ORIGINAL ARTICLE

ANDROGEN RECEPTOR EXPRESSION IN ENDOMETRIAL CARCINOMA AND ITS CORRELATION WITH ESTROGEN RECEPTOR AND PROGESTERONE RECEPTOR AND CLINICOPATHOLOGICAL FINDINGS

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Background: The objective of the study is to analyze the expression of androgen, estrogen and progesterone receptor in different types of endometrial carcinomas and to correlate the androgen receptor expression with estrogen and progesterone receptor and the clinicopathological parameters like lymphovascular invasion, grade of the tumour, size of tumour and extent of myometrial invasion. **Methods:** It is a cross-sectional analytical study design with a simple random sample of a total of 54 cases of different types of endometrial carcinomas from the year 2017. Immunohistochemical stains androgen receptor, estrogen receptor, and Progesterone receptor were applied in all the cases. The Pearson Chi-square test of independence was applied to measure association and P-value is calculated to check the significance of the results. **Results:** Androgen receptor expression was observed in 73% of low-grade endometrioid carcinomas, 62.5% of high-grade endometrioid carcinomas, 62% of serous, 20% of clear cell and 18% of carcinosarcomas, respectively. Androgen positive tumours were also positive for estrogen and progesterone in most of the cases, except 3 serous carcinomas and one low-grade endometrioid carcinoma. However, no significant relation was observed between androgen expression and prognostic parameters like the lymphovascular invasion, size of the tumour and myometrial invasion. **Conclusion**: Maximum expression of androgen receptor was observed in endometrioid and serous carcinomas, while carcinosarcomas and clear cell carcinomas showed minimum expression with no significant correlation between androgen receptor expression and clinicopathological parameters.

Keywords: Endometrioid carcinoma; Serous carcinoma; Clear cell carcinoma; Androgen receptor; Immunohistochemical stains

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INTRODUCTION

Endometrial carcinomas are the most common neoplasms in women around the world. It is the fourth most common malignancy in the western world after breast, lung, and colon[1]. It is the second most common malignancy after breast cancer in Pakistan according to Punjab Cancer Registry (http://www.punjabcancerregistry.org.pk/.) data published in 2016 with an incidence rate of 4.7%.

Formerly, endometrial carcinomas were categorized into two major groups based on histological features, i.e., Type I were estrogen-dependent tumours and Type II were estrogen-independent tumours. The favorable prognosis was observed among Type I tumours and it mainly comprises endometrioid tumours. While aggressive clinical outcomes were observed in Type II tumours. Most common malignancies in Type II include serous, clear cell carcinomas and carcinosarcoma.[1,2]

Recently molecular classification has been introduced. Molecular analysis has divided endometrial carcinoma into 4 groups according to the cancer genome atlas study. The first group includes cancer with low mutations rates and low DNA copy number, the second group comprises mismatch repair defects and hypermutated cancers, the third group includes ultramutated cancers having POLE mutations and the fourth group comprises cancer with low mutation rates, but high DNA copy number. First three categories correspond to Type I endometrioid carcinoma and the fourth category corresponds to Type II carcinomas.[3,4]

In the past, various studies have been conducted to study the role of estrogen and progesterone receptor in different types of endometrial carcinomas, as well as their therapeutic significance in these tumours.[5–7] However, few studies have been conducted to enlighten the expression of androgen receptors in these tumours and therapeutic significance of androgen receptor expression in high-grade endometrial carcinomas as so far no definitive endocrine therapy option is available for the high-grade endometrial

carcinomas.[4,7,8] Previous studies highlighted the correlation of AR with ER and PR expression, as well as with the prognostic parameters like the myometrial invasion, lymphovascular invasion, grade and stage of the tumours.[4,9]

Therefore, the current study aims to assess the androgen receptor expression in different types of endometrial carcinomas, including low-grade and high-grade endometrial carcinomas, serous carcinomas, clear cell carcinoma and carcinosarcomas. The study will also correlate the androgen receptor expression with the ER, PR expression and clinicopathological parameters like the myometrial invasion, type and grade of tumour and lymphovascular invasion. We will also discuss the potential therapeutic implication of antiandrogen therapy in endometrial carcinomas, as the role of antiandrogen therapy has been studied in the past in triple negative breast carcinomas and prostate carcinomas.[10,11]

Androgen receptor is a nuclear transcription factor, which initiates the steroid hormone action. This receptor is expressed in both the glands and stroma of the endometrium[8]. The proliferation of endometrium is dependent on the action of these steroid hormones like estrogen, progesterone, and androgens. Androgens and progesterone play a similar role in inhibiting the estrogen-driven proliferation of endometrium[6].

MATERIAL AND METHODS

This cross-sectional analytical study was conducted at Shaukat Khanum Memorial Cancer Hospital after approval from the institutional review board. A Total of 54 cases were retrieved from the electronic computerized Health Information System (HIS) from the year 2017, based on Simple Random Sampling Technique. Scanty, autolyzed and necrotic samples were excluded from the study. All the H&E slides were reviewed by the consultant. Among the total of 54 cases, there are 11 cases of carcinosarcomas, 5 cases of clear cell carcinomas, 8 cases of serous carcinomas, 22 cases of endometrioid grade 1 and 8 cases of endometrioid grade 2 and grade 3 tumours. Specimen nature included both endometrial curettings and hysterectomy specimens. 26 cases of curettings and 28 cases of hysterectomy were included. Prognostic parameters like the lymphovascular invasion, the extent of myometrial invasion and size of the tumour were calculated in the hysterectomy specimens only. Paraffin blocks were selected for immunohistochemistry. All sections were deparaffinized and incubated with antibody AR (441 clone), ER (6F11 clone) and PR (16 clone), using automated machine Leica Bond III. Subsequently, all the process was done as per manufacturer guidelines. Results were interpreted by two histopathologists including one consultant in each case and interpretation was done on the basis of intensity and proportion of staining pattern for all the three receptors on the basis of Liverpool Endometrioid Score. Intensity was given a score as weak =1, moderate=2 and strong=3 and the proportion was divided into three parameters, i.e., <10% =1, 10–20% =2 , 21–40% =3 and greater than 40% =4. The total score was calculated by multiplying the intensity and proportion of tumour nuclei staining for the hormone receptor. The total score was categorized as low(1–4), moderate (5–8) and high (9–12). Nuclear staining was considered as positive for all the three markers, while cytoplasmic non-specific staining was considered as negative. The expression was calculated predominantly in the glandular epithelial cells. (Table-1)

RESULTS

Total 54 cases of neoplastic endometrium including 11 cases of carcinosarcomas, 5 cases of clear cell carcinomas, 8 cases of serous carcinomas, 22 cases of endometrioid grade 1 and 8 cases of endometrioid grade 2 and grade 3 tumours were included in the study. There were 26 endometrial curettings and 28 hysterectomy specimens. The age range of endometrial carcinomas remains between 28 to 70 years. 12 cases were premenopausal patients with an age younger than 50 years and 42 cases were postmenopausal patients. Maximum incidence was observed in the age range of 50–70 years in postmenopausal patients.

Androgen receptor was applied in all the cases. Among total 54 cases, 29 showed positive AR expression. Positive expression was seen in 2 cases of carcinosarcomas, 1 clear cell carcinoma, 5 serous carcinomas, 16 cases of endometrioid grade 1 and 5 cases of endometrioid grade 2 and grade 3 carcinomas. The endometrioid liver pool score for all the AR-positive tumours is given in table-1.

AR expression was observed in 73% of low-grade endometrioid carcinomas, 62.5% of high-grade endometrioid carcinomas, 62% of serous, 20% of clear cell and 18% of carcinosarcomas. Maximum expression was observed in low grade endometrioid and serous carcinomas, whereas, the minimum expression was observed in clear cell carcinomas and carcinosarcomas.

Androgen receptor expression was also correlated with ER and PR receptor expression as mentioned in Table 2 below. All the tumours were triple positive for AR, ER, and PR except 3 serous carcinomas and 01 low-grade endometrioid tumours, which were negative for either ER or PR.(Table-2)

As far as the correlation of androgen receptor with the prognostic parameters like myometrial invasion, tumour size, lymphovascular invasion is concerned, these parameters were evaluated in 28 hysterectomy specimens.14 cases were AR-positive with 6 out of 14 cases showing greater than 50 % myometrial invasion, 8 out of 14 cases showing less than 50% myometrial invasion, while 7 out of 14 AR-negative tumours had greater than 50% myometrial invasion and 7 out of 14 AR-negative tumours showed a lesser degree of invasion. There is no statistical significance between AR expression and degree and extent of myometrial invasion (Table-3).

Only 1 case shows lymphovascular invasion out of all 28 hysterectomy cases with loss of expression for AR, ER, and PR, while the rest of the cases had no lymphovascular invasion (Table-4). Tumour size also did not show any statistically significant relationship with the AR receptor as AR-positive tumours showed a size range of 1–11cm and AR-negative tumours had a size range of 1–10 cm.

Table-1: The endometrioid live pool score for all AR positive tumours

% of Expression of AR in Endometrial Carsinomas			
Total Number of Cases n=54	**Low AR (L.S=1-4)**	**Moderate AR (L.S=5-8)**	**High AR (L.S=9-12)**
Total AR+ Carcinomas n=29	7	13	9
Low Grade Endometrioid Carcinoma n=16	4/16 (25%)	6/16 (37.5%)	6/16 (37.5%)
High Grade Endometrioid Carcinoma n=5	1/5 (20%)	3/5 (60%)	1/5 (20%)
Serous Carcinoma n=5	1/5 (20%)	3/5 (60%)	1/5 (20%)
Clear Cell Carcinoma N=1	0	0	1 (100%)
Carcinosarcoma n=2	½ (50%)	½ (50%)	0

Table-2: AR, ER and PR Expression among endometrial carcinomas

AR, ER, PR Expression Among Endometrial Carcinomas				
AR +ve tumours	**AR +ve, ER +ve, PR +ve**	**AR +ve, ER -ve, PR -ve**	**AR +ve, ER -ve, PR +ve**	**AR +ve, ER +ve. PR -ve**
Low Grade Endometrioid Carcinoma n=16	15	0	1	0
High Grade Endometrioid Carcinoma n=5	5	0	0	0
Serous Carcinoma Carcinoma n=5	2	2	0	1
Clear Cell Carcinoma n=1	1	0	0	0
Carcinosarcoma n=2	2	0	0	0

Table-3: Association between AR Expression and Myometrial Invasion

Test	**Myometrial Invasion <50%**	**Myometrial Invasion >50%**	**Total**	***p*-value**
AR +ve	8	6	14	.705
AR -ve	**7**	**7**	14	
Total	15	13	28	

p-value >0.05 is insignificant

Table-4: Association between AR expression and lymphovascular invasion

Test	**Lymphovascular Invasion Present**	**Lymphovascular Invasion Absent**	**Total**	***p*-value**
AR +ve	0	14	14	1.423
AR -ve	1	13	14	
Total	1	27	28	

p-value >0.05 is insignificant

DISCUSSION

Endometrial carcinomas are one of the most common gynecological malignancies in Pakistan as well as in western countries[9]. In the past, different studies have been conducted to study the expression of ER and PR in the endometrial carcinomas but very little has been observed about androgen receptor expression in these tumours. These studies on androgen receptor expression have emphasized on its therapeutic and prognostic significance as well as its correlation with the ER PR expression.[4,9]

Our study demonstrated the expression of AR in different subtypes of endometrial carcinomas. AR expression was seen in 62% of serous carcinomas, 20 % of clear cell carcinomas and 18 % of carcinosarcoma, 73% grade 1 endometrioid and 62.5% of grade 2 and grade 3 endometrioid carcinomas. Maximum expression of the androgen receptor was seen in serous and endometrioid carcinomas, while carcinosarcoma and clear cell carcinomas showed minimum expression.

Previous studies also showed androgen receptor expression in endometrial carcinomas. Zadeh *et al*., studied AR expression in 54% of all endometrial carcinomas with 20% of clear cell carcinoma, 70% of serous carcinomas, 50% carcinosarcomas, 60% of low-grade endometrial carcinomas and 70% of high-grade endometrial

carcinomas in the respective study.[4] These statistics are somewhat similar to our study.

In another study, AR expression was observed in 93% of endometrial hyperplasia, 74% in low-grade endometrioid carcinomas, 53% in high-grade endometrioid carcinomas and 41% of non-endometrioid tumours. The author also studied the positive expression of AR in metastatic lesions, when AR expression was lost in the primary tumours. AR lost was associated with aggressive behavior including high FIGO stage, lymphovascular invasion, non-endometrioid histology and decreased survival rate.[7,12] Ito *et al* also suggested low tumour stage and grade with better outcome in AR-positive tumours.[6]

Loss of expression of AR in leiomyosarcomas, uterine sarcomas, endometrial stromal sarcomas, and carcinosarcoma was also noted in the previous studies[13]. Our study also demonstrated positive expression in only 18% of carcinosarcomas with a score of 4 and 8 respectively.

Zadeh *et al* demonstrated strong AR expression in 5 out of 7 cases in serous carcinomas[4]. Hashmi et al. demonstrated positive expression in 3 out of 7 serous carcinomas with none of the clear cell carcinomas or carcinosarcomas showing AR expression.[9] However, no significant correlation was noted with the clinicopathological findings like lymphovascular invasion and myometrial invasion.[4,9]

AR-positive serous carcinomas were also ER-positive in our study. However many studies in the past supported the fact that high-grade serous carcinomas are not estrogen driven, while studies done in the recent past showed some degree of ER positivity in a proportion of serous carcinomas[14].

Endometrioid carcinomas expressed stronger expression of ER and PR in almost all cases, while non-endometrioid tumours were negative for both of these markers with few cases showing weak to moderate expression. Wei et al. demonstrated 80% reactivity for ER and PR in endometrioid carcinomas with 15–50% expression in FIGO grade 3 and 5–54% in serous carcinomas.[15]

Previous studies showed better prognosis of AR-positive tumours as compared to AR-negative tumours, but our study does not reveal any significant association with the prognostic parameters. But the major limitation of our study is the small sample size of 28 hysterectomy specimens with no follow up of the patients. More studies with large sample size are needed to establish the correlation of AR expression with patient outcome and prognostic parameters.

Androgen receptor positivity can have therapeutic implication in endometrial carcinomas as the role of antiandrogen therapy has been successfully established and used in prostate and triple negative breast carcinomas in the past.[16–18] So far, no definitive endocrine therapy option is available for high grade endometrioid and non-endometrioid tumours. Clinical trials need to be done and more studies are needed to establish the definitive role of antiandrogen therapy in endometrial carcinomas as implicated in prostatic carcinomas.

CONCLUSION

Our study demonstrated positive androgen expression in a subset of high grade endometrial carcinomas but did not showed any significant association between AR positivity and prognostic parameters. To conclude, larger studies and clinical trials are needed to be done in the future to establish the association between its positivity and prognostic parameters as well as the therapeutic significance of antiandrogen therapy in endometrial carcinomas with positive-AR expression.

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AUTHORS' CONTRIBUTION

MN, SM: Literature search, data collection, study design, study analysis, proof reading, write-up. NA, UH, MA: Proof reading, data collection, data interpretation, proof reading.

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