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Androgen Receptor Expression and Its Correlation with Clinicopathological Parameters in Iranian Patients with Triple Negative Breast Cancer

Azar Naimi[1], Maryam Soltan[1], Elham Amjadi[2], Parvin Goli[1], Amirhosein Kefayat[3]

1. *Department. of Pathology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*
2. *Department. of Pathology, Poursina Hakim Digestive Diseases Research Center, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*
3. *Department of Oncology, Cancer Prevention Research Center, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran*

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ABSTRACT

Background & Objective: Our knowledge about correlation of androgen receptor expression and clinicopathological properties of triple-negative breast cancer (TNBC) patients is inadequate, particularly in the Iranian population. The main aim of the present study was to assess the AR expression in TNBC Iranian patients and evaluate its correlation with their clinicopathological parameters.

Methods: Herein, 76 TNBC patients were evaluated for the AR expression by immunohistochemistry. The slides' staining intensity was investigated according to the average degree of nuclear staining and sub-classified into negative (0), weak (1), moderate (2), or strong (3). Subsequently, the positive cells percentage for each slide was assessed and sub-classified into <25% (1), 25-50% (2), 50-75% (3), and >75% (4). The aggregation of these two scores was used as the final score ranging from 0 to 7. While 4-7 scores were selected as positive, the others were included in the AR-negative expression group. Fisher's exact test was used to analyze the AR expression correlation with the clinicopathological parameters.

Results: Positive immunoreactivity for AR was observed in 8 out of 76 (11%) specimens. No-correlation (P>0.05) was observed between the AR expression and grade, stage, lymph node status, and Ki-67 level. The AR-positive patients exhibited older age at the time of diagnosis (P=0.0339) and larger tumor size (P=0.0224) in comparison with the AR-negative patients. Low percentage of TNBC patients expressed AR and no significant correlation was observed between its expression and most of the clinicopathological parameters.

Conclusion: AR may not be a suitable biomarker and treatment target for the Iranian patients with TNBC.

Corresponding Information: **Amirhosein Kefayat,** Dept. of Oncology, Cancer Prevention Research Center, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Email: Ahkefayat@yahoo.com

Abbreviations

AR: Androgen receptor
TNBC: Triple-negative breast cancer
PBS: Phosphate-buffer saline

Introduction

The most diagnosed cancer among women is breast cancer, worldwide. It is the 2nd leading cause of cancer-related deaths after lung malignancies (1, 2). It is a heterogeneous malignancy which can exhibit significant differences in biological behaviors, clinicopathological features, molecular profiles, and prognosis. Some breast cancer patients exhibit a relatively good prognosis, whereas others experience shorter overall and disease-free survival (3,4). The most common method to classify breast tumors is the status of three well-known receptors expression including progesterone, estrogen, and HER-2. Breast tumors that don't express any of the mentioned receptors are categorized as triple-negative breast cancer (TNBC). TNBCs are more likely to be poorly differentiated and display high invasiveness. The TNBCs represent significant clinical challenge due to shorter survival, unresponsiveness to the usual hormone therapies, and lack of targeted therapies (5,6). The standard therapeutic regimens for TNBC have not been established, and as a result, their mortality rate is

still high (7). Therefore, new prognostic indicators and therapeutic approaches must be developed for TNBC.

The androgen receptor (AR) is member of steroid receptor subfamily. This receptor has significant biological and therapeutic importance in prostate cancer. Many evidences support the determinative role of the androgen signaling pathway in breast tumors (8). The AR is deeply involved in the breast cancer pathogenesis and progression (9, 10). Some studies have reported the proliferative effects of androgens on the mammary tissue. But, it's mechanism of action is not well clarified. Also, animal models have shown that administration of androgen can induce tumor formation (11). In addition, AR expression was detected in more than two-third of all breast cancers. Moreover, this receptor was expressed by more than one-third of triple-negative breast cancers (12). Therefore, determination of AR status may provide additional information about TNBC patients' prognosis and also, play the role of a potential target for TNBC treatment. Also, this receptor represents a potential opportunity for the novel targeted treatment for these tumors which do not express common biomarkers (13-17). The AR role for stimulation of the cancer cells growth and its potential therapeutic significance was revealed first in the prostate cancer. Recently, some studies identified AR ability for acceleration of the breast cancer growth (18, 19). High proportion of breast tumors express AR (20,21). But, the effect of this receptor and its ligand in the breast tumor progression and the efficacy of AR as a therapeutic target for breast cancer aren't well studied (22,23). Emerging evidence demonstrate that women with high androgen levels exhibit an increased risk of developing breast cancer (24). Also, androgen can stimulate breast cancer cells' growth and proliferation which was inhibited by AR antagonist (25). Some studies have suggested a connection between androgens and breast carcinogenesis and introduced AR as a target for TNBC treatment. Also, recent retrospective studies suggested the AR status as an efficient prognostic biomarker for the breast cancer (26-28).

According to the best of our knowledge, the clinical value of the AR expression in TNBC patients is not well clarified. Although some studies announced the AR expression as the predictor of low risk of recurrence and death (29), some others demonstrated that AR positivity was correlated with the increased chance of mortality among women with triple-negative breast tumors (30). Therefore, more studies in different populations are needed for identifying the definite role of AR in TNBCs. The main aim of the present study is to evaluate the AR expression and its correlation with the clinicopathologic properties of Iranian TNBC patients.

Materials and Methods

To evaluate the AR expression and its association with clinicopathological properties of the Iranian TNBC patients, 76 TNBC specimens were included in a retrospective cohort study using paraffin-embedded tumor tissue specimens archived at the Pathology Department of Al-Zahra Hospital, Isfahan. This retrospective study was conducted at the Pathology Department of Isfahan University of Medical Sciences. All TNBC patients' primary tumors specimens from January 2012 to December 2017 were included. The Her2 was scored according to this approved scale: 0+(negative): Non-staining or mild membranous staining of tumoral cells (≤10%). 1+(negative): Extremely mild and incomplete membranous staining of ≥10% of tumoral cells. 2+(equivocal): Mild to moderate incomplete membranous staining of ≥10% of tumoral cells. 3+(positive): Intense complete membranous staining of ≥10% of tumoral cells. The cut off for estrogen receptor (ER) and progesterone receptor (PR) was 1%. The patients who received preoperative chemotherapy or were diagnosed with stage IV of the disease were excluded. Two pathologists reviewed all the specimens by themselves. The samples which were inconsistency with their clinical reports and data, were excluded. The clinical factors including age, type of surgery, adjuvant chemotherapy, menopausal status, and several pathological parameters including grade, lymph nodes status, stage, tumor size, and Ki-67 level were investigated. All the steps of this experiment were approved by the Ethical Committee of Isfahan University of Medical Sciences.

Immunohistochemistry

The 3–5 mm sections were incubation at 60 ºC (40 min) for de-paraffinization. Then, the samples were immersed in xylene and rehydrated in the decreasing ethanol solutions. To inhibit activation of the endogenous peroxidases, the samples were incubated in 0.3% hydrogen peroxide. The samples' antigen retrieval was done by heating in an 830-W microwave oven (60°C, 15 min) in 10 mmol/L sodium citrate buffer (pH=6.0). Subsequently, the slides were incubated with rabbit anti-human androgen receptor monoclonal antibody (Clone SP107, Master Diagnostica, Granada, Spain) at 4ºC overnight. The primary antibody was replaced with PBS for the negative control. HRP Polymer and DAP Plus Chromogen (Thermo Fisher Scientific, CA) were employed for the detection. Mouse anti-rabbit horseradish peroxidase-conjugated secondary antibody was incubated for 40 min at room temperature. The color was developed using diaminobenzidine (DAB) as a chromogen. The slides were extensively washed with PBS after each step.

Immunostaining Scoring

Two pathologists independently investigated the immunoreactivity of each slide using a semi-quantitative scoring system. They were completely unaware of the clinicopathological data of each sample. The quick score approach was employed for the AR status semi-quantitation (31). The slides' staining intensity was assessed for the average degree of nuclear staining at low power field (×10). The following scores were categorized as negative (0), weak (1), moderate

(2), or strong (3). Then, the percentage of cells with positive nuclei were assessed at high power field (×40). Also, the following scores were allocated as <25% (1), 25-50% (2), 50-75% (3), and >75% (4). The obtained scores from these two mentioned steps were aggregated to identify a final score which ranged from 1 to 7. The samples with final scores of 1-3 and 4-7 were designated as negative and positive, respectively (32).

Statistical Analysis

JMP software version 11.0 was used for all the statistical analyses. The relation of AR expression with each clinicopathological feature of TNBC patients was analyzed by employing the Fisher's exact test. A P-value<0.05 was considered significant.

Results

Seventy-six TNBC patients were investigated in this study. Table 1 illustrates the clinicopathological characteristics of the patients.

Correlation of AR Expression with Clinicopathological Parameters in TNBC Patients

The patients were divided into two groups according to the AR expression (Table 2). Only 8 patients (11%) exhibited positive immunostaining for the AR according to the utilized scoring method. The negative group contained 68 patients. The AR expression and clinicopathological parameters correlation was investigated. As illustrated in Table 2, patients with the positive expression of AR had older ages at the diagnosis in comparison with the patients with negative expression (P=0.0339). Also, 100% of the AR-positive tumors exhibited larger diameter than 2 cm. Therefore, AR expression was significantly (P=0.0224) correlated with triple-negative breast tumors size. No significant differences (P>0.05) were detected in the nodal status, grade, stage, and Ki-67 level between these two groups (Table 2).

Table 1. Clinicopathological characteristics of TNBC patients

Clinicopathological parameters	Patient number (n=76)	Proportion (%)
Age		
≤ 55	62	81%
> 55	14	19%
Type of surgery		
Lumpectomy	60	80%
Radical mastectomy	16	20%
Tumor size		
T1	15	20%
T2	55	73%
T3	5	6%
T4	1	1%
Nodal status		
N0	49	64%
N1	13	17%
N2	9	12%
N3	5	7%
Grade		
G1	0	0%
G2	16	21%
G3	60	79%
Stage		
I	13	17%
II	48	64%
III	15	19%

TNBC = triple negative breast cancer.

Table 2. Correlations between AR expression and clinicopathological parameters of the TNBC patients

Clinicopathological parameters	AR immunoreactivity		*P*-value
	AR-negative	AR-positive	
	No. of patients (%)	No. of patients (%)	
Total No. of patients	68 (89%)	8 (11%)	
Age			
≤ 55 years	58 (85%)	4 (50%)	0.0339
> 55 years	10 (15%)	4 (50%)	
Tumor size			
T1	20 (30 %)	0 (0%)	0.0224
T2-T4	48 (70%)	8 (100%)	
Nodal status			
N0	43 (63%)	4 (50%)	0.4715
N1-N2	25 (37%)	4 (50%)	
Grade			
I-II	15 (23%)	1 (12%)	0.9453
III	53 (77%)	7 (78%)	
Stage			
I-II	54 (79%)	5 (62%)	0.3674
III	14 (21%)	3 (38%)	
Ki-67 %			
≤ 14%	6 (9%)	1 (12%)	0.8127
> 14%	62 (91%)	7 (88%)	

AR= androgen receptor, TNBC= triple negative breast cancer, No=number

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Discussion

Androgen receptor is a novel emerging prognostic biomarker in breast cancer. However, there is limited information about the correlation between the AR expression and clinicopathological features of TNBC patients', especially in the Iranian population. Previous studies described AR to play a permissive role in the mammary tumors' development and growth (33-35). Therefore, AR has gained many attentions as a potential target for TNBC treatment.

In this study, androgen receptor expression and its correlation with clinicopathological features of TNBC were investigated in a retrospective cohort study. Although, other studies reported a considerably higher percentage of AR-positive TNBC patients, the AR expression was a less common feature in our patients. While other studies have reported up to 80% AR-positive status in the TNBC patients and mentioned AR as a potential target for TNBC treatment, among 76 TNBC specimens involved in this study, only 8 (11%) were positive for the AR expression. Therefore, it can be concluded that the expression of this receptor in TNBC patients in Iranian population is lower than other regions. The AR-positive patients had older ages at the diagnosis. As novel AR-targeting agents are developed and evaluated in clinical trials, and this may have potential benefits for this small group of older TNBC Iranian patients, who may not tolerate the systemic therapy Hence it is equally important to establish a robust set of biomarkers for identification of the TNBC tumors that are most likely to respond to AR inhibition (36, 37). Also, the AR expression was correlated with the tumor size and the AR-positive patients exhibited tumors with larger diameters in comparison with the AR-negative group. However, no significant correlation was observed between other investigated clinicopathological features and the AR expression.

Conclusion

Iranian TNBC patients exhibited a significantly lower number of AR-positive cases in comparison with other studies belonged to the other nationalities. Therefore, AR may not be an appropriate biomarker and potential therapeutic target for the Iranian patients with TNBC. To validate this finding, we recommend more comprehensive studies with larger sample size and evaluation of the AR expression with TNBC patients' survival.

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Conflict of Interest

The authors declared no conflict of interest.

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