Clinicopathological Characteristics and Androgen Receptor Expression of Triple Negative Breast Cancer: A Retrospective Study in Upper Egypt

Eman Mostafa Masoud[a,*] Nermeen Abdel-Moneim H. Kamel[a], Ahmed Mohamed Ali Abdallah[b], Dalia Ahmed Hamed Elsers[a]
[a]Department of Pathology, Faculty of Medicine , Assiut University, Assiut, Egypt
[b]Department of General Surgery, Faculty of Medicine, Assiut University, Assiut, Egypt

Abstract

Background: Breast cancer is a big challenging problem for public health. Triple negative breast cancer (TNBC) is a subtype of breast cancer which is more aggressive; with no specific treatment guidelines are available. It was noted that androgen receptor (AR) is expressed in TNBC, suggesting that anti-androgens are a promising strategy for treatment. Recently, it was found racial differences in the biologic behavior of TNBC.

Objectives: This study aims to assess the clinicopathological features of TNBC in Upper Egypt, and to evaluate the immunohistochemical (IHC) expression of AR in TNBC, in comparison to hormone receptor positive (HR+) invasive duct carcinomas (IDC) as a control group.

Patients and Methods: IHC expression of AR was examined in 45 TNBC specimens and 15 HR+ IDC (ER+ and PR+/-).

Results: Most of the TNBC cases were ≤50 years and their tumors had high histological grade, presence of lymphovascular emboli, lymph node metastasis and tumor necrosis while few cases revealed duct carcinoma in situ (DCIS) and most patients were stage I & II.TNBC group had significantly younger age, DCIS, higher nodal metastasis and necrosis compared to control group. AR expression was significantly higher in the control group.

Conclusion: TNBC occurs at young age and is associated with poor clinicopathological criteria, suggesting the presence of underlying BRCA mutations in our population. AR was expressed in a subset of TNBC, this makes AR an interesting drug target for those patients. Further molecular studies are recommended to uncover pathways of TNBC pathogenesis and improve its therapeutic options.

Keywords: triple negative breast cancer, clinicopathological features, aggressive.

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Introduction

Breast cancer is the most common cancer among women worldwide. Despite great diagnostic and therapeutic efforts, it still represents the most prevalent cancer as the American Institute for Cancer Research; AICR reported 18 million newly diagnosed cancer cases worldwide in 2018 **(Bray et al., 2018)**. According to the records from the Egyptian National Cancer Institute (NCI), breast cancer represents 18.9% of total cancer cases among women **(Darwish et al., 2017)**. Although significant progresses have been achieved for breast cancer treatment, such as anti-hormonal receptors and anti-HER2/neu therapies, the disease commonly acquires relapses and metastasis **(Groner and Brown, 2017)**. There is a specific breast cancer subtype, not expressing either ER, PR or HER2/neu. These cancers are defined as TNBCs that account for approximately 15–20% of all breast cancer worldwide **(Lee et al., 2020)** and 13.9% of breast cancer in Egypt according to NCI **(Eltohamy and Badawy, 2018).**

The TNBC is an aggressive type of breast cancer with limited options of treatment and differs from other types of invasive breast cancer in that they grow rapidly and spread faster, with limited treatment options, and a worse outcomes **(Nedeljković and Damjanović, 2019)**. Over 50% of TNBCs recur after a transient response to initial treatment and more than 37% of those patients die within 5 years **(Hu et al., 2019)**. Systemic chemotherapy and/or radiotherapy are still representing the only offered treatment options and no specific treatment guidelines for TNBCs are available. Continuous research for finding specific target therapy is the aim of scientists.

A recent study by **Cho et al. (2021)** revealed ethnic differences in the behavior, treatment and mortality among women with TNBC. African-American women have high prevalence of TNBC with worse clinical outcomes than European-American women**.** These racial differences in the biologic behavior of TNBC might be due to several factors as population genetics, tumor heterogeneity, increased expression of genes and somatic genomic mutations which have direct link to breast cancer **(Prakash et al., 2020).**

AR is an emerging prognostic marker and therapeutic target in breast cancer.AR is a member of the nuclear steroid hormone receptor family.AR gene is a single-copy gene located on chromosome X q11.2-q12 and can stimulate or suppress both cell proliferation and apoptosis, depending on the concurrent signaling pathways activated **(Gerratana et al., 2018)**. AR is over expressed in 70–90% of all breast cancer

but varied from 0 to 53% in TNBC patients **(Gerratana et al., 2018)**. Tumor response has been observed following AR-directed therapy. This makes AR a potentially interesting drug target for many breast cancer patients.

The aim of this study is to: 1. Describe the clinicopathological features of TNBC patients in Upper Egypt. These features include age, size, stage, grade, and presence of lymphovascular emboli, lymph node metastasis, DCIS and tumor necrosis. 2. Evaluate the IHC expression of AR in TNBC. 3. Assess the difference between the clinicopathological features and AR expression of TNBC and hormone receptor positive IDC as a control group.

Patients and Methods

The present study includes forty five specimens of IDC that were diagnosed as TNBC and fifteen specimens of hormone receptor positive (ER+ and PR+/-) IDC (as a control group). The specimens were taken from the archived paraffin blocks of Surgical Pathology Laboratories, Assiut University Hospital, Faculty of Medicine and South Egypt Cancer Institute, Assiut University during the period from May 2017 to May 2019. All cases were either modified radical mastectomy or conservative breast surgery with axillary evacuation.

Clinicopathological data of the patients including age, size, stage were collected from referral clinical reports and patient's files. Pathological evaluation was done by examination of the hematoxylin and eosin (H&E) stained slides to evaluate the presence DCIS, lymphovascular emboli, necrosis and tumor grading.

Histological grading was carried out using the Nottingham-combined histologic grade. Scores were assigned for the proportion of tubule formation (score 1-3 with 3 being poor tubular formation), the degree of nuclear pleomorphism (1-3 with 3 showing high degree of pleomorphism) and the mitotic count (1-3 with 3 being a high mitotic count). The scores are combined to give a grade I (total score 3-5), grade II (score 6 or 7) and grade III (score 8 or 9), where grade I tumors are the most differentiated and grade III are the least.

Staging of breast cancer in the present study was done according to The American Joint Committee on Cancer; AJCC (8^{th} edition).

ER, PR, and Her-2/Neu IHC slides of all cases were retrieved and revised by three observers. The assessment of these markers was performed according to the updated College of American Pathologist; CAP) recommendations in which < 1% tumor cells were immunoreactive for ER or PR was considered as negative **(Allison et**

al., 2020). Regarding Her-2/Neuimmunostain, the specimen was considered negative (score 0) if no membrane staining was observed or if staining that was incomplete and is faint/barely perceptible in ≤10% of tumor cells **(Wolff et al., 2018).**

Immunohistochemical AR staining and evaluation

IHC staining for AR was performed on 4-µm thick sections using streptavidine – biotin peroxidase technique. The sections were routinely deparaffinized, rehydrated through graded alcohols to distilled water.

The detection of AR expression byIHC was carried out using AR (concentrated, rabbit monoclonal antibody, Thermo Fisher Scientific, Catalog number: MA5-16412).

Antigen retrieval for AR was carried out using diluted antigen retrieval solution DakoEnVisionTM FLEX Target Retrieval Solution, Citrate buffer, Low PH 6.1 (50x, Code DM829), by microwaving the slides at 800 W for 3 min. Slides were washed in phosphate buffer saline two times 3 min for each. Blocking of endogenous peroxidase activity was performed using DakoEnVisionTM FLEX Peroxidase Blocking Reagent (Code SM801) that was applied for 5 min. Rabbit polyclonal antihuman AR antibody (dilution 1:100) was applied to tissue sections and incubated overnight (~20 hrs) at 4ºC in a wet box. The resulting immune complex was detected using a universal staining kits (Dako LsAB2 system peroxidase catalog K0673; Dako, Carpinteria, California, USA) at room temperature, and following the instructions attached within the kit. The positivity was identified as brownish nuclear staining of tumor cells

Section of prostate was used as positive control for AR, and they were incubated in each staining session. Additional section was processed in the aforementioned sequence as negative control but the primary antibody was omitted and PBS was used instead.

The immunostaining expression in tumor cells was noted as brownish staining of the nucleus. Staining expression was assessed with regard to the percentage of positive cells and the intensity of the stain using the Histoscore according to **Kneubil et al. (2017)**. Histoscore (H-score) system was applied to quantify IHC-AR expression with a range of 0-300. H-score was achieved by semi-quantitative assessment of both the intensity (classified as absent (0), weak (1+), moderate (2+) and strong (3+)) and the percentage of positive cells according to the following formula:

H-score = 1 x (% cells 1+) + 2 x (% cells 2+) + 3 x (% cells 3+).

H-score of nuclear expression was calculated for the overall tumor of each case. H-score ≤150 was considered weak expression and H-score >150 was considered strong expression.

The study was approved by the Institutional Ethics and Research Committee of the Faculty of Medicine, Assiut University, Assiut, Egypt.

Statistical analysis

Statistical Analysis: All data was collected and analysis using SPSS version 24 (Statistical Package for Social Science). Data were presented as number, percentage, mean± standard deviation (SD). Chi²-test was used to compare the nominal data of different groups in the study. P value < 0.05 was considered statistically significant.

Results

Clinicopathological features of the TNBC group

Regarding the TNBC group, most of them (60%) were ≤ 50 years old. The mean tumor size was 4.3 ± 2.3 cm. Twenty five specimens were grade III, while only 2 and 18 cases were grade I and II respectively. Most of the specimens showed presence of lymphovascular emboli, lymph node metastasis and tumor necrosis in 55.6%, 71.1% & 60% of the studied specimens respectively. While only 11 cases revealed the presence of DCIS. Regarding pathological stage, most patients (68.8 %) were stage (I –II) and only 31.2% were stage III.

Clinicopathological features of control group

Regarding the control group, most of them were > 50 years old with the mean age was 56 ± 12.4 years. The mean tumor size was 3.9 ± 1.6 cm. Sixty % of the specimens were grade III, while the remaining cases were grade II. Sixty % of the studied specimens (60%) showed absence of lymph node metastasis and tumor necrosis was absent in the entire control group. Lymphovascular emboli and DCIS were detected in 60% of the specimens. Regarding pathological stage, most patients (80 %) were stage (I –II) and only 20% were stage III.

Differences between the control group and TNBC group

The mean age of TNBC group was significantly lower in comparison to the control group (p= 0.011)**.** The presence of nodal metastasis was significantly higher in TNBC in comparison to the control group (p= 0.012)**.** Concerning the DCIS, the presence of in situ component was significantly lower in TNBC group as compared to the control group (p= 0.011)**.**

The presence of necrosis was significantly higher in TNBC group in comparison to the control group (p=0.000), **Figure (1).**

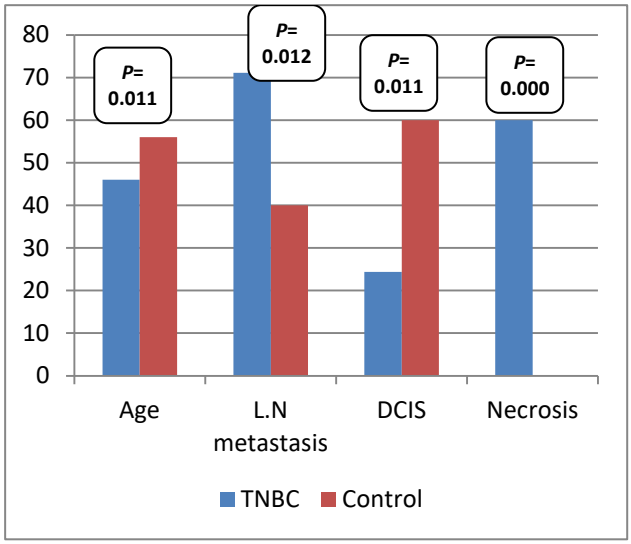

Figure 1: Significant difference between TNBC group and control group as regards age, lymph node metastasis, DCIS and tumor necrosis

No significant difference was detected between the studied groups as regard to tumor size (p= 0.937), grade (p= 0.301), stage (p= 0.092), and lymphovascular invasion (p= 0.784).

Immunohistochemical results of AR in the studied groups

Among TNBC group, thirty seven specimens (82.2%) had negative AR nuclear expression while only eight specimens (17.7%) had positive AR nuclear expression **(Table 1).** The different degrees of intensity of AR expression in TNBC were illustrated in **(Figure 2).** AR was expressed in all 15 studied specimens of the control group **(Table 1)**

Table (1): H-score of IHC-AR expression in the studied cases

H-score of AR	TNBC (n= 45)		Control Group (n= 15)		P-value
	No.	%	No.	%	
Strong positive	2	4.4	9	60.0	0.000***
Weak positive	6	13.3	6	40.0	
Negative	37	82.2	0	0.0	
Median (Range)	0 (0-300)		180(10-285)		0.000***

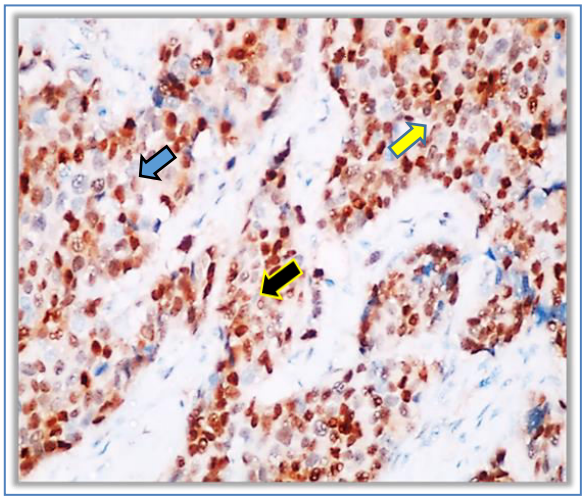

Figure 2:IDC, Grade III, TNBC group, x400 showing heterogeneous AR expression as most of the tumor cells demonstrate strong AR expression (yellow arrow) while others show weak (black arrow) and moderate expression (blue arrow).

Differences between the AR expressions in the studied groups

It was noticed that AR expression was significantly higher in the control group

compared to TNBC group (p= 0.000) **(Table 1).**

Discussion

TNBC is characterized by more aggressive course and easier distant metastases with significant molecular heterogeneity and poor prognosis. Due to the lack of a standard surgical treatment and chemotherapeutic regimen for TNBC, it has become an area of interest for medical research **(Xie et al., 2021)**.

In the present study, most of the studied cases of TNBC group were ≤ 50 years, in agreement with **Qiu et al. (2016)** and **El-Kinaai et al. (2018)**. They reported that the mean age of the TNBC group was 48.95 and 46.26 years old respectively. However, other studies have reported the occurrence of TNBC in older age. **Aapro and Wildiers (2012); Radosa et al. (2017)**reported that the mean age of the TNBC group was 70 and 54 years old respectively. This disagreement may be due to different ethnic conditions.

El-Kinaai et al. (2018) reported that multiparty, young age at first pregnancy, obesity, duration of use of oral contraceptive are risk factors that can contribute to increased risk for development of TNBC in young Egyptian women. Use of oral contraceptive for more than one year is associated with a 2.7 fold increased risk for developing TNBC **(El-Kinaai et al., 2018).** Additionally, positive family history, BRCA gene mutation may contribute to the appearance of breast cancer in young age especially TNBC **(Sharma et al., 2014).**

The present study showed that TNBC patients had relatively large tumor size. This may be explained by high proliferation rate of TNBC as described by previous study which reported high level of Ki67 that may attribute to large sized tumor **(Abdollahi and Etemadi, 2016).**

Most of the studied TNBC cases present at stage I and II**.** The detection of IDC in stage I and II despite high-grade neoplasia may be explained by the advances made in the screening programs and awareness about regular self-examination among women. The present finding is in agreement with the study of **Urru et al. (2018)** but is in disagreement with the study of **Qiu et al. (2016)**who reported high tumor stage of TNBC group. This situation may be related to geographical and ethnic differences.

The present study showed that most of the studied cases of TNBC are grade III. This finding is in agreement with the study of **Urru et al. (2018)**, but in disagreement with the study of **Arora et al. (2019)**who reported a higher prevalence of grade I and II more than grade III among TNBC

patients. The study of **Kuo et al. (2012)** showed that TNBC was markedly associated with high mitotic count, marked nuclear pleomorphism and low tubule formation. Loss of cellular differentiation is a common feature of TNBC tumors. TNBC tumor cells look like cancer stem cells; this may explain the predominance of grade III among the current results.

In the present study, TNBC cases showed higher rate of nodal positivity, which is in agreement with the findings of **Khanna et al. (2018)**and higher rate of lymphovascular invasion in agreement with **Ahn et al. (2017); Agarwal et al. (2016).** They reported that lymphovascular invasion is commonly observed in TNBC patients. This may be explained by the results of previous researches which revealed higher levels of intra-tumoral vascular endothelial growth factor (VEGF) and hypoxia inducible factor-1a (HIF-1a) in TNBC than in any other types of IDC. The higher expression of VEGF and HIF-1a in TNBC is associated with induction of both lymphatic and vascular angiogenesis resulting in proliferation, aggressive tumor behavior and high nodal stage.

In the current study, necrosis was an important morphological feature in the TNBC documented in 60% of the studied biopsies, this observation is similar to the results of **Rao et al. (2013)**. Extensive necrosis is a prognostically unfavorable feature in IDC, especially TNBC and this may reflect the rapid growth rate which exceeds tumor-sustaining angiogenesis to a substantial degree**.**

The present study showed that TNBC often lacks association with an overt in situ component, this finding is in concordance with study of **Thike et al. (2010).** The low frequency of association between TNBC and DCIS could be explained by the rapid progression of TNBC to invasive cancer and/or obliteration of the DCIS precursor by the rapidly growing invasive component.

AR is the most frequently expressed biomarker in breast cancer; playing a role in the genesis and development of breast cancer. Currently, it is one of the most studied biomarkers in TNBC; therefore, detecting AR expression could be another milestone in the management of TNBC **(Xu et al., 2020)**.

The current results revealed AR expression in only 18% of TNBC cases, however previous studies in Egypt have investigated the prevalence of AR expression among TNBC patients in different centers. AR expression was detected in 9/26 cases (34.6%), 27/90 cases (30%) and 21/77 cases (27%) at Cairo University by **Ismael, Khairy et al. (2019)** at Tanta University by **Farag et al.**

(2017)and at Zagazig University by **Zakaria et al. (2016)** respectively. This wide range of AR expression among TNBC patients in different studies may be explained by variations in number of the involved patients in each study (26, 90 and 77 cases respectively), the cut off value of AR positivity (≥1% in the first study or ≥10% in the other two studies), the primary antibody source (the first study used a mouse polyclonal antibody (Thermo Medical Catalog number: MS-433- R7), the second study used a mouse monoclonal AR, (ab9474 1:500 dilution) and the third study used a mouse monoclonal anti-AR (abcam, clone [AR 441] (ab9474) dilution 1:100) and the use of different methods for testing and the patient selection criteria.

The current results revealed that AR expression was significantly higher in the control group (100%) in comparison to TNBC group. Many studies have reported that AR expression was higher in ER+IDC compared to TNBC. These included two studies from Egypt by **Aleskandarany et al. (2016); Samaka and Younes (2016).** They reported that the percentage of AR expression in ER+IDC was 64% and 73% respectively.

The higher expression of AR among the control group in comparison to TNBC is explained by the fact that, both estrogen and androgen hormone receptors belong to the steroid hormone receptors family. Receptors within this family are classified into subclasses based on the structure of their DNA and ligand-binding domains; ER and AR belong to the third subclass. The ER is the ancestral prototype from which all of the other class 3 nuclear receptors have evolved. This revealed the common evolutionary origin of AR and ER, so in absence of ER, the AR expression is also lost **(Honma et al., 2021)**.

Luminal androgen receptor is a molecular subtype of TNBC with a gene expression profile mimicking luminal subtypes despite being ER-negative and enriched in hormonally regulated pathways including steroid synthesis (high AR expression), this explains expression of AR in some cases of TNBC group **(Pietri et al., 2016)**. This may suggest the therapeutic role of anti-androgens in those patients.

Previous study by **Xie et al. (2021)** reported that in AR-positive TNBC subtype patients, anti-androgens such as bicalutamide is well tolerated and could be proposed as an alternative to cytotoxic chemotherapy in such patients with better overall survival and disease free survival outcomes.

In conclusion, TNBC is characterized by aggressive features as large tumor size, high tumor grade, lymph node metastasis and extensive necrosis. Its existence among younger age group may suggest the

presence of underlying BRCA mutations in our population. Thus, we recommend that predisposing factors as BRCA 1 mutations should be uncovered in reproductive age group IDC especially those with TNBC.

Also, TNBC patients may benefit from anti-androgen treatment as it is well tolerated, with significant lower toxicity than that of chemotherapy.

Further molecular studies are recommended to identify the several signaling pathways that may contribute to TNBC pathogenesis and improve its therapeutic options and clinical outcomes.

Abbreviations: TNBC; triple negative breast cancer, AR; androgen receptor, IHC; immunohistochemical/immunohistochemistry, HR; hormone receptor positive, IDC; invasive duct carcinomas, DCIS; duct carcinoma in situ, AICR; the American Institute for Cancer Research, NCI; National Cancer Institute.

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