

Original Article

Evaluation of the Androgen Receptor Status in Invasive Ductal Carcinoma of Breast

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ABSTRACT

Background and Objective: Determination of hormone receptor status in the management of breast cancer is well-established. The aim of this study was to evaluate the frequency of androgen receptor (AR) expression in invasive ductal carcinoma of breast.

Materials and Methods: For this purpose, 55 cases of invasive ductal breast carcinoma were examined using a monoclonal antibody against AR on formalin-fixed paraffin-embedded archival material. The results were correlated with the results of estrogen and progesterone receptors (ER and PR) previously done immunohistochemically on the specimens.

Results: It was found out that AR was positive in 24 cases (43.6%). In addition, AR was positive in 33% (3) of grade 1, 45% (16) of grade 2, and 38% (15) of grade 3 tumors. Previously, ER and PR were done on 34 cases including 5 grade 1, 18 grade 2, and 11 grade 3 carcinomas. Among the grade 1 cases, 2 out of them were AR positive which were also ER and PR positive but 2 (11%) out of grade 2 and 3 (27%) out of grade 3 tumors were AR positive and ER negative. Also, 5 (28%) out of grade 2 and 3 (27%) out of grade 3 tumors were AR positive and PR negative. In grade 2 tumors, correlation between ER and PR negativity with AR positivity was significant.

Conclusion: AR expression is common in invasive breast carcinomas. Some high grade carcinomas are ER and PR negative and AR positive. We suggest that immunohistochemical evaluation of AR may help in providing more information about steroid receptors in breast carcinomas.

Key words: Androgen receptor, Breast cancer

Introduction

Determination of hormone receptor status as a therapeutic tool and in the management of breast cancer, particularly as a guide to predict efficacy of hormonal therapy is well-established (1,2). The expression of estrogen receptor (ER), in particular,

is thought to be of great importance, predicting an approximately 50% to 75% response rate to hormonal therapy, while ER-negative tumors have less than 15% chance of response (3,4). Estrogen and progesterone receptors have also gained widespread acceptance as independent prognostic parameters in breast carcinoma (5-7). Androgens are also thought to have

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an important role in breast cancer. The risk of breast cancer is increased in post-menopausal women with high estrogen levels as well as in women with high androgen levels (8,9). Many studies have reported that primary invasive breast carcinomas contain ER and progesterone receptors (PR) in approximately 55-65% and 45-55% of cases respectively (10,11).

Although several studies have examined ER and PR and their correlation with other prognostic indicators, little is known about the role of androgen receptor and its prognostic value in breast carcinoma (12-16). Since invasive breast carcinoma is one of the most common malignancies in Iranian women and to the best of our knowledge, there is no study on androgen receptor (AR) status in Iranian patients, the purpose of the present study was to analyze expression of AR in paraffin-fixed tissues in a subset of patients from a university hospital and to correlate AR expression with ER and PR expression as well as histological grade for invasive ductal carcinomas of breast.

Materials and Methods

In this cross-sectional study, a total of 55 cases of invasive ductal breast carcinoma were obtained from the files of the Department of Pathology (Firoozgar hospital, Tehran University of Medical Science, Tehran, Iran). Determination of tumor grade was performed according to standardized guidelines (17). The cases were classified into three grades: well differentiated (GI), moderately differentiated (GII), and poorly differentiated (GIII). The following information was obtained from all patients' medical records (when available): age, ER, and PR results.

Formalin-fixed, paraffin-embedded tissue blocks were cut into 4-5 μm thick sections that were mounted on poly-l-lysine precoated slides. The sections were deparaffinized, rehydrated, and rinsed in distilled water. Immunohistochemical assay for AR was performed on sections using standardized streptavidin biotin peroxidase complex method.

Heat induced antigen retrieval using autoclave method was applied. The monoclonal mouse anti-human androgen receptor antibody (Signet, USA) was used. As a positive control, sections of human prostate were included with each run as well as normal breast tissue surrounding the tumors as an internal control. Negative controls, omitting the primary antibody

were also included with each slide run.

Samples were scored as positive when at least 10% of nuclei were immunoreactive.

For statistical analysis of data, chi 2 test using SPSS software (version 15.0) was applied. A P value less than 0.05 was considered to be significant.

Results

The patients ranged in age from 26 to 75 years, (mean =51.3 years) and 27 (49.1%) out of 55 patients were younger than 50 years (Table 1). Out of 55 studied cases, 9 (16%) were grade I, 33 (60%) grade II, and 13 (24%) cases were grade III. AR was expressed in 24 (43.6%) cases (Figure. 1&2). AR was positive in 3 (33%) of grade I, 16 (48.5%) of grade II, and 5 (38%) of grade III tumors (Table 2). No association between tumor grade and AR expression was identified. Previously, immunohistochemical staining for ER and PR was done on 34 cases including 5 grade I, 18 grade II, and 11 grade III carcinomas. ER and PR were positive in 18 (53%) and 11 (32%) cases respectively. Among the grade I cases, 2 (40%) were AR-positive which were also ER and PR positive but of grade II tumors 6 were ER-negative. Out of them, 2 (33.3%) were AR-positive. Also 11 cases were PR-negative. Out of them, 5 (45.5%) were AR-positive. The correlation between ER and PR negativity and AR positivity in grade II tumors was significant ($p = 0.034$, $r = 0.5$) and ($p = 0.017$, $r = 0.564$) respectively. In grade III tumors, 9 were ER-negative, out of them 3 (33.3%) were AR-positive and all 11 cases were PR negative, out of them, 4 (36.4%) were AR-positive. The correlation between ER and PR negativity with AR positivity in grade III tumors was not significant.

Table 1. Distribution of IDC and AR expression in different age groups

Age group	Number of IDC	AR
26-35 yr	4 (7.3%)	2 (8.33%)
36-45 yr	11 (20%)	3 (12.5%)
46-55 yr	20 (36.4%)	8 (33.33%)
56-65 yr	15 (27.3%)	8 (33.33%)
66-75 yr	5 (9%)	3 (12.5%)

IDC: Invasive ductal carcinoma

AR: Androgen receptor

Table 2. Positive immunoreactivity for steroid receptors in invasive ductal carcinoma

G1 IDC	G2 IDC	G3 IDC
ER-positive (%) 2/11 (18)	4/5 (80)	12/18 (66.5)
PR-positive (%) 0/11 (0)	4/5 (80)	7/18 (38.9)
AR-positive (%) 5/13 (38.5)	3/9 (33.3)	16/33 (48.5)

G1: grade 1 (well differentiated)

G2: grade 2 (moderately differentiated)

G3: grade 3 (poorly differentiated)

IDC: invasive ductal carcinoma

ER: estrogen receptor

PR: progesterone receptor

AR: androgen receptor

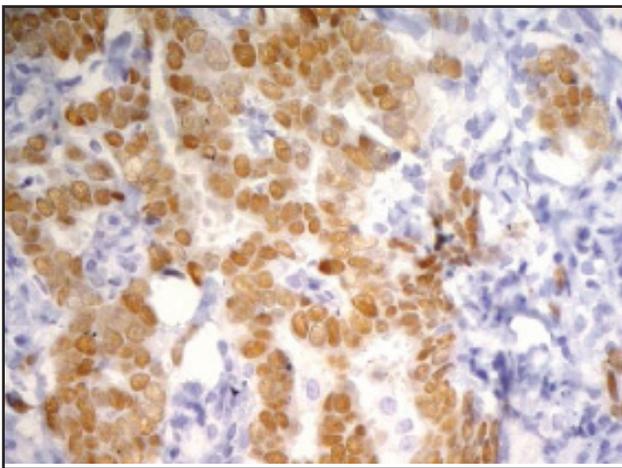


Figure 1. Tumor cell nuclei immunoreactive for AR in Grade III tumor

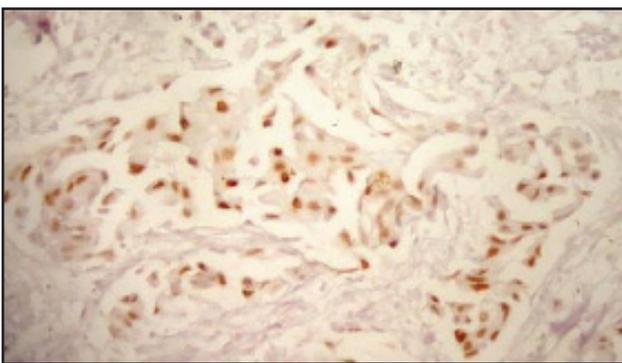


Figure 2. Tumor cell nuclei immunoreactive for AR in Grade II tumor

Discussion

The prognostic and therapeutic significance of ER and PR expression in breast cancer is well-established

but the importance of AR expression is less well-recognized. Our results showed that AR expression is a common feature of invasive breast carcinomas. The current study also showed AR expression in a significant number of ER and PR negative breast cancers.

Previous studies have focused on the biologic and therapeutic significance of ER and PR in breast carcinoma and few but increasing numbers of studies have dealt with the role of AR in breast cancer. Like our study, Moifar et al have shown the frequent expression of AR in breast carcinoma cells most notably poorly differentiated breast carcinomas that were AR-positive but ER-negative (16). In one of the largest studies of AR status in breast cancer (1371 patients), Bryan et al found a highly significant association between AR status and survival ($p < 0.001$) and found that AR positively influenced the response of the primary tumor and metastasis to tamoxifen therapy. In a more recent study on 88 patients, Agoff et al showed that AR expression was significantly associated with disease-free survival using univariate analysis and focused on ER-negative tumors (18).

Also, Nicolas Diaz-Chio et al have discussed the supporting evidence which propose that androgens themselves are actively involved in breast carcinogenesis and its clinical behavior (19).

In our study, expression of AR was more prevalent in peri- and post-menopausal women (Table 1), which in part may be due to high prevalence of breast carcinoma in this age range. Bryan et al (20) did not find a significant correlation between AR and menopausal status in their patients, but Agoff et al found that AR expression not only correlated with increasing age, but also was highly significantly correlated with menopausal status (18). The incidence of breast cancer is high in postmenopausal women when androgenic levels are high and the risk of breast cancer increases in women with high estrogen levels and in those with high androgen levels (8,9,21). It has been shown that immunohistochemical determination of androgen receptor may be a marker to increase sensitivity for identification of the primary site in metastatic tumors of skin (22). As a therapeutic standpoint, Hardin et al have shown that the androgen dehydroepiandrosterone sulfate (DHEAS) inhibits growth of ER-, PR-negative, and AR-positive breast

cancer cells, and may be as an effective treatment for a population, previously excluded from hormone therapy (23).

Conclusion

Androgen receptor is common in invasive breast carcinomas. Some high grade carcinomas are ER- and PR-negative but AR-positive. We suggest that immunohistochemical evaluation of AR may help in providing more information about steroid receptors in breast carcinomas and could be helpful in diagnosis of origin in metastatic high grade breast cancers. It could also yield useful information for establishing new hormonal therapeutic strategies and evaluating the prognostic outcome in estrogen negative breast carcinoma patients.

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