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Evaluation of Histopathological Features and Immunohistochemical Expression of Androgen Receptor in Invasive Breast Carcinoma and its Correlation with ER, PR and Her 2Neu

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Conflict of interest: Nil

Abstract

Background & objectives: Breast malignancy is the leading cause of death in women and is associated with advanced presentation in developing countries due to various socio-economic factors. These patients can be managed by Neoadjuvant chemotherapy (NACT) with the aim of local and systemic control. Androgen receptor (AR) is an emerging biological marker in the field of breast carcinogenesis. AR is a steroid hormone belonging to nuclear receptor family which binds to androgen ligand, and translocates protein to the nucleus where transcription of androgen responsive genes takes place.[8] It is known that mammary epithelial proliferation can be inhibited by androgens. Many publications have documented the presence of AR on the breast cancer cells, but the exact percentage of AR positive cases differs among various studies.

Aim/Objectives: Hence, this study was undertaken to assess the clinical characteristics of AR expression in breast carcinoma and elucidate the correlation with hormonal markers such as estrogen receptor (ER), progesterone receptor (PR) and Her 2 neu and to evaluate the prognostic value and provide a therapeutic tool for Breast carcinoma.

Methods: This was a single centre study conducted on 102 breast carcinoma specimens over a period of 2 years. Informed consent was taken from all patients. Haematoxylin and eosin slides were studied for histopathology and immunohistochemical slides were studied for hormonal markers and HER-2 neu expression.

Results: AR expression was significantly associated with independent risk factors (ER, PR) but not with clinicopathological characteristics.

Conclusion: This result may suggest AR is correlated with histological subtype and can be adopted as a potential biomarker.

Keywords: Androgen receptor, Breast malignancy, Neoadjuvant chemotherapy, Mammary epithelial proliferation, Steroid hormone

Introduction

Breast malignancy is the leading cause of death in women across the world as well as in India.[1] More than a million develop the disease every year.[2] It has been estimated that 1 out of every 9 women will develop breast cancer during her lifetime and approximately 30% of them will die of the disease.[3] In India, although age adjusted incidence rate of breast cancer is lower (2.8 per 1,000,000) than United Kingdom (95 per 1,000,000) but mortality is at par.[4] Breast carcinoma is associated with advanced presentation in developing countries due to various socio-economic factors. These patients can be managed by Neoadjuvant chemotherapy (NACT) with the aim of local and systemic control.[5] It has been appreciated that breast carcinoma is a heterogeneous disease with various histological appearances. Histopathological factors like the tumor size, tumor grade and axillary lymph node metastasis as well as biomarkers including oncogenes and tumor suppressor genes play a major role in prediction of its outcome.[6] Breast carcinoma is hormone dependent and the steroid hormones induce the proliferation of breast cells by binding to the irrespective receptors. Receptors family includes estrogen (ER), progesterone (PR), androgen (AR) and vitamin D receptor. Estrogen and progesterone receptors have been accepted universally for predictive and prognostic values.[7]

Androgen receptor (AR) is an emerging biological marker in the field of breast carcinogenesis.[7] AR is a steroid hormone belonging to nuclear receptor family which binds to androgen ligand, and translocate protein to the nucleus where transcription of androgen responsive genes takes place.[8] AR has biological and therapeutic utilization in prostate cancer, but its use in breast cancer treatment is limited because of the wide spread and effective use of anti-estrogen hormonal therapies.[9] Many publications have documented the presence of AR on the breast cancer cells, but the exact percentage of AR positive cases differs among various studies.

Androgen receptor can reportedly accelerate cell proliferation of ER negative breast cancer and triple negative breast cancer (TNBC).[10-12] The main reason is that AR competes with ER for binding to androgen responsive elements. This leads to tumor cell growth.[13] Synergy between Her/2 neu and AR is reinforced by positive feedback loop mechanism. This promotes Her/2 neu transcriptional up regulation and then activates related downstream pathways, accelerating AR positive tumor growth.[14,15] AR promotes tamoxifen resistance, may be by regulating Cyclin D1 expression and promoting cell cycle progression.[16]

Combinations of surgery, hormonal treatment, chemotherapy, post- operative radiation and Trastuzumab are the current therapeutic approaches for breast carcinoma. The choice between hormonal therapy which has minimal side effects and chemotherapy which has high morbidity and risk, is a major responsibility of the clinician.[7] Therefore, an accurate assessment of ER, PR and human epidermal growth factor receptor 2 (Her/2 neu) status of breast cancers by the pathologist is very essential.

Hence, this study was undertaken to assess the clinical characteristics of AR expression in breast carcinoma and elucidate the correlation with hormonal markers estrogen

receptor ER, PR and Her/2 neu and to evaluate the prognostic value and provide a therapeutic tool for Breast carcinoma.

Materials and Methods

This was a single center, cross sectional study conducted on tru-cut biopsies, excision biopsies and mastectomy specimens from cases of breast carcinoma received in a tertiary care center over a period of two years (between June 2018 and June 2020) .The samples which had an extensive tumor necrosis without sufficient viable tumor cells for accurate evaluation of the IHC results were excluded.

Method of collection of data

Informed consent was documented from all the patients included in the study. Detailed clinical history and results of relevant investigations was collected from patients' case files. The specimens were received in 10% formalin; the standard protocol for surgical grossing was followed.

After a detailed specimen description, multiple sections from the tumor and the surgical margins were taken. After conventional processing and embedding in paraffin wax, sections of 3- 5µm thickness was cut using Leica JUNG RM 2025 model rotator microtome and stained with haematoxylin and eosin for histopathological study. In addition, 4µm sections were cut from a paraffin block of tumor tissue and taken on 4 glass slides coated with adhesive (poly-L-lysine) for IHC to detect AR, ER, PR and HER-2 neu overexpression.

Processing For Immunohistochemistry

The technique for IHC included antigen retrieval in citrate buffer in a microwave oven. The heat induced antigen retrieval breaks the formalin induced cross linkage there by exposing the epitopes to the antibody action. 3% hydrogen peroxide is used to block the endogenous peroxidase. Incubation with primary mouse monoclonal antibody against androgen receptor protein (Biogenex Clone F39.4.1),followed by linking with secondary antibody(Biogenex) and enzyme labeling with streptavidin- horseradish peroxidase. Chromogen was developed with diaminobenzidine (DAB) and counterstained with haematoxylin. Positive and negative controls were run with each batch of slides. In addition, the adjacent normal breast tissue in each section served as an in-built positive control for ER and PR and negative control for HER2/ neu and AR.

The hematoxylin and eosin stained slides were studied for the tumor histology, distribution, Scarff Bloom Richardson (SBR grading), margins and lymph node metastasis as per the standard reporting protocol. The immunostained slides were examined for nuclear staining in case of ER, PR and membrane staining for HER/2 neu. The intensity of nuclear staining for AR was examined and scored as (<10% - none, 10-25% - weak, 26-50% - moderate and >50% - strong).

Statistical Analysis

Data was entered in Microsoft excel and SPSS Version18.0 software was used for analysis. All the quantitative variables such as age, duration of disease and tumor size were summarized using descriptive statistics where ever possible. All the qualitative variables like ER, PR,Her2/ neu and androgen receptor were analyzed and presented using frequency and percentage. Chi square test was used to compare the androgen receptor expression with respect to ER, PR and Her2/neu.

Results

102 breast malignancy specimens were examined of which 7 samples did not qualify the inclusion criteria and were excluded from the study. The remaining 95 samples were included in the study. Mean age in the present study was 50.87 years. 90 (94.73%) cases were diagnosed as

invasive breast carcinoma of no special type (IBC NST), 3 (3.15%) were diagnosed as invasive lobular carcinoma and 2 (2.10%) were diagnosed as invasive breast carcinoma with medullary features as shown in figure 1. Fig 2 shows the grading of breast carcinoma according to Scarff Bloom Richardsons (SBR) score and table 1 shows expression of ER, PR and Her2 neu in SBR grade. Fig 3 shows the distribution of ER, PR, Her2 neu and AR in the sample specimens.

Androgen Receptor

Androgen receptor expression was positive in 53 subjects and negative in 42 subjects of the total cases. Integrated score was calculated as per the method described by Alshenawy H A et al.[6] based on the percentage of cells showing nuclear positivity for androgen receptor and the intensity of staining. If the score was more than or equal to 2, it was considered as positive result and less than 1 was considered as negative result as seen in fig 4. Table 2 shows the expression of AR in clinicohistological parameters. Expression of androgen receptors in the SBR grade was evaluated. Maximum positive expression of androgen receptor was found in SBR grade I. Expression of androgen receptor in SBR grade 1 was compared with that in SBR grade 2 & 3. The p value was for the same was 0.09. A statistically significant p value was noted in the relation of AR with that of ER, PR as seen in Table 3.

Discussion

In hormone dependent tissue like breast, the pathophysiology of tumors is governed by steroid hormones such as ER, PR and AR.[17] Androgen receptor is expressed in most of the breast cancers irrespective of ER/PR status. Although AR has structural similarity to ER/PR, it is less understood. Among various prognostic markers ER, PR and Her 2 neu are the most important and helps the clinicians to decide further management. However, ER and PR positive tumors have been reported to have a relapse rate. Hence there is need for studies to identify additional marker besides routinely evaluated.[18]

Our study included 95 females of breast cancer, with a mean age group of 50.87 years. Maximum number of cases was seen in the age group of 40 – 60 years which was similar to the studies conducted by Chottanapund S et al,[19] Anand A et al,[5] and Vellaisamy G et al.[20] The most common histological type was IBC NST accounting to 94.8% which was similar to the studies conducted by Agrawal A et al,[7] with 85% of IBC NST , Chottanapund S et al[19] with 95.79% of IBC NST and Mishra AK et al,[21] with 84% of IBC NST. Also, the expression of ER was 58.9% and the expression of PR was 56.8% which was similar to the studies conducted by Anand A et al,[5] Alshenawy HA et al[6] and Vellaisamy G et al.[20] The expression of Her 2 neu receptor is 21.05% which is similar to the studies conducted by Vellaisamy G et al [20] and Safarpour D et al.[22]. The most common molecular subtype was luminal followed by triple negative. Our study cohort included a population with poor outcome which is similar to the study done by Anand A et al.[5] This could be due to late detection of the disease in the developing countries and the patients being referred to a tertiary care center for treatment.

A number of studies are conducted on expression of androgen receptors in the breast of which it is observed that the Indian studies showed 40% to 60% of breast tumors expressing the receptors whereas the western studies showed 60% to 80% of expression of the receptor. In our study, androgen receptor expression was 55.78% which was similar to the other studies conducted in India as shown in Table 4. In the present study maximum positivity for androgen receptors was

encountered in lower stages that is stage I (100%) which is similar to the studies conducted by Anand A et al[5] (69.7%), Alshenawy H A et al[6] (70.2%) and Yu.Q et al [23](81.4%). P value could not be found out due to low sample size. Our study states that the lower histological grade tumors show maximum positivity for androgen receptor as compared to the higher grades with a p value of 0.09. This finding is similar to the other studies conducted by Alshenawy HA et al,[6] Agrawal A et al,[7] Vellaisamy G et al[20] and Moinfar F et al.[24]

In the current study, 82.1% of the ER positive cases expressed androgen receptor positivity with a significant p value which is consistent with the reported rate of 60-90%.[25-27] However, some studies indicate AR may act as a tumor suppress or, in this likely mechanism is that AR can competitively bind estrogen responsive elements to inherit the transcriptionally active components of ER.[28] In addition AR can directly bind to p300, a coactivator factor for competitive binding with ER and then inhibits the function and downstream signaling pathways of ER, thus suppressing tumor growth in luminal breast cancer. Indeed AR is also regarded as a good prognostic factor .In fact, presence of AR in ER positive breast cancer shows better prognosis in terms of disease free survival and overall survival.[29,30] This finding was indistinguishable from the studies conducted by Anand A et al,[5] Safarpour D et al,[22] Chottanapund Set al,[19] Vellaisamy G et al[20] and Yu.Q et al.[23] However, Alshenawy HA et al[6] showed a significant p value only for ER positive cases. Besides, 83.3% of PR positive cases show positivity for androgen receptor expression with a significant p value.

AR expression accounts for 60% in Her2 positive breast cancer patients, which is similar in our study. AR expression in Her 2 positive breast cancer patients predicts a worse prognosis which may be involved in mediating Wnt/ B catenin and Her 2 signalling pathways. This study did not show a significant p value for Her 2 neu positive cases expressing androgen receptor positivity In the Her 2 neu expressing group, occurrence rate is variable and future studies are required for predicting its prognosis.

ER, PR and Her 2 neu are known as the immunohistochemical surrogate markers for molecular subtypes of cancer.[31] In this study a significant proportion of luminal tumors expressed androgen receptor positivity. This finding was similar to the studies conducted by Niemeier LA et al,[32] Collins L C et al[33] and Q Yu et al.[23] Triple negative tumors (86.2%) showed loss of AR expression which depicts a poor prognosis. This finding was similar to the various studies published by Anand A et al,[5] Niemeier LA et al,[32] Vellaisamy G et al,[20] Collins LC et al[33] and Yu.Q et al.[23]

The use of IHC in breast cancer has become an integral part of a complete and comprehensive histopathological report. In terms of prognosis and prediction of response to treatment, in addition to histopathological grade and tumor subtype, hormone markers have become the main stay requirement for the oncologists. AR functions as a tumor promoter in ER -ve breast cancers, including HER2 + ve and triple-negative (TNBC) breast cancers, this serves as a poor prognostic factor. AR has also been shown to be predictive of the potential of response to adjuvant hormonal therapy in ER + ve breast cancers.

Conflicting results exist due to intrinsic molecular differences between tumors and the scoring method for AR positivity. Applying AR expression status to guide treatment in different breast cancer sub-types has been suggested. AR will be a feasible biomarker for breast cancer, so clinical trials using AR antagonists in breast

cancer are active. Targeting AR alone or other therapeutic agents provides alternatives to existing therapy for breast cancer. Therefore, AR expression will be necessary if AR-targeted treatment is to be used. However our investigation found AR expression was significantly associated with independent risk factors (ER, PR, Her/2 neu) but not with clinicopathological characteristics. This result suggests AR is correlated with histological subtype and can be adopted as a potential biomarker.

Figures and Tables

Fig 1: Histomorphological types of breast carcinoma: Inset image A, shows microscopic image of invasive breast carcinoma of no special type with SBR Grade 2 under high power. B shows microscopic image of invasive breast carcinoma of no special type with cribriform pattern under high power. C shows microscopic image of invasive lobular carcinoma with solid growth pattern. Non cohesive small cells of lobular morphology in sheets are present. D shows microscopic image of invasive breast carcinoma of no special type with medullary pattern. Syncytial architecture with pushing margins and tumour infiltrating lymphocytes can be noted.

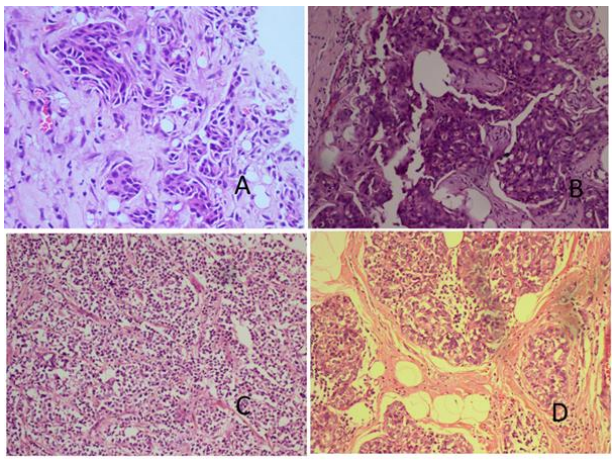

Figure 1: Histomorphological types of breast carcinoma:

Fig 2 Distribution of Scarff Bloom Richardsons score: 67 (70.50%) cases belonged to grade 2 with SBR score of 6-7 followed by 15 (15.8%) cases of Grade 3 with a score of 8-9 and 13(13.7%) cases of grade 1with score of 1-5.

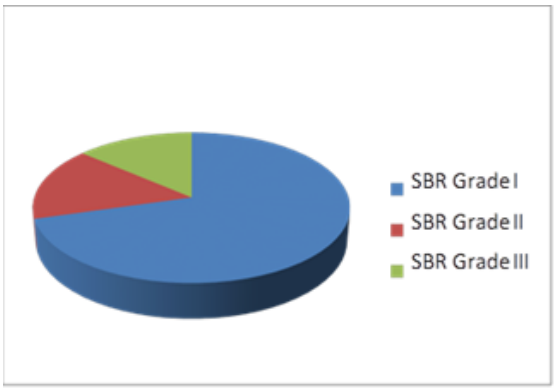

Figure 2: Distribution of Scarff Bloom Richardsons score

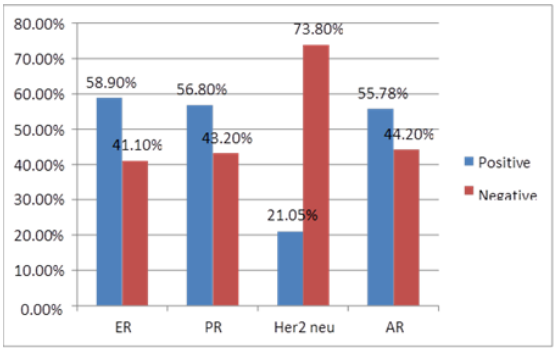

Figure 3: Distribution of ER, PR, Her2neu and AR in the sample specimens

Fig 4 Immunohistochemical staining of Androgen receptor: Inset image A shows weak AR positivity and B shows strong AR positivity.

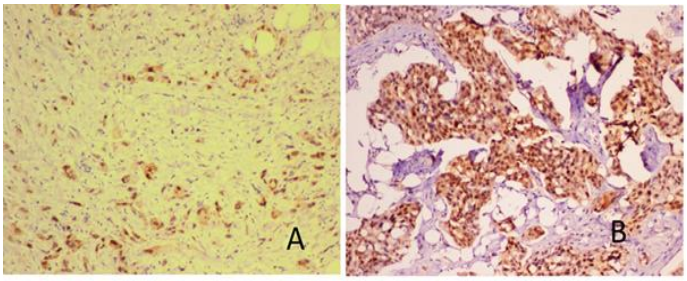

Figure 4: Immunohistochemical staining of Androgen receptor

Table 1: Expression of ER, PR& HER2neu In SBR GRADE

SBR Grade	**Number**		**ER**	**PR**	**HER2neu**
Grade 1	12	Positive	08(66.7%)	08(66.7%)	04(33.3%)
		Negative	04(33.3%)	04(33.3%)	08(66.7%)
Grade 2	69	Positive	43(62.3%)	40(58%)	13(18.9%)
					05(equivocal) (7.2%)
		Negative	26(37.7%)	29(42%)	51(74%)
Grade 3	14	Positive	05(35.7%)	05(35.7%)	04(28.6%)
		Negative	09(64.3%)	09(64.3%)	10(71.4%)
Total	95		95	95	90

Table 2: Expression of AR in clinicohistological parameters

		Number	**AR Positive (53)**	**AR Negative (42)**
Age Group	<40years	19	11(20.7%)	08(19%)
	40–59years	53	32(60.4%)	21(50%)
	60-79years	20	08(15.1%)	12(28.6%)
	>80years	03	02(3.8%)	01 (2.4%)
Menopausa L Status		34	21	18
		61	32	24
Molecular Subtypes	Luminal	58	47	11
	Her 2 Enriched	8	2(25.0%)	6(75.0%)
	Triple Negative	29	4(13.8%)	25(86.2%)
SBR Grade	Grade I	13	10(76.9%)	03(23.1%)
	Grade Ii	67	36(53.7%)	31(46.3%)
	Grade Iii	15	07(46.7%)	08(53.3%)

Table 3: Relation of AR status with ER, PR, HER 2 NEU

Hormonal Receptors And HER2 NEU & KI 67		**Androgen Receptors**		**Total**	**P value**
		Positive	**Negative**		
ER	Positive	46	10	56	<0.0001
		82.1%	17.9%	100.0%	
	Negative	7	32	39	
		17.9%	82.1%	100.0%	
PR	Positive	45	9	54	

		83.3%	16.7%	100.0%	<0.0001
	Negative	8	33	41	
		19.5%	80.5%	100.0%	
HER2neu	Positive	12	8	20	
		60.0%	40.0%	100.0%	0.498
	Negative	36	34	70	

Table 4: Comparision of Androgen receptor status

Study	**Androgen Receptor Expression**
Anand A et al [5]	56%
Alshenawy HA et al [6]	71%
Agrawal A et al [7]	43.7%
Niemeier LA et al [32]	80%
Safarpour D et al [22]	87.8%
Chottanapund S et al [21]	80%
Vellaisamy G et al [20]	52%
Mishra AK [21]	40%
Moinfar F et al [24]	60%
Collins LC et al [33]	77%
Yu.Q et al [23]	72.5%
Present study	55.78%

Conclusion

This study highlights the significant association of AR expression among ER/PR positive tumors. This suggests that androgen receptor could be an indicator of better prognosis. Routine assessment of AR may help better personalize treatment for breast cancer and can be target and novel bio marker in breast cancer. Decreased sample size limits our study. However, follow up studies of correlation between AR expression and cancer specific survival statistics need to be done for definite assessment of the prognostic value of AR in breast carcinoma.

Abbreviations

AR- Androgen receptor

ER- Estrogen receptor

HER 2 neu –Human epidermal growth receptor

IBC NST – Invasive breast carcinoma no special type

IHC- Immunohistochemistry

PR- Progesterone receptor

SBR - Scarff Bloom Richardsons score**.**

TNBC – Triple negative breast cancer

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