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Clinicopathological characteristics of triple negative breast cancer and its correlation with prognostic markers: Analysis in a tertiary care center

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ABSTRACT

Triple negative breast cancer is defined as breast cancer with negative immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR) & Her2neu.These cancers have more aggressive clinical course, poor prognosis and distinctive metastatic pattern. They account for 10-17 % of all breast cancers. The management of these cases is challenging and needs extensive research to establish their relationship with basal like breast cancer. This study was undertaken with an objective to know the incidence of triple negative breast cancer in our population and analyze them with respect to different clinicopathological parameters and determine biological behaviour which can help in proper management of these patients. The study was conducted in Department of Pathology, S.C.B. Medical College , Cuttack from July 2015 to December 2016. This is a prospective study carried out to determine clinical characteristics of triple negative breast cancer including age, family history of breast , endometrial ,ovarian or stomach cancer. Tumour pathology was reviewed to determine histological type, grade , staging and IHC status. Of 341 patients diagnosed with breast cancer, 112 (32%) were identified to be triple negative breast cancer. Majority cases were seen in 4th-5th decades of life with adverse pathological characteristics of high histological grade (42%) and frequent nodal metastasis (60%).
We conclude that triple negative breast cancer is common in 4th to 5th decades of life, with adverse biological behaviour suggested by high histologic grade and frequent nodal metastasis. Further research regarding BRCA status and other IHC parameters is required to subcategorize triple negative breast cancer into different prognostic groups.

INTRODUCTION

Human breast carcinomas represent a heterogeneous group of tumors that are diverse in behavior, outcome, and response to therapy. Triple negative breast cancer (TNBC) is defined as breast cancer with negative immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR) and Her2neu. These cancers have more aggressive clinical course, poor prognosis and distinctive metastatic pattern. TNBCs constitute 10%20% of all breast cancers; more frequently affect younger patients, and are more prevalent in African-American women [1]. TNBCs are generally larger in size, are of higher grade, have lymph node involvement at presentation, and are biologically more aggressive [2]. Despite having higher rates of clinical response to presurgical (neoadjuvant) chemotherapy, TNBC patients have a higher rate of distant recurrence and a poorer prognosis than women with other breast cancer subtypes [2,3].

TNBC is a highly diverse group of cancers, and subtyping is necessary to better identify molecular-based therapies**.** Using microarray analysis new taxonomy for breast cancer based on their molecular features, the gene expression microarray based class discovery studied five molecular breast cancer subtypes: luminal A, luminal B, normal breast-like, HER2, and basal like [4] . Basal-like breast cancer has been extensively characterized on the basis of gene expression profiles, but recently it is being defined on the basis of immunehistochemical (IHC) staining patterns,

particularly in retrospective studies where material for expression profiling may not be available. The IHC pattern that best defines basal-like tumors is under investigation and various combinations of ER, PR, HER2-, CK5/6+ and EGFR+ have been tested.

This study was undertaken in the high-risk group of breast cancer with the triple-negative phenotype (estrogen receptor-negative, progesterone receptor negative, and HER2-negative) with an objective to know the incidence of triple negative breast cancer in our population and analyze them with respect to different clinicopathological parameters and determine biological behaviour.

MATERIAL & METHOD

This study was conducted in Department of Pathology, S.C.B. Medical College, Cuttack during the period from July 2015 to December 2016. This is a prospective study where triple negative invasive breast cancers documented by ER, PR and HER2 negativity in immunohistochemistry (IHC) were taken into consideration. Different clinicopathological parameters and prognostic indicators including age, tumor size, family history of breast, endometrial, ovarian or stomach cancer, histological grade, nuclear pleomorphism, mitotic score, tubule formation/ score, histological subtype, associated ductal carcinoma in situ, lymphovascular invasion and nodal status were evaluated and compared.

Histological grade, nuclear pleomorphism, mitotic score, tubule formation and histological subtype were assessed in accordance with standard guidelines (BR Grading system). Ductal carcinoma in situ (DCIS) was classified according to nuclear grade. Tumor margin, necrosis, degree of lymphocytic infiltrates and growth pattern were reviewed. Tumor margin was considered infiltrating when there were tongue like protrusions of cancer cells into the surrounding stroma, beyond the general contours of the tumor. A pushing margin was one with generally rounded peripheries. Necrosis was assessed as present or absent. Lymphocytic infiltrates were stratified into mild, moderate and marked, and assessed on the basis of the foci of lymphocytes present in the tumor. When less than a third of the tumor incorporated lymphocytic infiltrates, a third to two-thirds of the tumor included lymphocytes and more than two-thirds of the tumor harbored lymphocytic accompaniment, they corresponded to mild, moderate and marked lymphocytic infiltrates, respectively. Trabecular growth inferred groups of tumor cells arranged in bars and beams, whereas syncytial growth was defined by tumor cells intimately apposed and nestled against one another without distinct cytoplasmic membranes, forming a large syncytium.

RESULTS

341 women diagnosed with primary breast cancer between July 2015 to December 2016 in the Department of Pathology, SCB Medical College, Cuttack were subjected to IHC for ER, PR and Her2 neu. On the basis of immunohistochemical finding reports, 112 of 341 (32%) cases were triple negative for ER, PR and Her2neu.

Clinicopathological characteristics of 112 triple negative breast cancers are shown in Table 1. Ten (8.5%) patients were in the age group of 3rd to 4th decade. 54 (48.5%) patients were in the age group of 4th to 5th decade. 23 (20%) patients were in the age group of 5th to 6th decade. 25(22%) patients were in the age group of 6th to 7th decade. Triple-negative breast cancers in our study cohort were mostly high grade/grade 3 (47 out of 112, 42%) and T2 tumors (35 out of 112, 31%). Infiltrative ductal carcinoma was the commonest subtype (84 out of 112, 75%). Family history of breast and other carcinomas was enquired. Two patients had family history of breast cancer and one patient had family history of gastric carcinoma. Majority belonged to infitrating duct carcinoma histologic subtype (96-85%). 60 patients (54%) didn't have lymphatic invasion followed by 52(46%) who didn't have invasion at the time of presentation. Metastasis in>4 lymphnodes (51-45.5%), lymphocytic infiltration(109-98%) and infiltrating margin (84-75%) were common among these patients.

Table 1. : Clinicopathological characters of triple negative breast cancer patients.

Clinicopathological parameters	Number of cases (%)
Age in years	
30 -40	10(8.5)
40-50	54(48.5)
50-60	23(20)
60-70	25(22)
Tumor Size (in mm)	
< 20	16 (14)
> 20	96 (86)
Histologic Grade (BR Grade)	
Low	28 (25)
Intermediate	35 (31)
High	47 (42)
Not Assessable	02 (02)
Histologic subtype	
IDC (NOS)	96 (85)
Metaplastic	04 (3.5)
Mucinous	04 (3.5)
Primary Sarcoma	03 (2.6)
IDC with intraductal component	05(5.4)
Lymphatic invasion	
Present	52 (46)
Absent	60 (54)
Lymph Node Status	
No Nodal metastases	45 (40)
Metastases in 1 to 3 LN	16(14)
Metastases in ≥ 4	51 (45.5)
Margin	
Infiltrating	84(75)
Pushing	28(25)
Necrosis	
Absent	07(06)
Present	105 (94)
Lymphocytic Infiltration	
Present	109 (98)
Absent	03 (02)
Vascular Invasion	
Present	51 (45.5)
Absent	61 (54)

DISCUSSION

The World Health Organization has defined various

histopathological features of invasive breast carcinoma and classified these carcinomas into 19 categories. But these classification does not reflect disease outcome. Therefore, there has been recent interest in subtyping of breast carcinomas into triple negative and basal type which tend to be of high histological grade with limited therapeutic options. This study aimed to pathologically determine the TNBCs , document their incidence in patients of a tertiary care center and critically analyze them in respect to different clinicopathlogical characteristics and prognostic indicators.

TNBC is a high risk breast cancer that lacks the benefit of specific therapy that targets these patients.[5] The incidence of TNBC in this study stands at 32%, which is more than the range of 10%20% generally reported in the literature.[1]The reason may be the limited number of cases included in our study which may not be reflecting a correct data. There are scant data on triple-negative breast cancer in Asian women. The main characteristics of TNBCs that have emerged from the literature illustrate that they more frequently affect younger patients (<50 years). In India, the triple-negative subtype accounted for 5% of breast cancers derived from surveillance data, with a predominance of postmenopausal women in whom cancers are diagnosed at more advanced stages with more frequent nodal metastases. In Japan, the triple-negative subtype accounted for 15.5% of breast cancers derived from surveillance data of the Registration Committee of the Japanese Breast Cancer Society.[4]

In the present series, the maximum number of patients (54 or 48.5%) harboring TNBC were in the early postmenopausal phase of 40 -50 years, and the incidence of women who were 40 years or less among this cohort was 8.5% of breast cancer. This finding corroborate with the finding observed by Badve and Thike et al [4,6]. The pathological characteristics in our series reveal a morphologically aggressive phenotype, with the majority of cases being grade 3 infiltrative ductal carcinomas with frequent histological identification of necrosis and size >20mm. When ductal carcinoma in situ was present, it was predominantly of high nuclear grade. Triple-negative breast cancers have been observed to have rounded pushing margins, we found that in our study such an appearance was seen in minority of cases (28 patients or 25%). These findings are comparable with findings observed by Thike et al [4]. Unusually, a few tumors of special subtypes were encountered among the triple-negative breast cancers, suggesting that triple negativity can occur in all histological subtypes of breast cancer with possible implications on their pathogenesis, progression and prognosis. This study showed an increasing incidence of axillary lymph node metastases with enlarging tumor size observed in 51 patients (46%), unlike the findings of Dent et al[7]. However this finding are similar to findings observed by Thike et al [4]. Lymph node metastasis, infiltrating margin and vascular invasion were more commonly encountered in these patients indicating bad prognosis and aggressive behaviour.

Triple negative breast cancers are sometimes used synonymously with basal like tumors which are again subdivided into 5 categories basing on gene expression profiling. Since it is not possible to do molecular analysis in every case of TNBC, the authors suggest that presence of central fibrosis and small amount of lymphocytic infiltration are factors associated with development of distant metastasis.[8,9]

CONCLUSION

In summary, our study documents clinicopathological features of 112 TNBCs derived from a cohort of 341 invasive breast carcinomas diagnosed in the department between July 2015 to december 2016, affirming their generally more adverse histological characteristics. In this study, a correlation between familial history and triple negative breast carcinoma could not be established. However BRCA mutation study was not done to establish familial correlation. The cohort is small and study in a large population to establish the correlation is required.

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