear, it has been claimed to be of myoepithelial origin.[9] Because of the fact that it shows cytokeratin positivity in both epithelial and mesenchymal elements, the term 'metaplastic carcinoma' has been applied to them.[10] Most of these high grade neoplasms show a basal-like phenotype, few being positive for hormone receptors or HER-2 over-expression (0–8%).[3,11,12]

The prognosis of MpBC is reported to be worse than breast adenocarcinoma.[13] The worse prognosis of MpBC can not only be explained by greater size but also with histopathological heterogeneity, higher proliferation index and poorer differentiation although there is less incidence of axillary lymph node involvement as compared to intraductal carcinoma (IDC) of breast.

Epidemiology

Metaplastic carcinoma is commonly diagnosed in women >50 years of age. It usually presents as T2 disease, with a mean tumor size of 3.4–4.4 cm. The incidence is <1% of all invasive breast carcinoma, with a relatively higher prevalence in African American or Hispanic women (20%).[6,9] Most studies report a lower rate of axillary nodal involvement than that is seen with IDC.[14,15]

Pathological Subtypes

Wargotz and Norris classification differentiates metaplastic breast cancers into 5 subtypes. Spindle cell type is the most common type and shows cells forming poorly cohesive sheets or predominant spindle cell morphology.[3,6,11]

Carcinosarcoma is defined as a biphasic – composed of50% malignant-looking spindle cells and 50% pleomorphic bipolar cells or polymorphic cellular populations. It is less immunoreactive to cytokeratin and the high degrees of cellularity, nuclear pleomorphism and mitotic activity in the spindle cell component

distinguish it as spindle cell carcinoma.[15]

The squamous cell carcinoma subtype demonstrates infiltrating squamous carcinoma with polygonal cells, eosinophilic cytoplasm and possible keratin pearl formation.[6,11]

Matrix-producing carcinoma is defined as an invasive breast carcinoma with a direct transition of carcinoma to cartilaginous or osseous matrix without an intervening spindle cell component.[16]

The osteoclastic giant cell subtype shows intraductal or infiltrating carcinoma contiguous or mixed with spindle cell or sarcomatous stroma plus osteoclastic cells.[6]

Clinical Presentation

Clinically, the usual presentation is with palpable breast mass in women more than 50 years of age.[7,17] MpBC commonly presents as a rapidly growing mass, usually greater than 2 cm.[9,18] A study from California, USA found the mean tumor size of 4.62 cm in patients of metaplastic breast cancer.[19] The mean age and the median size were 59 years and 3.4 cm respectively in a retrospective study done between 1976 and 1997 at Mayo clinic.[20] A study conducted at Taiwan found median age to be 50.5 years, and median tumor size to be 4.8 cm.[21] Median size of 3 cm was observed by Verma et al in 2012.[22]

Fixation to the underlying deep tissues or to the skin has been reported, in one study, in over 20% of patients.[18] Nodal involvement has been shown to be less common compared to typical breast adenocarcinomas, with incidence ranging from 6 to 26%, as reported by Wargortz et al, Rayson et al, Gutman et al and many other authors.[15,20,23-26] Oberman[27] reported lymph nodal metastases in only 2 (6.9%) of 29 patients. Pitts et al.[28] observed that 7 out of 29 patients (24.1%) had axillary nodal metastasis. However, some studies have found a higher incidence of nodal metastasis. Chao et al[21] found that 50% of their patients had nodal metastases at the time of diagnosis. Tse et al[11] and Esbah et al[29] found axillary lymph node metastases in 56% and 63.4 % of their patients respectively.

MpBC tumors have a high metastatic potential and preferred route of metastasis is hematogenous rather than lymphatic.[5,8,27] Lung and bone metastasis are more common.[15,23,27] Esbah et al found that more than half of their MpBC patients developed local and distant metastasis during 5 years of follow-up, and distant metastatic sites were mostly lungs and brain.[29]

The incidence of stage IV disease at presentation for MpBC is higher than with intra ductal carcinoma (IDC). Park et al found that 10.3% of their patients with MpBC had metastatic disease at the time of diagnosis, compared to only 0.9% of patients with IDC.[30] Pezzi et al found that MpBC patients present with advanced stage, as compared to invasive breast cancer.[14]

MpBC has been associated with increased risk of local recurrence. Local recurrence ranged from 35-62% in node negative MpBC within 5 years of diagnosis.[15,23-25] Rayson et al noted a 53% risk of local recurrence within 2 years.[20]

Imaging Characteristics

MpBC is seen as a high density mass on mammogram with either circumscribed, obscured, irregular and/or spiculated margins.[7,17,27,30] Yang et al. reported a more benign appearance on mammography, including a round or oval shape and circumscribed margins.[8] The MpBC lesions are often non-calcified.[8] If calcifications are present, the pattern is amorphous, coarse, punctuate or pleomorphic.[17,30] Park et al. described a high rate of architectural distortion associated with MpBC.[30]

Sonographically, MpBC appears as heterogeneous or hypoechoic solid mass or a mixed cystic and solid mass.[8,17,30] MpBC shows posterior acoustic enhancement.[3] On MRI, MpBC looks like an irregular mass with speculated margins, often intermediate to increased T2 signal intensity, and isointense or hypointense on T1 weighted imaging.[17,31] Velasco et al. reported an increase in T2 hyperintensity in cancers of 91% of patients with MpBC.[31]

Immunohistochemical Characteristics

MpBC show a basal / myoepithelial phenotype indicating that they belong to the morphological spectrum of 'basal-like' breast carcinomas.[12,32-37] MpBC usually presents as triple negative or basal-like breast cancer.[12,38] MpBC shows consistent over-expression of epidermal growth factor receptor (EGFR).[39,40] Leibl and Moinfar, in their study, found that 14 out of 20 patients were positive for EGFR expression.[41] Only few show positivity for hormone receptorsor HER-2 over expression (0–8%).[11,12] Esbah et al found in their study that one patient was ER positive (7.1%), 2 patients were PR

positive (14.3%) and 1 patient was HER-2 positive (7.1%). Lower ER, PR and HER-2 overexpression were reported in studies done by Bae et al., 2011; Lim et al., 2010 and Toumi et al., 2011.[42-44]

Metaplastic carcinomas, in consistence with their basal-cell phenotype, express basal keratins (CK5/6, CK14).[33] Cytokeratins can be used to differentiate between MpBC and spindle cell lesions of the breast.[37,45-47] Carter et al.[35] found that pankeratin (MNF116) is the most sensitive marker (93%), followed by cytokeratins 14 (90%), for identifying MpBC. Several studies have found AE1/AE3 expression, ranging from 63% to 100% in MpBC.[25,48-51]

Markers for myoepithelial differentiation have been found in MpBC. Reis-Filho et al.[36] found frequent positivity for SMA and CK14, as well as immunoreactivity for S100 protein, p63, maspin and p-cadherin. Dunne et al.[33] reported focal staining for smooth muscle actin (SMA) in 79% (11/14) of MpBC cases. Other studies have found consistent expression of maspin and cadherins in sarcomatoid breast carcinoma.[34]

p63 has emerged to be a very useful marker for MpBC. Koker and Kleer[52] reported expression of p63 in all 10 spindle cell carcinomas examined. Leible et al.[32] found positive staining for p63 (70%), SMA (60%), S100 protein (45%) and CD10 (80%). Tse et al. found p63 to be a useful marker in the diagnosis of MpBC with a sensitivity of 65% and specificity of 96% and an accuracy of 78%.[53] Nassar et al found OSCAR, WS-KER and p63 to be the most sensitive and specific markers for identifying MpBC.[54]

Sitterding et al found alphaB-crystallin to be a sensitive (81%) and specific (100%) marker for basal-like breast carcinomas.[55] Glbert et al found that the majority of their cases were positive for cytokeratin 5/6 (58%), p63 (59%), KIT (24%) and EGFR overexpression (66%) but no EGFR or KIT activating mutations were present.[56]

Prognosis

Tumor stage, histologic subtype and size of the tumor have appeared to be important prognostic factors. Prognosis of the patients with metaplastic breast carcinoma depends on the stage of the disease. Kaufman et al, Chao et al and Clark et al found that Stage I and II patients had a better survival rate than stage III and stage IV patients.[18,21,58] Pitts et al. observed an overall survival rate of 47%, and a 5-year disease-free survival rate of 43%.[28] Kaufman et al. reported that the overall survival rate of 44%, with an estimated 5-year survival for TNM stages I, II, and III of 56%, 26%, and 18%, respectively.[18]

Tumor size has been found to be a very important prognostic factor. Kaufman et al, Wargotzet al and Oberman found that the size of the tumor at the time of initial treatment best correlated with prognosis.[18,26,27] Chao et al found that patients with a size less than 5 cm had a better survival rate.[21]

Many studies have found tumor subtype to be important in prognosis. Wargotz et al found poorest 5 year overall survival rates for those diagnosed with carcinosarcoma and the best for those with matrix-producing carcinomas (5 year survival rate of 49% and 68%, respectively).[23,25] Barnes et al found that patients with adenosquamous cell carcinoma tended to have a better outcome than the other variants of MpBC combined.[58]

Many studies have indicated that status of the axillary lymph nodes in the patients with metaplastic carcinoma do not correlate with prognosis.[18,27,28] However, a study done by Chao et al found that axillary lymph node status at the time of diagnosis was strongly associated with survival of the patients.

Treatment

The response of MpBC to systemic chemotherapy has been consistently poor. Rayson et al 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.[20] Bae et al. reported no survival advantage of adjuvant chemotherapies in 42 of 47patients with MpBC.[42] Chao et al confirmed the ineffectiveness of adjuvant chemotherapy on disease-free survival during 3 to 9 years of follow-up in MpBC.[21] Chen et al. reported 83% progression rate in patients, who received neoadjuvant chemotherapy. They also found no response to anthracycline, vinorelbine or cyclophosphamide based regimens and a partial response with a taxane based regimen (17.6%).[59] Hennessy et al found only 10% complete response rate in patients with MpBC undergoing neoadjuvant chemotherapy.[60] Cardoso et al. documented 16.7% response rate to chemotherapy in metastatic MpBC.[61]

Only few studies have found chemotherapy to be of benefit in patients with MpBC. Gutman et al found both

disease-free and overall survival benefit with adjuvant chemotherapy in stage 1 and 2 MpBC patients.[24]

Conclusion

MpBC is a rare disease entity accounting for less than 1% of all breast carcinomas. MpBC comprise of ahetero-geneous and histologically diverse group consisting of both epithelial and mesenchymal elements. MpBC is characterized by a larger size at presentation, lower rates of axillary nodal involvement, higher rates of both local recurrence and metastasis and higher rates of ER, PR and Her2 negativity. Markers like AE1/AE3, SMA, p63 are consistently expressed and are useful in the diagnosis. All MpBC's are aggressive, have a poorer prognosis and show a sub-optimal response to systemic therapies when compared to other invasive breast cancers. Further research is needed for formulating comprehensive treatment plans and specific treatment guidelines which are lacking at present.

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Cite this article as: Wani FA. Metaplastic breast cancer: Pathological subtypes, clinical presentation, imaging characteristics, Immunohistochemistry, treatment and prognosis. Int J Med Sci Public Health 2014;3:1029-1033.
Source of Support: Nil
Conflict of interest: None declared