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Metaplastic carcinoma breast: Three year histopathological analysis at a tertiary care centre of Kashmir

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Abstract

Background: Metaplastic breast carcinomas (MBCs) comprise a rare but aggressive subtype of breast cancer and represent less than 5% of invasive breast carcinomas. Histologically, metaplastic breast carcinoma is characterized by the presence of divergent cellular differentiation and heterologous elements, including squamous, spindled, sarcomatoid /pleomorphic, chondroid, and osseous differentiation.

Material and Methods: Histopathologic characteristics of 11 cases of metaplastic carcinoma of breast encountered over a period of three years from May 2016 to May 2019 in our institute.

Results: We encountered 11 cases of metaplastic breast cancers out of 226 primary breast malignancies. Two were breast conservation surgeries and the rest were modified radical mastectomies. The histopathological patterns encountered included squamous, chondroid, sarcomatoid and mixed histologic subtypes. Median tumor size was 3.5 cm, majority were triple-negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2. All except two patients had lymph nodal metastasis.

Conclusion: Metaplastic breast carcinoma is a rare type of breast cancer associated with a poor prognosis. Most patients in this series had high-grade, triple-negative tumors and were treated with optimal therapy.

Keywords: Metaplastic carcinoma, triple negative, immunohistochemistry

Introduction

Metaplastic breast carcinomas (MBCs) comprise a rare but aggressive subtype of breast cancer and represent less than 5% of invasive breast carcinomas^[1]. Aggressive biological parameters like high histological grade are more frequently found in metaplastic breast carcinoma compared to invasive ductal carcinoma of breast, which demands a more aggressive treatment^[2]. Histologically, metaplastic breast carcinoma is characterized by the presence of divergent cellular differentiation and heterologous elements, including squamous, spindled, sarcomatoid/pleomorphic, chondroid, and osseous differentiation^[1, 3-8]. Most metaplastic breast carcinomas do not express the estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER2) (i.e., "triple negative")^[1]. Patients with metaplastic breast carcinoma generally have poorer outcome when compared with high-grade invasive ductal carcinoma and they rarely benefit from conventional chemotherapy or hormonal therapy^[9, 10]. Except for the rare low-grade adeno-squamous and fibromatosis-like metaplastic carcinomas which are most likely to be identified at an early stage, patients with metaplastic breast carcinoma often presents with higher tumor stage and have a more aggressive clinical course compared with classic ductal and lobular carcinomas of the breast^[11]. Surgery (\pm radiation) is the standard treatment for most metaplastic breast carcinomas. Metaplastic carcinoma is often negative for estrogen receptor and human epidermal growth factor receptor 2, limiting the use of hormonal therapy and HER2 targeted therapy^[12]. The median age at the time of presentation ranges in the literature from 48 to 59 years^[13]. Metaplastic breast carcinoma more commonly presents as a rapidly growing mass, and it has been consistently reported to be present in size larger than typical breast cancers, generally greater than 2 cm^[14]. Metaplastic breast carcinoma presents with axillary lymph nodal involvement less frequently than standard invasive breast cancer,

despite the larger tumor size, the incidence of axillary lymph node metastases spans between 6% and 26% [15] which is substantially lower than the expected frequency of axillary lymph nodal involvement in larger invasive breast cancers of greater than 50% [16]. Immunohistochemical panel can be used as a surrogate for molecular classification including; estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), epidermal growth factor receptor (EGFR) and cytokeratin 5/6 (CK 5/6) [17]. In this study we analysed the clinical presentation, histopathological and immune-histochemical features of metaplastic carcinoma breast over a period of three years in a tertiary care centre of Jammu and Kashmir India.

Material and methods:

Study was conducted in the post graduate department of pathology at Sher-I-Kashmir institute of medical sciences Soura Srinagar. It was three years study from 2016 to 2019. 11 cases of metaplastic carcinomas of breast were included in the study. All the specimens were fixed in 10% neutral buffered formalin for 24 to 48 hours. Following this specimens were grossed as per the standard grossing protocols and were processed using an automated tissue processor. Routine Hematoxylin & Eosin staining was done and the sections containing tumor were subjected to relevant immunohistochemistry.

Immunohistochemistry: Four micron tissue sections were cut from the paraffin blocks containing both tumor as well as benign tissue. Sections were mounted on charged slides coated with poly L-lysine and were subjected to immunohistochemical (IHC) procedure using polymer based biotin-free detection system. For immunohistochemistry, primary mouse monoclonal antibody and a secondary antibody for estrogen receptor (ER), progesterone receptor (PR), HER-2/neu staining from Dako Corp. Glostrup, Denmark were used. 10% or more of positively stained cells was used as the cut-off. In each tumor section, positive and negative controls were available. HER2 was defined positive when a strong complete membranous staining (3+) in 30% or more of invasive tumor cells was seen (according to latest ASCO-CAP guidelines).

Results:

All the cases of metaplastic breast carcinoma encountered in our study were female patients with age ranging from 33-80 years with a mean age of presentation being 56 years. The patients presented clinically with a breast lump and radiology (Ultrasound and mammography) was suggestive of mitotic pathology. Preoperative Fine needle aspiration cytology was done in nine cases of which 4 were reported as high grade infiltrating ductal carcinoma, 4 showed a dual population of epithelial and spindle cells while one showed chondroid elements along with infiltrating ductal carcinoma. Trucut biopsy was done in five cases, of which four showed features of metaplastic carcinoma, while one showed leiomyosarcomatous component only.

This study included 9 mastectomies (Fig.1) and 2 breast conservation surgeries. The tumor size ranged from 3 cm to 6 cm with a median size of 3.5 cm. In 7(63.6%) cases right breast was involved while left breast was involved in 4 (36.3%) cases. Nipple areola was involved in 3 (27.2%) cases. Most of the cases had an infiltrating ductal carcinoma component associated with the metaplastic component which was of the NOS type, infiltrating lobular carcinoma

was not seen in association with metaplastic carcinoma in our study. In situ component of carcinoma was seen in two cases and was of the high grade solid and comedo type. All cases except 2 were Scarf Bloom Richardson (SBR) grade III, 2 cases were SBR grade II. In 7 cases the tumors showed squamous differentiation as the metaplastic component, 2 showed spindle cell differentiation, one case showed predominant chondroid differentiation (Fig. 2) while one case showed leiomyosarcomatous differentiation. 9 out of 11 specimens were T2 tumors while one each were T1 and T3. Contrary to what has been stated in literature all except two of our cases showed lymph node metastasis. Immunohistochemistry for ER, PR and Her 2 were done in 10 cases. 9 of these cases were triple negative for ER, PR and Her-2neu, one case was equivocal for Her2. The tumor with leiomyosarcomatous component was positive for smooth muscle actin (SMA) and cytokeratin immunostains. In one case immunostains for vimentin and p63 were positive.



Fig 1: Gross photograph of metaplastic carcinoma breast showing gray white colored firm growth

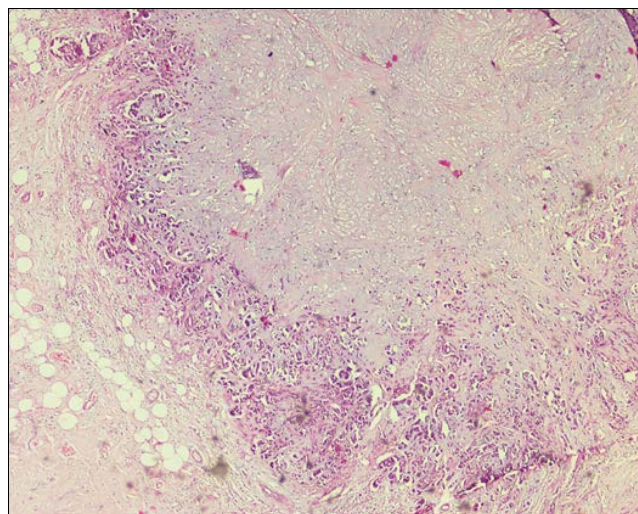


Fig 2: Metaplastic carcinoma breast with cartilaginous component and infiltrating ductal carcinoma (H&E 40X)

Discussion

The actual pathogenesis of metaplastic breast carcinoma is not known but there are many theories that have been put forward to clarify the morphological diversity of this tumor. These theories include genetic and non-genetic mechanisms.

Some reports suggest an origin from cancer stem cells or origin from myoepithelial cells or their progenitors. While some report the theory of transformation of the carcinomatous component into the sarcomatous, through epithelial to mesenchymal transition (EMT) [18]. Recently, the contribution of micro RNAs in evolution and progression of breast cancer had been suggested. Overall decrease in the level of miR-200f, which is an important modulator of Epithelial to mesenchymal transition was found which further supports the association between metaplastic breast carcinoma and EMT [19]. Pathological classification of metaplastic breast carcinomas (MBCs) and its differential diagnosis is challenging due to the diversity of the histological patterns, rarity of the diagnosis and lack of consensus on the most appropriate classification for this group of tumors. Metaplastic breast carcinomas comprise a rare but aggressive subtype and represent less than 5% of invasive breast carcinomas [1]. In our study out of 226 cases of primary invasive breast carcinomas we found 11 (4.8%) cases of metaplastic breast carcinoma which is in concordance with previous studies. Metaplastic breast carcinomas may arise with or without an accompanying conventional in situ or invasive mammary carcinoma, and limited studies demonstrate clonality between these components in most of the cases investigated [20]. Metaplastic breast carcinoma is a subtype of invasive breast carcinoma pathologically defined by the presence of heterologous and divergent differentiation, including any combination of chondroid, osseous, pleomorphic / sarcomatoid, spindle, or squamous components [5-8]. This rare tumor is composed of a mixed group of neoplasms containing both glandular and non-glandular patterns with epithelial and/or mesenchymal components. Epithelial type of metaplastic breast carcinomas is further classified into: 1) squamous cell carcinoma, 2) adenocarcinoma with spindle cell differentiation, 3) adeno-squamous carcinoma, whereas mixed type of metaplastic breast carcinomas is classified into: 1) carcinoma with chondroid metaplasia, 2) carcinoma with osseous metaplasia, and 3) carcinosarcoma [21]. In our study the pure epithelial type of metaplastic breast carcinomas was seen in 9 cases with most common being squamous cell carcinoma component seen in 8 cases while 1 case of carcinoma with spindle cell differentiation were also seen. 2 cases showed mixed type of metaplastic breast carcinomas with one case each of carcinoma with chondroid metaplasia and carcinosarcoma with leiomyosarcomatous component.

All patients in our study were females with median age at the time of presentation being 52 years which is in concordance with the literature. The patients presented with lump in the breast and the median tumor size was 3.5 to 4cm. This is typical of metaplastic breast carcinoma in which tumor size at presentation is frequently larger than 3 cm. Large tumor size is believed to result from rapid growth rate owing to poorly differentiated or undifferentiated tumors compared to invasive ductal carcinoma which has a relatively long preclinical phase that allows early detection by imaging studies [2]. Breast conserving surgery and adjuvant radiotherapy were reserved for small sized tumors. In our series, only two patients had breast-conserving surgery while as nine patients underwent total mastectomy. In contrast with other studies 9 out of 11 of our cases showed lymph nodal metastasis. The metastasis recorded in the nodes was due to ductal carcinoma component. Previous studies report that MBC was associated with low incidence

of axillary metastasis despite large tumor size and high histologic grade [10]. The paucity of nodal involvement was attributed to the presence of sarcomatous elements [2]. In our study immunohistochemistry was done in 11 cases out of which 9 cases were triple negative for ER, PR and Her2 neu. This finding was in concordance with the previous studies. Despite molecular classification of metaplastic breast carcinomas that is similar to basal-like or claudin-low subtypes of infiltrating ductal carcinoma, patients with metaplastic breast carcinoma experience inferior breast cancer outcomes compared with conventional infiltrating ductal carcinoma [22].

Metaplastic breast carcinoma tends to present with a larger primary tumor size, infrequent axillary lymph node involvement, high histological grade and heterogeneity, as well as p53 and Ki-67 overexpression. These feature may contribute to metaplastic breast carcinoma being more chemotherapy resistant. There is limited literature available on the guidelines regarding the use of radiation therapy (RT) in the adjuvant setting for treatment of metaplastic breast carcinoma the published data has shown to comprise of small patient cohorts [23].

Conclusion

The current knowledge regarding metaplastic breast carcinoma is quite limited. Metaplastic breast carcinoma being a rare and heterogenous neoplasm of the breast with regards to biological and morphological features as well as different classification and treatment strategies. Metaplastic breast carcinoma is a rare type of breast cancer and is associated with a poor prognosis. Most patients in our series of cases had high-grade tumors which were triple-negative for ER/PR and Her 2 neu on immunohistochemistry. Metaplastic breast carcinoma presents with axillary lymph nodal involvement less frequently than standard invasive breast cancer, despite the larger tumor size.

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