Metastatic Pattern in Triple Negative versus Triple Positive Invasive Ductal Carcinoma of Breast: Single Center Experience

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ABSTRACT

Background: Breast carcinoma presents with various subtypes based on expression of hormone receptors for estrogen (ER) and progesterone (PR) and human epidermal growth factor receptor 2 (HER2) gene amplification. This study was planned to gain insight into metastatic behavior of two such immunohistochemical subcategories, namely triple negative and triple positive breast carcinoma.

Material & methods: A group of patients with known triple negative breast carcinoma (TNBC) and triple positive breast carcinoma (TPBC) in immunohistochemical analysis were enrolled in the study. Detail history was documented and Technitium-99m MDP skeletal scintigraphy was done. Findings were recorded and finally statistical tests were done using Microsoft Excel and SPSS.

Result: About 53.3% of the patients presented with lymph node metastasis, 68.8% of them were triple negative and 31.2% were triple positive. Skeletal and hepatic metastases were found in 25% cases of TPBC group, while history of lung metastasis was documented in 5% cases of TNBC group. Bone scintigraphy revealed positive scan in about 25% subjects of the triple positive group but none of the triple negative group (p value 0.025).

Conclusion: TNBC shows propensity for lymph node metastasis, while TPBC tends to metastasize skeletal system.

Keywords: Breast carcinoma, Invasive ductal carcinoma, Metastasis, Triple negative, Triple positive.

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INTRODUCTION

Breast carcinoma is a spectrum of multiple pathological entities, with distinct morphological and clinical features. Advancement of genomic and immunohistochemical methods has enhanced our knowledge regarding breast carcinoma biology, leading to more appropriate classification of breast carcinoma subsets (1). One such classification based on cellular markers indicating availability of targeted therapies has currently gained prominence. It relies on standard immunohistochemical methods and categorizes breast carcinoma into three main groups: (a) hormone sensitive i.e. ER or PR positive, (b) HER2 positive, (c) ER, PR and HER2 negative, also termed triple negative (2-4). Besides, an emerging body of data strongly suggests that another subtype which includes positive for ER, PR and HER2 amplification, or triple positive breast carcinoma (TPBC) deserves to be a separate entity considering clinical and translational perspective (5-7).

Regarding breast carcinoma prognosis, the three markers ER, PR and HER2 demonstrates independent predictive value (8, 9). ER is expressed in majority of breast carcinomas, about 80–90%. PR is also expressed in nearly 80% cases and both ER, PR has been found to be time-dependent prognostic factors. About 15–20% of breast carcinomas overexpress HER2. But association with several other poor prognostic markers like tumor grade, negative steroid receptor status etc. masks its prognostic significance. Therefore, it has been established that combined receptor expression represents breast carcinomas better than individual receptor status (9, 10). As for example, TNBC subtype is generally more aggressive, affects younger age with higher tumor grade and advanced stage at presentation including locoregional recurrence and metastasis. TPBC, on the other hand shows better outcome possibly due to receptor positivity enabling role of hormonal treatment and targeted therapy (11).

Triple negative breast carcinoma has been widely researched, generating evidence regarding its important characteristics and strongly establishing this as a distinct subtype of breast carcinoma. However, despite growing indications, authors urge for further studies and trials to

illustrate whether triple positive category should be entitled as a separate subtype with distinct characteristics and management (7). With this background, the current study is designed to gain insight into metastatic behavior of these two immunohistochemical subcategories, by analyzing a small group of patients referred to our institute for bone scan.

METHODOLOGY

This cross-sectional descriptive study was conducted at Institute of Nuclear Medicine and Allied Sciences (INMAS), Mitford from May - October 2022. Subjects were selected from breast carcinoma patients referred to the institute for bone scintigraphy. Detail history was documented, including immunohistochemical analysis and other imaging reports revealing any distant metastases. Only those patients with triple negative or triple positive in immunochemistry report were enrolled in the study. Then Technitium-99m MDP bone scan was done 3-4 hours after injecting 20 mCi of radiotracer. Scan findings were also documented. Finally, statistical tests were done using Microsoft Excel and SPSS.

RESULTS

Total 30 females were included in the study, age ranging from 26 – 75 years (mean ± SD 44.9 ± 10.9 years). All of them were diagnosed cases of invasive ductal carcinoma. Majority was moderately differentiated (about 67%), followed by poorly differentiated (23%) and well differentiated (10%). Out of 30 subjects, 18 (60%) were triple negative, and 12 (40%) triple positive in immunohistochemical analysis. There was no statistically significant association between tumor grading and immunohistochemical categories (p value 0.724).

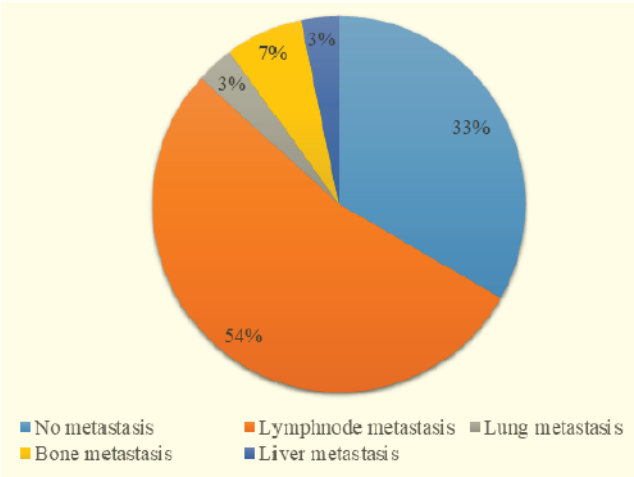


Figure 1: Percentage of known metastatic sites among study subjects

Nearly 70% patients had known metastasis, lymph node being the commonest site (54%). Rest comprised of bone, lung and liver metastases (Figure 1). When correlated with immunohistochemistry, lymph node metastasis was found predominantly in TNBC group (68.8%). On the other hand, all patients with known bone and liver metastasis were triple positive (Figure 2).

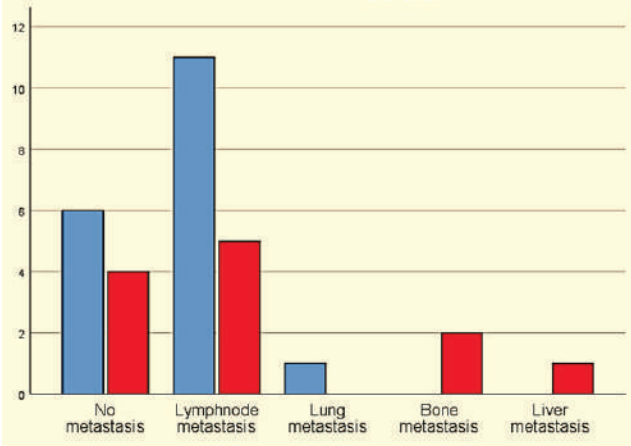
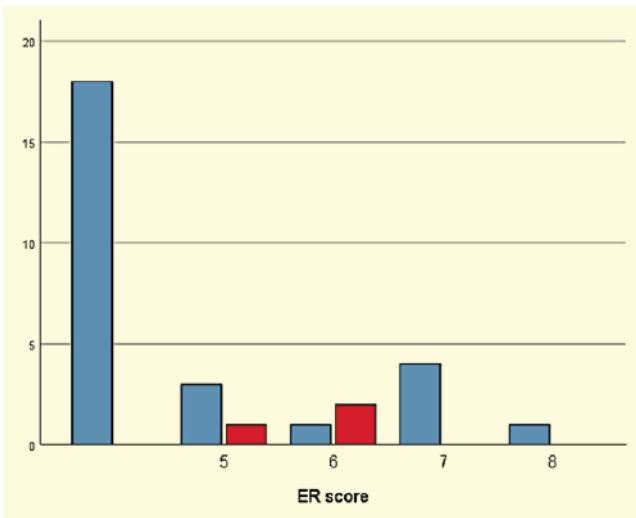
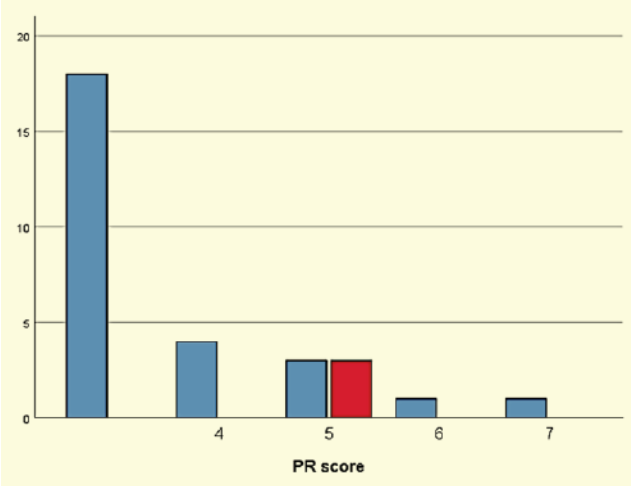


Figure 2: Known metastatic sites among TNBC and TPBC groups of breast carcinoma patients shown in red. (TNBC= Triple Negative Breast carcinoma, depicted in blue; TPBC= Triple Positive Breast carcinoma)

Bone scan done in INMAS, Mitford revealed osteoblastic metastatic lesion in 10% subjects, and all were TPBC cases (p value 0.025). Cross-tabulation with ER, PR, HER2 scores showed that positive scans were associated with ER scores 5, 6; PR score 5 and HER2 scores 2+, 3+ (Figure 3). The associations were statistically significant when tested with chi square test (p value 0.007, 0.010 and 0.014 respectively).





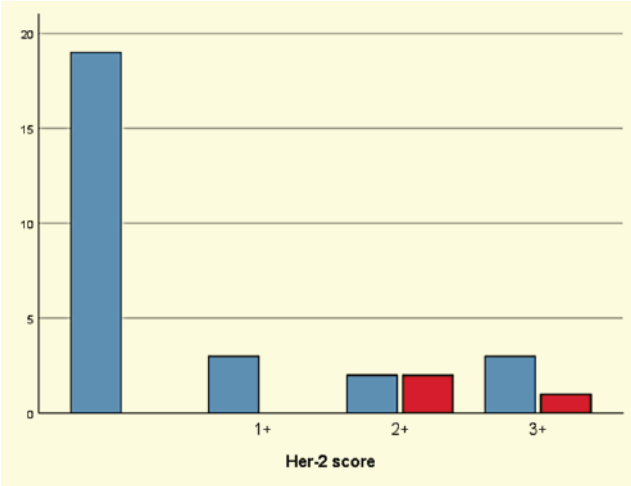


Figure 3: Number of positive and negative bone scans across increasing ER, PR, HER2 scores. Blue bars indicate scan negative for osteoblastic skeletal metastasis, and red bars indicate scan positive for osteoblastic skeletal metastasis.

DISCUSSION

Breast carcinoma is the most common malignancy in female population. Apart from gender, age is the most important risk factor associated with this disease. It is established by various studies that the incidence rate of breast carcinoma increases significantly with age and reaches maximum around the age of menopause (12, 13). This is also reflected in the current study as the mean age of our subjects was about 45 years which is within the worldwide natural menopausal age range (14). However, TNBC is reported to be a disease affecting relatively younger age group, but in this study mean ages of TNBC and TPBC groups were identical (approximately 45 years). The reason behind this discordance may be the racial / ethnic variance of study population, as well as small sample size.

Breast carcinoma has been classified from time to time based on multiple factors including etiology, clinical features, molecular traits, and treatment response. For many years, tumor size was the main deciding factor, but eventually it was deemed insufficient when similarity of prognostic and therapeutic aspects was considered. Later, a histological classification system gained popularity. However, recently gene expression profiling is used to classify breast carcinoma subgroups. This approach, relying on expression of estrogen, progesterone receptor, and the HER2 is at present the most common classification system for breast carcinoma. Its main utility is to guide therapeutic planning and to predict clinical outcomes, because certain treatment strategies, like hormonal therapy or targeted therapy are only beneficial when corresponding receptors and targets are expressed by the tumor cell (15-17).

Patterns of differentiation or gene expression can dictate characteristic metastatic sites for breast carcinoma (18). Several authors reported the skeletal system to be a common site of initial metastasis in case of ER, PR positive breast carcinomas. On the contrary, triple-negative breast carcinomas are known to demonstrate a lower incidence of bone metastases (1, 18-20). These observations are in concordance with the present study.

Axillary lymph node involvement is a very important prognostic factor for breast carcinoma outcome prediction. Calster et al. reported TPBC to be more likely to have lymph node metastasis, which is in contrast to our study (9). However, they also mentioned that lymph node positivity is not a universal finding for HER2 over-expression and only 8 out of 23 studies so far supported this observation (21). Another study found that locoregional recurrence and distant metastasis were higher in TNBC due to its aggressive nature but there was no definite pattern (11).

In this study, moderate ER, PR score in Allred scoring and overexpression of HER2 were associated with positive bone scan. Kim et al. described association of HER2 overexpression with micro metastases in the bone marrow in 20-60% cases of breast carcinoma (22). Some authors found higher rate of recurrence in breast carcinoma patients having low Allred score for PR (23). Correlation of scoring with metastatic outcomes are still relatively underexplored, and requires further investigation.

CONCLUSION

Immunohistochemical classifications of breast carcinoma are useful for planning appropriate therapy and prediction of outcome. Different subtypes show distinct traits of behavior, which needs to be researched extensively, especially in context of our ethnicity. In this small single center study, propensity for lymph node metastasis was observed in triple negative breast carcinoma, while triple positive category demonstrated tendency to metastasize skeletal system. Besides, moderately positive ER, PR, HER2 scores were more associated with bone metastases. Multicentric studies with larger sample size should be conducted to further investigate these observations.

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