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STUDY OF CORRELATION OF INFLAMMATORY CELL INFILTERATION SCORE WITH TUMOR GRADE, NODAL STATUS, ER, PR, HER-2 NEU STATUS IN PATIENTS OF STAGE 2 AND 3 BREAST CANCER IN A TERTIARY CENTER, KOLKATA

Dr. Deepika Pandey[1], Dr. Mohit Pradhan[2], Dr. Gautam Mandal[3]

[1]Senior Resident, Department of Pathology, AIIMS, Kalyani, India
[2]Junior Resident, Rajendra Institute of Medical Sciences, Ranchi
[3]Associate Professor, Department of Pathology, Chittaranjan National Cancer Institute, Kolkata

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Corresponding author: Dr. Deepika Pandey
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Abstract

Breast Cancer is the most common cancer in women in India and constitute one–third of women's cancers and is second reason of mortality after lung carcinoma.[1]

It is the most commonly diagnosed malignancy in most cities in India, and 2nd most common cancer in females in the rural areas. As the disease burden and mortality rate is very high, evaluation of several parameters that influence survival rates among women with breast cancer may help design early detection, predict the prognosis and frame a suitable line of treatment.[2] The link between inflammation and cancer was first suggested in 1863.[3] Chronic inflammation is known to increase the risk of cancer development, such as colon cancer in inflammatory bowel diseases.[4]

There is good evidence that the development of cancer and its progression are dependent on a complex interaction of the tumour and the host inflammatory response.[5]

Aim: This study aims to correlate the relation of inflammatory cell infilteration with tumour staging, nodal status, ER, PR, HER-2 NEU status of breast cancer.

Material and Method: The proposed study was a cross sectional study with mostly prospective observation and with some retrospective observation, included 74 patients of stage II and stage III breast carcinoma who underwent MRM in Cancer Institute from 2017-2018. The various clinical and histopathological prognostic parameters along with inflammatory cell infilterate score in invasive breast carcinoma patients were studied and correlated. The inflammatory cell infilterates was assessed according to Klintrup-Makinen (K-M) criteria. It is scored on 4 point scale where score 0 defined no increase in inflammatory cell infilterate, score 1 defined as mild or patchy increase ,score 2 denoted as prominent inflammatory response with some cancer cell destruction and score 3 as florid cup like response. Further it is classified as low group score (score 0-1)and high group score (score 2-3) .[6]

Result: There was significant association between inflammatory cell infiltrate score and grade of tumor (p=0.0005) (TABLE 1) .58.1% ,54.1% and 37.8% of the cases were ER, PR and Her-2/neu positive respectively. ER negative tumors (74.19%) were showing statistically significant (p= 0.01) association with high inflammatory cell infilterate score (ie. Score 2 and 3). Similarly PR negative tumors (64.7%) were showing statistically significant association (p= 0.04) with high inflammatory cell infilterate score. No such correlation was found between between HER-2 /NEU status and nodal involvement with inflammatory cell infilterate score (TABLE 3).

Keywords: Breast cancer, Invasive ductal carcinoma, ER , PR , HER-2/Neu ,grade of tumor, Nodal status, inflammatory cell infilterate score.

Introduction

Prognosis of breast carcinoma depends on various clinical factors, histopathological parameters, hormone receptors and molecular based markers . Hormone receptors are ER, PR, molecular based markers are like oncogenes (eg.myc), protooncogenes(eg.HER-2/Neu) and tumor suppression gene P-53, proliferative marker (eg.Ki-67),apoptosis gene(Bcl-2) and cell cycle regulators (eg.cyclins). Study of ER, PR and HER-2 expression by IHC is routinely performed for breast carcinoma. Their expression is found to be lower in Indian population as compared to Western Population. [7]Estrogen receptor status is regarded at present as the most powerful predictive marker in breast cancer management. Many studies have reported that patients with ER-positive tumor have a longer disease-free survival than the ER -Negative tumor. HER-2 is individually associated with poor survival in breast carcinoma. No adjuvant therapy is available for ER/PR HER2/neu negative (triple negative) tumors.[8,9]

Both Innate and adaptive immune cells constitute part of tumor stroma. The cellular mediators of inflammation are important part of the local environment of tumors. In some malignancies, inflammatory microenvironment are present before a malignant change occurs and in other types of cancer, an oncogenic change induces an inflammatory condition that act as promoter for the development of tumors. Though the main function of the immune system is to monitor tissue homeostasis, protect against invading or infectious pathogens and finally to eliminate damaged cells but several clinical and experimental studies on carcinogenesis have revealed the complex relationship between immune cells and its promoting effect on tumor. It helps in the proliferation and survival of malignant cells, promotes angiogenesis and metastasis, take off adaptive immune responses, and change responses to hormones and chemotherapeutic agents.[10,11]The stroma mainly consists of (1) the nonmalignant cells of the tumor such as carcinoma associated fibroblasts, specialized mesenchymal cell types distinctive to each tissue environment, innate and adaptive immune cells,[9,10] and vasculature with endothelial cells and pericytes[12,13] and (2) the extracellular matrix consisting of structural proteins like collagen and elastin, specialized proteins like fibrilin, fibronectin, and elastin, and proteoglycans [14].

The aim of our study is to correlate the association of tumor grade and receptor status with that of host inflammatory response.

Materials and Method

The study was performed after obtaining the approval from ethical and scientific committee of Tertiary Cancer Institute.

Study population*:* 74 Patients those who were getting operated in the hospital for breast Carcinoma were selected for this study after getting proper consent. After routine histopathological confirmation of Invasive Ductal Carcinoma (stage II and III) as a diagnosis, tumor inflammatory cell infilterate score was assessed and those having known ER,PR and HER-2/neu by immune-histochemical techniques were included in this study.

Study design*:* 2 years Cross sectional study with mostly prospective observation and with some retrospective observation (2017-2019)

Result

Out of 74 cases ,58.1%(43 cases) was ER positive. 54.1%(40 cases) were of PR positive status .In 37.8%(28 cases) HER-2/Neu status was positive. There was significant association between inflammatory cell infiltrate score and grade of tumor (p=0.0005) [TABLE 1]. ER negative tumors (41.9%) were showing statistically significant (p= 0.011) association with high inflammatory cell infilterate score (ie. Score 2 and 3). Similarly, PR negative tumors (45.9%) were showing statistically significant association with high score. No such correlation was found between between HER-2 /NEU status and nodal involvement with inflammatory cell infilterate score.

Table 1: Inflammatory cell infiltrate score and Grade of tumor

Inflammatory cell infiltrate score	Grade of tumor		TOTAL
	2	3	
0	1	1	2
Row %	50.0	50.0	100.0
Col %	2.5	2.9	2.7
1	13	11	24
Row %	54.2	45.8	100.0
Col %	32.5	32.4	32.4
2	22	5	27
Row %	81.5	18.5	100.0
Col %	35	14.7	36.5
3	4	17	21
Row %	19	81	100.0
Col %	10	50	28.4
TOTAL	40	34	74
Row %	54	46	100.0
Col %	100.0	100.0	100.0

Table 2A:Inflammatory cell infiltrate score and combined ER, PR, HER2/neu expression status

combined ER, PR, HER2/neu	Inflammatory cell infiltrate score				TOTAL
	0	1	2	3	
ER+, PR+, Her2-	2	6	3	12	23
Row %	9.5	28.6	14.3	57.1	100.0
Col %	100.0	25	11.1	57.1	31.1
ER+, PR-, Her2-	0	3	2	7	12
Row %	0.0	25	20	70	100.0
Col %	0.0	12.5	7.4	33.3	16.2
ER+, PR-, Her2+	0	1	0	0	1
Row %	0.0	100	0	0	100.0
Col %	0.0	4.2	0	0	1.4
ER+, PR+, Her2+	0	3	0	1	4
Row %	0.0	75	0.0	25	100.0
Col %	0.0	12.5	0.0	4.8	5.4
ER-, PR-, Her2+	0	9	10	1	20
Row %	0.0	39.1	43.5	4.3	100.0
Col %	0.0	37.5	37	4.8	27
ER-, PR-, Her2-	0	2	12	0	14
Row %	0.0	13.3	80	0.0	100.0
Col %	0.0	8.3	44.4	0.0	18.9
TOTAL	2	24	27	21	74
Row %	2.7	32.4	36.5	28.4	100.0
Col %	100.0	100.0	100.0	100.0	100.0

Table 2B: Inflammatory cell infiltrate score and combined ER, PR, HER2/neu expression status

Combined ER,PR HER2/Neu	Low inflammatory score (score 0 &1)	High inflammatory score (2&3)	Total
ER+, PR+, Her2-	8	15	23
Row %	34.8	65.2	100.0
Col %	30.8	31.2	31.1
ER+, PR-, Her2-	3	9	12
Row %	25	75	100.0
Col %	12.5	18.8	16.2
ER+, PR-, Her2+	1	0	1
Row %	100	0	100.0
Col %	3.8	0	1.4
ER+, PR+, Her2+	3	1	4
Row %	75	25	100.0
Col %	11.5	2.1	5.4
ER-, PR-, Her2+	9	11	20
Row %	45	55	100.0
Col %	34.6	22.9	27
ER-, PR-, Her2-	2	12	14
Row %	14.3	85.7	100.0
Col %	7.7	25	18.9
TOTAL	26	48	74
Row %	35.1	64.9	100.0
Col %	100	100	100.0

Table 3: Inflammatory cell infiltrate score and number of positive lymph nodes

Inflammatory cell infiltrate score	Number of positive lymph nodes				TOTAL
	0	1-3	4-9	≥10	
0	0	0	2	0	2
Row %	0.0	0.0	100.0	0.0	100.0
Col %	0.0	0.0	6.2	0.0	2.8
1	8	6	9	1	24
Row %	33.3	25	37.5	4.1	100.0
Col %	40.0	33.3	28.1	25	32.4
2	8	11	8	0	27
Row %	29.6	40.7	29.6	0.0	100.0
Col %	40.0	61.1	25	0.0	36.5
3	4	1	13	3	21
Row %	19	4.8	61.9	14.3	100.0
Col %	20.0	5.5	40.6	75	28.4
TOTAL	20	18	32	4	74
Row %	27.1	24.3	43.2	5.4	100.0
Col %	100.0	100.0	100.0	100.0	100.0

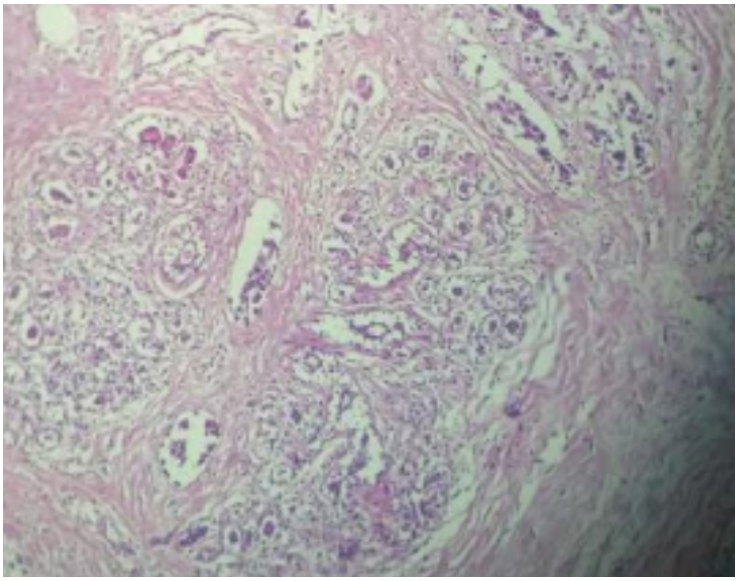

Figure 1: Inflammatory cells (score 0s) at 10X objective

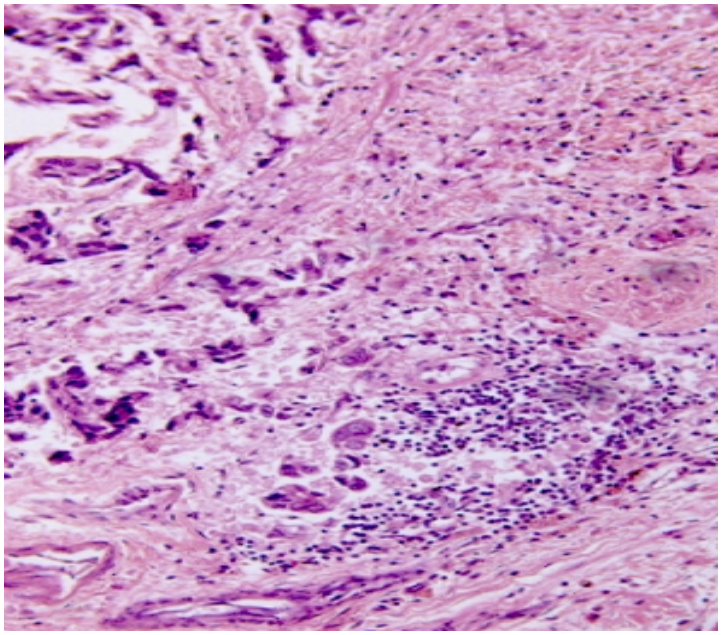

Figure 2: Inflammatory cells at invasive margin (score 1) at 40X objective

Discussion

Association of Inflammatory cell infiltrate score with grade of tumor, HER2/neu expression status, ER expression status and PR expression status

In this study Corrected Chi-square (χ^2) test showed that there was significant association between inflammatory cell infiltrate score and grade of tumor (p=0.0005). Higher grade of tumors were found in higher Inflammatory cell infiltrate score.

Ashraf et al[1] in 2016 showed that there is significant relationship between number of mast cells (inflammatory cell infilterate) and increase in disease grade (p <0.001).

ER negative tumors (31 cases) were showing statistically significant (p= 0.01) association with high score (2 and 3). 74.2% (23 cases) of ER negative tumors had high inflammatory infiltrate

score (2 and 3). ER positive tumors had no such association.

PR negative tumors (34 cases) were showing statistically significant (p= 0.04) association with high score (2 and 3). 64.7% (22 cases) of PR negative tumors had high inflammatory infiltrate score (2 and 3). PR positive tumors had no such association.

Present study showed that ER & PR negativity were associated with high inflammatory infiltrate. Also high grade tumors bring high inflammatory response. In study of associatioin of Combined ER ,PR and HER2/Neu status and inflammatory infilterate score triple negative showed max high inflammatory score (85.7% ie.12 cases) and triple positive showed max low inflammatory infilterate score (75% ie. 9 cases) (TABLE 2A and 2B).

Mohammed et al [15] in 2012 showed in their study that patients who had tumor with high inflammatory infiltrate had higher tumor grade ($p<0.001$) and also inflammatory cell infilterate was positively associated with absence of ER ($p<0.001$) and absence of PR ($p<0.01$) which is consistent with findings in our study. It also shows higher percentage of lymphocyte cell infiltrate at the invasive margin ($P<0.001$), higher percentage of plasma cell infiltrate at the invasive margin ($P<0.001$) and higher percentage of other inflammatory cell infiltrate (neutrophils, eosinophils, basophils and mast cells) at the invasive margin ($P<0.001$).

Also Adriana Knopfelmacher et al [16] showed that all 13 cases of their study with PR ≥90% ,≤1 mitotic figure and absence of dense chronic inflammation around ductal carcinoma in situ had a low score. A low score was not found in any case with at least two of the following negative PR ,> 1 mitotic figure and/or presence of dense chronic inflammation.This association of PR with inflammatory score was consistent with our study.

In present study out of 46 HER2/neu negative tumors 28 (61%) tumors showed high inflammatory cell infiltrate score (2 and 3) and 18 (39%) tumors showed low score (0 and 1). The p-value was 0.178 and it was insignificant.

Out of 28 HER2/neu positive tumors 19 (67.8%) showed high score (2 and 3) and 9 (32.14%) has low score (0 and 1). The p-value was 0.077 and it was insignificant. So, overall HER2/neu status had no impact on the inflammatory infiltrate.

Association of Inflammatory cell infiltrate score and Nodal status

In this study high inflammatory score group (score 2 and 3) had no significant (p=0.88) association with high nodal involvement group (4-9 and ≥10 involved nodes) and low nodal involvement group (0 and 1-3 involved nodes). 32.43% (24 cases) of tumors with high inflammatory infiltrate score showed high number of node involvement and 32.4% (24 cases) showed low number of node involvement.

Also low inflammatory score group (score 0 and 1) had no significant (p=0.57) association with high nodal involvement group (4-9 and ≥10 involved nodes) and low nodal involvement group (0 and 1-3 involved nodes). 16.2% (12 cases) of tumors with low inflammatory infiltrate score showed high nodal involvement and 19% (14 cases) showed low nodal involvement.

DeNardo et al [17ss] (2007) concluded that the outcome of an immune response toward a tumor was largely determined by the type of immune response elicited. A tumor-directed immune response involving cytolytic CD8+ T cells, Th1 cells and NK cells appeared to be protective against tumor development and progression. On the other hand, the immune response involving B cells and activation of humoral immunity, and/or a Th2 polarized response the probable outcome was promotion of tumor development and progression.

Conclusion

1) High inflammatory response was associated with high grade of tumor.
2) Inflammatory response was high in triple negative tumors, ER negative tumors and also in PR negative tumors.
3) No association of high inflammatory response was seen with HER-2/Neu status and nodal involvement.

Results:

High inflammatory cell infiltration was associated with high grade of tumor. Triple negative, ER negative and PR negative tumors were associated with high inflammatory cell infiltration. No such association was seen with HER2/Neu status and nodal involvement.

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