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Pathology

Metaplastic Breast Carcinoma: A Review

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ABSTRACT Metaplastic Breast Carcinoma is a unique and aggressive type of breast cancer identified by the W.H.O. owing to its morphological features and heterogeneity. It consists of combinations of mesenchymal and carcinomatous components and shares similarities with Invasive Ductal Carcinoma and benign lesions, with a predilection towards presenting as a case of triple negative (ER, PR, Her2/Neu) breast cancer with a large tumor mass. Treatment paradigms range from radical surgery to adjuvant chemotherapy, with poor prognosis also showcasing metastatic preferences to the lung and brain, thus lowering the overall efficacy of the treatment and management strategies. This extensive review of literature summarizes the incidences, clinical features, pathological and molecular diagnosis along with treatment modalities with a note on prognosis.

KEYWORDS : Breast cancer, metaplastic breast cancer, systematic-review

Introduction:

The latest edition of the W.H.O. classification of tumours of the breast published in 2012 encompass contributions from an international panel of breast pathologists, incorporating current knowledge of breast neoplasms, with updates on classification based on improved clinical pathobiological and molecular genetic information.[1] Metaplastic Carcinoma of the Breast (MCB) was first described in 1973 by Huvos et al and was defined as a mammary carcinoma with mixed epithelial and sarcomatoid components.[2]

Breast cancer is the most frequently diagnosed cancer in women worldwide, with MCB only occurring in between 0.02% and 5% of all breast carcinoma patients.[3] MCB represents 0.25% to 1% of all breast cancers diagnosed annually.[4,5] MCB have both epithelial and mesenchymal components and it is not uncommon to find 2-3 components coexisting in the same tumour.

The prognosis is worse, so early diagnosis and treatment can be life saving.[6] Breast tissue contains various tissue components that are under the influence of hormones thus presenting with varied pathology and correlation with clinical presentation, history and examination findings along with radiological assessment can help reduce a misdiagnosis.[7]

Clinicopathological Features:

MCB predominantly occurs in patients over 50 years of age, however a few case series have shown a median age of 45.5 years.[3,6] Female preponderance is obvious but rarely male metaplastic breast carcinoma patients were reported in case series.[8] Although there are fewer tendencies to involve axillary lymph nodes, it has been reported in 0-53% in some studies.[9]

It manifests as a rapidly growing and palpable large mass indicating a high potential for distant metastases.[10] It may be present unusually as a non-palpable lump. It is frequently lymph node negative but has a greater propensity to metastasize via hematogenous route.

Patients may present with rapidly growing palpable breast lumps with or without palpable axillary lymph nodes. Nipple discharge / retraction and skin changes are less likely.

A study conducted by Nguyen, et al. presented a case of metastatic Squamous Cell Carcinoma (SCC) presenting as a solitary lung mass with regional lymph node metastases and a single satellite lesion in a patient with a history of metaplastic SCC of the breast.[11] A major site of secondary tumour development can be the lung among breast cancer patients, and thus pathologists face a challenge when differentiating it from primary SCC of the lung.

As conducted in a study by Rayson D, et al. at the Mayo clinic, data suggested that adjuvant chemotherapy with the use of 'standard' regimens for adenocarcinoma of the breast may be relatively ineffective for MBC. It was found that patients below 60 years of age had representations of a more aggressive form of MBC.[12]

Radiology:

On imaging, MCB shows an irregular or circumscribed mass with speculated portion on mammography. However, MCB can mimic benign mass with circumscribed, round or oval masses on mammogram.

They are predominantly lobular and present as well circumscribed hypoechoic solid mass with posterior acoustic enhancement or solid irregular mass or mixed cystic mass on ultrasound. MCB shows T2 hyperintensity on magnetic resonance imaging.[13]

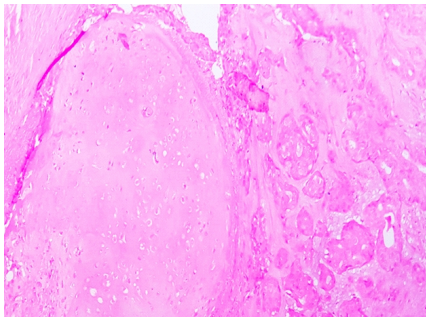
In a study conducted by Bian T, et al. mammography images were available for 13 patients of which 84.6% had dense breasts. 7 patients possessed irregular shaped masses with only 1 case presenting with micro-calcifications. On sonography they found 9 patients with irregular shaped masses with 10 patients demonstrating complex echogenicity.[14]

Pathology:

The Wargotz and Norris classification, as described in their 1989-90 studies differentiates MCB into 5 subtypes: spindle cell, squamous cell, matrix-producing, carcinosarcoma and MCB with osteoclastic giant cells.[15]

In an extensive study by Rakha EA, et al. found that the antibodies to a broad spectrum of cytokeratins (AE1/AE3 and MNF116) are most frequently positive in MBC (approximately 80%). Basal cytokeratins (34βE12, CK5/6, CK14 and CK17) are positive in approximately 70%. Luminal cytokeratins (CK8/18, CK7 and CK19) are positive in approximately 30-60%. Myoepithelial markers are also frequently positive, particularly p63. Estrogen receptor (ER), progestogen receptor (PR) and HER2 are usually all negative. CD34 (a marker often positive in phyllodes tumours) is consistently negative in MBC.[16]

In a study by Galera P, et al. 19; All 30 cases (100%) of MCB were positive for CK-OSCAR, emphasizing that CK-OSCAR is more sensitive than other individual CKs in diagnosing MBC.[17]



Chondroid Metaplastic Breast Carcinoma, chondroid differentiation (left) invasive ductal component (right)

Molecular Diagnosis & Current Advancements:

MBC belongs to a group of neoplasms called spindle neoplasms of the breast (SNB). SNB primarily includes phyllodes tumour (PT), fibromatosis and primary nonspecific sarcoma (PNS) and MBC.

Nguyen et al. reported that apart from the routine markers used for squamous differentiation, the metastases were also positive for estrogen receptor (ER) and GATA-3 on cytologic material obtained by transbronchial FNA, suggesting that immunoreactivity for ER and GATA-3 may support a diagnosis of metastatic SCC in the context of a prior metaplastic SCC of the breast.[11]

Establishing MCB as a sub-type of breast cancer with pronounced epithelial to mesenchymal transition (EMT) phenotype, Czapiewski P, et al. aimed at analysing the relationship with CD99 (due to its growing evidence of its expression in other tumors of mesenchymal, hematopoietic and even epithelial origin) with EMT (vimentin, e-cadherin, twist) and proliferation markers (ki-67, c-myc, cyclin D1, topoisomerase 2), and molecular sub-types of breast carcinomas.[18] Czapiewski P, et al. found that in a group of 122 patients, CD99 membrane expression was seen in 14 (11.5%) cases: strong in 11 (9%) and moderate in 3 (2.5%), with a strong expression of CD99 in triple negative sub-types. Although further studies are required to explain its role in molecular pathogensesis, it was established that CD99 correlates with selected proliferative markers and low ER/PR receptor status.[18]

Treatment & Prognosis:

The treatment regimens for rare types of breast cancers are still under various trials and practicing clinicians often face challenges when recommending one, based upon the axillary involvement, adjuvant therapy, and surgical intervention. The aim of most of these regimens, when concerned with MCB, is the rate of disease free survival (DFS) and overall survival (OS).

Wargotz et al. did not find any surgical advantage for patients treated with chemotherapy or radiation for metastatic disease.[19] Rayson D, et al. concluded that the median survival from detection of metastatic disease was eight months.[12] Rayson D, et al. used a combination of adjuvant chemotherapy, chemotherapy with subsequent tamoxifen and/or radiation, with doxirubicin having only 1 response in 7 of their patients and hormonal therapy having less response and tamoxifen none, especially in ER and PR positive patients.[12]

In a study conducted by Warren et al. radiation therapy (RT) was supported for patients with MBC following a lumpectomy or mastectomy. Out of the 1501 patients in the trial, comparing univariate rates of OS and DSS according to use of RT using the Kaplan–Meier method, and stratifying patients on the type of surgery, either lumpectomy of mastectomy, Warren et al. calculated the OS for RT with lumpectomy 65.5% at 10 years and disease specific survival (DSS) at 79.4%. Patients with mastectomy and RT gave results of OS of 47.7% for 10 years. The 10-year DSS rate for mastectomy patients receiving RT was 55.0 and 65.3% in patients not receiving RT. This also suggests that patients of MBC are subjected to aggressive treatment because of the higher stages of presentation.[20]

Nelson RA, et al. compared MBC to Intraductal carcinoma of breast (IDC) for treatment and survival differences and found that five-year DSS rates were significantly worse for patients with MBC than for IDC patients (78 vs. 93 %, $p < 0.0001$) and for patients with receptor-negative MBC than receptor-negative IDC (77 vs. 85 %, $p < 0.0001$).[21]

Pezzi et al. found out that more patients of MBC were given chemotherapy due to the advanced AJCC (American Joint Committee on Cancer) stage.[22]

In another study conducted by Bae et al. it was found that the patients of MBC had a poorer clinical outcome than patients of IDC. Bae et al. reported that three-year disease-free survival (DFS) rate was 78.1% in the MBC group and 91.1% in IDC group and patients with lymph node metastasis who underwent adjuvant chemotherapy, the three-year DFS rate was 44.4% in the MBC group and 72.5% in the triple negative group (TN-IDC).[6]

Aydiner et al. found that metaplastic histology was significantly correlated with worse 3-year progression-free survival (PFS) ($51 \pm 9\%$ vs. $82 \pm 6\%$) and OS ($68 \pm 8\%$ vs. $94 \pm 4\%$) compared with TNBC histology. Patients who received taxane-based chemotherapy regimens or adjuvant chemotherapy had significantly better PFS.[23]

Efficacy of anthracycline based regimens in sarcomas and MBC and sensitivity of BRCA1 and BRCA2 mutations in tumours to these regimens, led Lamya et al. to illustrate increased sensitivity of BRCA1 mutated cancers to anthracycline therapies, irrespective of pathological classification. Poly Adp-Ribose Polymerase (PARP) inhibitors and platinum-based chemotherapy should be strongly considered.[24]

Conclusion:

Early detection and management of breast lumps is integral in improving the morbidity and mortality associated with breast cancer. Thorough knowledge of aggressive and treatment resistant variants is key so that early intense therapies can be instituted. MCB is a rare and uncommon variant with adverse and poor prognosis.

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