Original Research Article

Clinicopathologic Profile Of Androgen Receptor Expression In Primary Breast Carcinoma And Its Relation With Estrogen, Progesterone, Her-2 Receptor Status And Molecular Subtypes

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Abstract

Background: The prevalence rate of AR expression in breast cancer and its clinical relevance is an area of active research. **Objective**: To study the expression of AR in primary breast cancer and correlated this expression pattern with clinical, pathologic parameters and hormone receptor(ER,PR,HER-2 Status)expression. **Methods**: Sixty three breast cancer cases were studied using AR immunohistochemistry, and its expression was correlated with different clinicopathologic parameters (Age,histopathological subtype,grade) along with ER, PR, Her-2/neu expression and AR with nuclear staining(>10%)was considered positive. **Results**: AR was expressed in 40(63.5%) breast carcinoma cases out of 63 examined. The mean age of patients was 6th decade (range: 25-76 years). There was a statistically significant correlation between AR expression with age ($p < 0.05$). Positive AR expression was seen in 4 (10%) of grade I, 35(87%) of grade II, 1(3) % of grade III carcinoma and Negative AR expression was seen in 1 (4%) of grade I, 20(87) % of grade II, 2(9 %) of grade III carcinoma. Positive AR expression was seen in 38(64%) of infiltrating ductal carcinoma, 2(100%) of mucinous carcinoma.AR negativity was seen in 21(36%)of infiltrating ductal carcinoma,1(100 %) of medullary carcinoma and 1(100)% of Invasive papillary carcinoma. Positive AR expression was seen in 25% of luminal A, 24% of luminal B, 24 % of Her2 like and 27% of TNBC. **Conclusion**: Positive AR immunostaining was associated with advanced age,certain histopathological subtypes,low grade tumors,ER,PR status and molecular subtypes. However, this finding will need to be confirmed by large cohort studies.

Keywords: Androgen receptor, breast carcinoma, estrogen/progesterone receptor.

Introduction

Breast cancer is one of the most common malignancies in females worldwide.The incidence of breast carcinoma is rapidly increasing in India. Currently, according to the International Agency for Research on Cancer, breast cancer is the most common cancer in Indian females. The treatment of breast cancer is based on a multi-modality approach. Analysis of the hormone receptor has been accepted as a standard procedure, in the routine management of patients with breast cancer. Triple negative breast cancers (TNBCs) are those which are negative for expression of estrogen receptor (ER), progesterone receptor (PR),and human epidermal growth factor receptor (HER-2 neu). TNBC is considered to be an aggressive form of breast cancer as they do not benefit from the standard targeted therapies. The traditional prognostic and predictive markers of breast carcinoma include histological subtype,grade of the tumor, and clinical stage of the disease which is based on tumor size, lymph node status, and the presence or absence of distant metastasis. In the past two decades, biomarkers such as hormone receptors (estrogen/progesterone receptor [ER/PR]) and Her-2 growth factor receptor have gained importance due to implications in prognosis and clinical management. In spite of these, the outcome is difficult to predict in a subgroup of cancers which are ER-negative or triple negative and the search for new markers continues. Androgen receptor (AR) is one such emerging biomarker. It belongs to the steroid hormone nuclear receptor family similar to ER and PR.It has been hypothesized that androgens influence the development of breast cancer by its conversion to estradiol or by its binding to a subset of estrogen-responsive element or by its direct binding to AR [1,2]. Thus, AR is thought to play a central role in its initiation, progression of breast cancer, and its response to therapy.It had been previously documented in other studies that AR is highly expressed in breast cancer with an expression rates ranges between 60% and 80%[3-7]. AR is often associated with lower grade of the tumor. In studies by Hu *et al* [4]. and Agoff *et al*, [9]. AR expression and patients survival depend on the status of ER. Hence, there is a need to study the coexpression of these receptors to assess better prediction of patient's survival. There is limited literature from India, on role of AR in breast cancer [10-12]. There is emerging evidence that the androgen signaling pathway also may play a critical role in normal and malignant breast tissue [2,3]. In particular, AR is expressed in normal breast epithelial cells and in approximately 70–90% of invasive breast carcinomas, a percentage equal to or higher than that of either estrogen receptor (ER) (70–80%) or progesterone receptor (PR) (50–70%)[4, 27].This study was undertaken to study the relationship of AR status with clinicopathological parameters and biomarkers. The objective was to study the following: (a) Expression of AR in Biopsies and resection specimens of Breast carcinomas (b) Relationship of AR with clinicopathologic features, ER, PR, and Her-2 status and molecular subtypes.

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Materials and Methods

Patient variables

This is a retrospective study approved by the Institutional Ethics Committee. The study included mastectomy/Biopsy specimens of ductal carcinoma in female patients with known hormone receptor status (ER, PR, and Her2).Patients with inadequate clinical data or unavailable slides and blocks were excluded from the study. A total of 63 patients were included in this study. Patient demographic details (age) and histopathological parameters such as histopathological tumor type, grade of the tumor (Modified Bloom‑Richardson grade) and hormone receptor status (ER, PR, and Her‑2 receptor) and molecular subtypes were studied.

Immunohistochemistry

Immunohistochemistry (IHC) for biomarker AR was performed using polymer technique on tissue sections of 4–5 m thickness adhesive slides. The slides were incubated overnight at 60°C. Antigen retrieval was performed using pressure cooker method in citrate buffer. The slides were incubated with primary rabbit monoclonal antibody at room temperature for 30 min. Subsequently, the slides were incubated with secondary antibody and immunoreactivity was detected using diaminobenzidine as chromogen. The slides were counterstained with Harris's hematoxylin. AR‑positivity was noted along with internal controls. Tumors with ≥10% nuclear staining of neoplastic cells were considered as positive.For ER and PR tumor cells with at least 1% stained cells were considered as positive. Her‑2 status was interpreted according to the American Society of Clinical Oncology/College of American Pathologists guideline recommendations. A score of both 1+ and 2+ were considered as negative.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences version 15.0 software.The Chi-square test was used to assess the association between clinicopathological variables and AR positivity. A value of $P < 0.05$ was considered as statistically significant.

Results

AR expression was noted in 63.5% (40/63) of tumors in this study. AR with strong nuclear staining in more than 10% of tumour cells are considered as positive (Figure 1). The relationship between various clinicopathological parameters and biomarkers with AR expression is depicted in (Table- 1). The mean age at diagnosis was 6th decade and Patients were above the age of 50 years (Table- 2). High AR expression (56 %) was noted in patients aged above 50 years, it was statistically significant (p=0.02). AR positivity was noted in 10%, 87 %, and 3% of Grade I, II, and III tumors, respectively (Table-1). Low‑grade tumors had significantly higher AR expression (Table 1, Figure 2). Positive AR expression was seen in 38(64%) of infiltrating ductal carcinoma, 2(100%) of mucinous carcinoma.AR negativity was seen in 21(36%) of infiltrating ductal carcinoma, 1(100 %) of medullary carcinoma and 1(100) % of Invasive papillary carcinoma (Table-3).

Table 1: Relationship between AR expression and different clinicopathological parameters in 63 breast carcinomas

Patient and tumor characteristics	Total cases 63		P value (AR+ Vs AR-)	
Age (years)	**N (n%)**	**AR +**	**AR-**	**P Value**
≤ 50	28 44%)	14(35%)	14(61%)	0.02
>50	35 56%)	26(65%)	9(39%)	
Histologic grade.				
Well Dif.	5(8%)	4(10%)	1(4%)	0.13
Mod. Dif.	55(87%)	35(87.5%)	20(87%)	
Poorly Dif.	3(5%)	1(2.5%)	2(9%)	
Estrogen receptor				
Negative	36(57%)	20(50%)	16(70%)	0.06
Positive	27(43%)	20 (50%)	7(30%)	
Progesterone receptor.				
Negative	42(67%)	25(62.5%)	17(74%)	0.17
Positive	21(33%)	15(37.5%)	6(26%)	
Her2				
Positive	30(48%)	20(50%)	10(43%)	0.3
Negative	33 (52%)	33 (52%)	13(57%)	
Luminal A				
Positive	16(25%)	12(30%)	4(17%)	0.13
Negative	47(75%)	28(70%)	19(83%)	
Luminal B				
Positive	15 (24%)	12 (30%)	3(13%)	0.06
Negative	48 (76%)	28 (70%)	20(87%)	
HER 2over expression				
Yes	15(24%)	8(20%)	7(30%)	0.17
No	48(76%	32(80%)	16 (70%)	
Triple negative				
Yes	17 (27%)	9(22.5%)	8(35%)	0.14
No	46(73%)	31(77.5%)	15(65%)	
Histopathologic Type				
IDC	59(94%)	38(64%)	21(36%)	0.28
Mucinous carcinoma	2(3%)	2(100%)	0	
Medullary carcinoma	1(1.5%)	0	1(100%)	
Invasive papillary carcinoma	1(1.5%)	0	1(100%)	

Table 2: Age distribution

Age group(Decade)	Number of Cases
3rd decade	5
4th decade	6
5th decade	17
6th decade	26
7th decade	8
8th decade	1
Total	63

Table 3: Histopathological diagnosis

HPE Diagnosis	Number of Cases
IDC Grade I	1
IDC Grade II	52
IDC Grade III	1
Mucinous carcinoma	2
Medullary carcinoma	1
Invasive papillary carcinoma	1
DCIS with micro invasion	2
RCB III	1
IDC with neuro endocrine Differentiation	2
Total	63

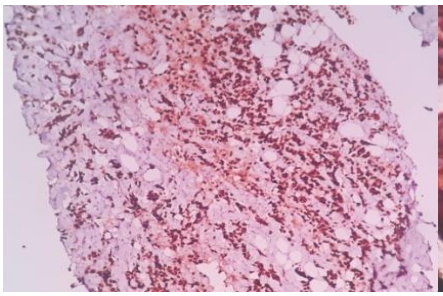

Fig. 1: Androgen receptor diffuse,strong nuclear Positivity (100x)

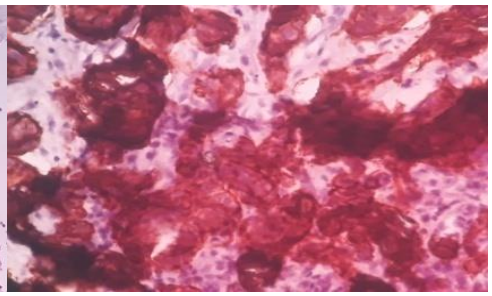

Fig. 2: AR strong, diffuse positivity in well differentiated (IDC) breast tumor (100x)

Expression of AR was also noted either as scattered or clustered positivity in the luminal cells of terminal ductal‑lobular unit (TDLU) of normal breast epithelium adjacent to the neoplasm. Expression of ER, PR, and Her‑2 receptors was noted in 50% (*n* =27), 38% (*n* =21), and 50% (*n* =33) respectively. AR was expressed in 50% of ER‑positive tumors (Figure 4). Among ER‑negative tumors, AR was expressed in 50% of the tumors that belong to high grade. AR was expressed in 38% of PR‑positive tumors (Figure 4). Among PR‑negative tumors, AR was expressed in 62% of the tumors that belong to high grade. AR expression showed a association with ER positive and PR negative tumors .In Her‑2 positive tumors as well as Her 2 negative tumors,AR expression was similar seen in 50% of the tumors(Figure 3). Among luminal A, luminal B, Her‑2 overexpression, and triple‑negative cancers, the rates of AR expression were as follows: 30%, 30%, 20%, and 22.5% respectively (Table-1, Figure 5). Luminal A and luminal B tumors had significantly higher AR expression compared to Her‑2 overexpression tumors and triple‑negative tumors (Table-4, Figure 4). AR expression was significantly higher in nontriple negative tumors as compared to triple‑negative tumors. Many of our study variables shows positive and negative association with androgen receptor and some did not attain statistical significance.

Table 4: Molecular subtypes & AR Immunohistochemistry

Molecular subtypes	Number of cases	AR+	AR-
Luminal A	16	12	4
Luminal B	15	12	3
Her 2 over expressive	15	8	7
TNBC	17	9	8
Total	63	40	23

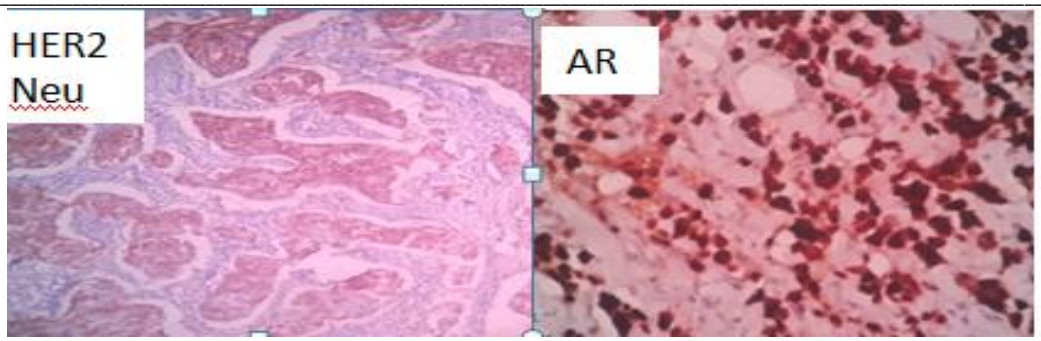

Fig. 3: Her2 (100x magnification) and AR positive (400x magnification)

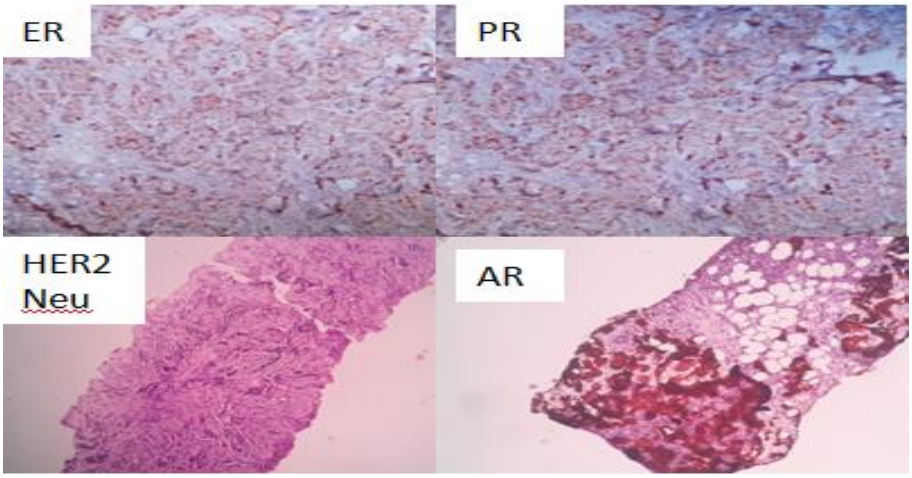

Fig. 4: Luminal A subtype: ER, PR: nuclear positive, Her2 Neu : Negative, AR: Nuclear positive (100x magnification)

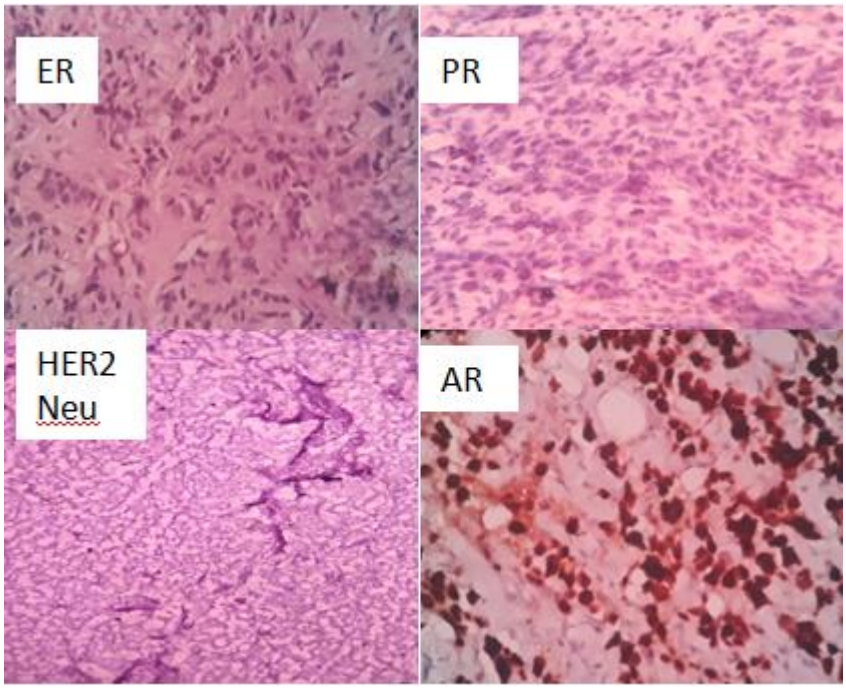

Fig. 5: TNBC: ER, PR, Her2 Neu : Negative, AR : Strong nuclear positive (400x magnification)

Discussion

Androgen receptor may be a good prognostic factor because of its association with increasing age, low grade breast cancer, certain

breast cancer histology, estrogen receptor, progesterone receptor status, her2 neu status and molecular breast cancer subtypes. However, this finding will need to be confirmed by large cohort studies [18].AR is highly expressed in breast cancer.The positive rates of expression of AR vary mostly from 60% to 80% in the literature[2‑7]. In this study, the expression rate was 63.5% which was similar as compared to the Western literature. An Indian study by Mishra *et al*[10]. and a large study from Poland[15] reported lower rates of expression 40% and 43.4%, respectively.

The varied rates of expression may be attributed due to the methodology used and the geographical distribution of the population studied.

AR expression is significantly associated with ER/ PR/HER2 status and positively related to well-differentiated tumors. Although AR status in ER-positive cancers is not an independent prognostic factor, it might provide important additional information on prognosis and become a promising object for targeted therapy [20, 30, 31].

The AR was a significant independent prognostic factor for both overall survival and disease-free survival [21, 28].

Qing Qu et al., suggested that AR expression was associated with low risk of recurrence of breast cancer. It could be used to identify the low-risk patients earlier and guide clinical decisions[21].

Aleskandarany et al., found that nuclear AR immunostaining was significantly associated with features favouring good prognosis including older age groups, lower histologic grade.Similarly in this study we have found older age groups, lower histologic grade (grade I,II) expressed strong nuclear AR immunostaining[1,29].

Samaka et al., found a significant relation between AR expression and the patient's age and no significant relation with histologic type. In this study we have found older the age groups (>50 yrs) and certain histopathological subtypes like Infiltrating ductal carcinoma grade I &II,Mucinous carcinoma expressed strong AR in contrast to Negative AR expression by medullary and papillary carcinoma[1,22].

Triple negative breast cancer (TNBC) represents the most lethal breast cancer subtype, accounting for around 15% of all breast cancer diagnoses and being associated with an increased risk of relapse at distant sites, mostly occurring within the first 3 years from diagnosis .

Molecular diagnosis allows the stratification of breast cancer into four major subtypes based on the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) . Targeted therapies blocking the functions of ER or HER2 have exhibited prominent clinical benefits in patients with tumors positive for the ER or HER2 receptors. However, the clinical outcome of a large number of patients remains poor due to 30-40% of breast cancer cases being ER-negative and 70-80% being HER2-negative. Furthermore, 15-20% of patients with triple negative breast cancer (TNBC) are negative for ER, PR and HER2. TNBC is a distinct subtype of breast cancer that is characterized by frequent recurrence and metastasis, and chemotherapy is currently the only available systemic treatment approach. Chemotherapy has been effective; however, it results in strong side effects and high costs [25, 34-38].In recent years, the application of genomic profiling techniques has allowed to dissect the heterogeneity of TNBC.At least four main TNBC subtypes have been defined [17], including the luminal androgen receptor (LAR) class, which is enriched for hormonally regulated pathways and is dependent on AR signaling. The LAR subtype accounts for approximately 10–15% of TNBC and LAR-type breast cancer cell lines are sensitive to AR antagonists. These findings suggest AR may be a valuable prognostic marker in TNBC [23,25,34-38]. AR is found to be expressed by immunohistochemistry in 60–80% of breast cancers, less frequently in estrogen receptor negative as compared to estrogen-receptor positive tumors.In our study AR frequently expressed in estrogen receptor negative as compared to estrogen-receptor positive tumors [23, 30, 31].In TNBC series, the rate of AR-positive cases is generally 20–40%, with few studies showing rates up to 60%.Preclinical evidence shows that the AR effect depends on tumor subtype: in estrogen receptor-positive cancer cells AR activity is able to inhibit tumor growth, whereas in TNBC AR seems to retain an oncogenic effect .

With regards to the prognostic role of AR expression in patients cohorts, available evidence supports an association between AR expression and favorable prognosis for estrogen receptor-positive tumors [23, 32, 33].

In this study, the triple negative cases were 27%. This is within the documented range for triple negative cases (15-20%) of Kohler et al., [1].AR was expressed in 22.5% of the TNBC cases in this study.Patnayak, et al observed a subset of TNBCs (20%) is positive for AR similar to our study., and that is within the wide range of 6.6 to 75% documented by Rampurwala et al. These subsets of patients are possible candidates for the promising anti-androgen target therapy [1, 23,26]. The correlation of AR+status with other clinicopathologic characteristics such as older age, ductal histology and few special subtypes, lower histologic grade in this study is also consistent with other studies assessing AR by immunohistochemistry or evaluating the LAR molecular subtype [22, 23].Antiandrogen therapy may be tried in those TNBCs expressing AR as the TN cancers do not respond to standard targeted therapy and are aggressive in nature. However, results from multi‑institutional studies with better sample size and follow‑up data should be analyzed before advocating anti‑androgen therapy for TNBCs showing AR positivity [24].

The strength of this study is that it has been done in a small group of patients, where the clinicopathological data regarding the role of AR is sparse. Lack of follow up and AR expression is not correlated with overall survival and disease‑free survival data, which may add information regarding the prognostic point of view are limitations in this study.

Conclusion

In conclusion, positive AR expression was associated with certain clinicopathological features like increasing age(above 50 yrs),low grade tumors,IDC as well as some special histological types, ER/PR‑positive and negative tumors and luminal subtypes (A&B). Also, a subset of TNBC cases showed positive AR expression. AR was expressed in a higher percentage of Her2‑positive tumors in ER‑negative subset and in triple‑negative tumors. The significance of these findings needs to be validated in a larger cohort.[2]These results introduce the current potent, next-generation AR- antagonist as possible target therapy in breast cancer. Further researches on AR expression in breast cancer are recommended on a larger scale with follow up and survival to validate the current results. [23]

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