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Androgen Receptor Expression in Endometrial Carcinoma and its Correlation with Clinicopathologic Features - A Cross Sectional Study

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ABSTRACT

Introduction: Endometrial cancer is the most common gynecological malignancy in the Western countries. Traditionally, endometrial cancers have been divided into two groups. Type I and Type II tumors. The majority of endometrial cancers are hormone dependent, and hormonal dysregulation is linked to disease development and progression. The role and expression of estrogen and progesterone receptors (ERα and PR) in endometrial cancer have been extensively studied. Hormonal therapy targeting both PR and ERα is used in treatment of endometrial cancer. The response rate to such treatments is usually low. Androgen receptor (AR) is a hormone receptor less studied in endometrial cancer, although a target for treatment in other cancers. It is expressed in several tissues, including the uterus, where its role is largely unknown. Recently, also in breast cancer treatment, targeting AR has been suggested beneficiary for specific subgroups of patients. Given the similarities of breast and endometrial cancers, exploring AR expression in endometrial cancer might reveal new therapeutic strategies. Additionally, AR status in malignant endometrial lesions may be related to clinical phenotype and could represent a novel biomarker for prognosis.

Objectives: The objective of the study is to evaluate the frequency of androgen receptor expression in different subtypes of endometrial carcinoma and to correlate the expression with clinico-pathologic features.

Methodology: The present study is a cross sectional study conducted at the Department of Pathology, Government Medical College Thrissur from 01/01/2020– 30/06/2021.The study included all hysterectomy specimens diagnosed with endometrial carcinoma. Sample size was 85. Endomertrial carcinoma grading and histological typing was determined for each case from routine H and E sections. The immunohistochemical vii staining using AR antibody was done. AR immunohistochemical scoring was based on Liverpool endometrial steroid quick score.AR expression was correlated with age , parity ,menopausal status , clinical features ,tumor grade, histological type ,myometrial invasion, T stage and lymph node status. Data thus obtained was analysed using software SPSS version 20.0.the statistical test used is Fischer exact test . P value less than 0.05 was considered statistically significant .

Results: Most of the patients were in the age group of 51-60 years. Among the 85 patients, 69 were postmenopausal and 5 were nulliparous. Most of the patients presented with post menopausal bleeding. More than half of myometrial invasion was noted in 37 cases.15 cases were in T3 stage and 8 cases showed lymph node involvement. There were 71 cases of endometrioid,5 cases of serous,7 cases of carcinosarcoma and one case each of clear cell carcinoma and dedifferentiated carcinoma. Endometrioid carcinoma showed AR positivity in 28% cases. 20% of serous , 57% of carcinosarcoma and 100% dedifferentiated carcinoma showed positive AR expression. Considering the FIGO grade, 27.5% of grade I , 26.7% grade II and 40% grade III endometrioid carcinomas showed positive AR expression.

Conclusion: Except clinical feature (p=0.049),no significant association between AR expression and other pathological variables was identified. No significant association of AR expression with tumor grade or histological type was noted.

Key words – Endometrial adenocarcinoma; Immunohistochemistry; Androgen receptor viii

International Journal Dental and Medical Sciences Research
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I. INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in the Western countries and accounts for approximately 4% of all cancers worldwide (1). Bokhman in 1983 classified endometrial carcinoma into type I and Type II. Type I accounts for 80%, show low grade endometrial morphology and have a favorable clinical outcome. Type I (endometrioid carcinoma) arises in the background of unopposed estrogen stimulation due to obesity or anovulatory cycles. These tumors are often preceded by endometrial hyperplasia and generally express estrogen and progesterone receptors. Patients with type I tumors are generally younger (premenopausal or perimenopausal), present at an early stage. Endometrioid carcinoma is graded into grade 1, 2 and 3 by FIGO. Type II tumors occur in older patients in the background of endometrial atrophy, and are not related to hormonal factors. Type II endometrial cancer which is less common (20% of cases) are characterized by high histologic grade and serous or clear cell morphology (2). Uterine serous carcinomas are highly aggressive, and have a predilection for deep myometrial and lymphovascular invasion, peritoneal and distant metastatic spread. Serous carcinomas can cause relapses in 50% of cases and account for cancer deaths in 40% of cases. There are high chances of recurrence even in the presence of minimal uterine disease. This aggressive clinical course associated with uterine serous carcinomas necessitates the need for improved therapeutic strategies. Androgen receptor (AR) is a hormone receptor less studied in endometrial cancer, although a target for treatment in other cancers. It is expressed in several tissues, including the uterus, where its role is largely unknown. Treatment targeting AR or androgen synthesis is therefore one of the main therapeutic elements in patients with hormone dependent prostate cancer. Recently, also in breast cancer treatment, targeting AR has been suggested beneficiary for specific subgroups of patients (3). Given the similarities of breast and endometrial cancers, exploring AR expression in endometrial cancer might reveal new therapeutic strategies. Additionally, AR status in malignant endometrial lesions may be related to clinical phenotype and could represent a novel biomarker for prognosis.

Objectives

• To evaluate the frequency of androgen receptor expression in different subtypes of endometrial carcinoma

• To correlate AR expression with clinico-pathologic features

II. METHODOLOGY

All hysterectomy specimens of endometrial adenocarcinomas received in the Dept. of Pathology Government Medical College Thrissur, were studied. Sections were taken for H&E to assess the histological type & tumour grade. Immunohistochemical staining of formalin-fixed paraffin-embedded tissue was done. 4 micrometer thick sections were taken for IHC. Sections were deparaffinized and dehydrated. Antigen retrieval was performed by pressure cooking and stained with AR immunohistochemical marker. For detection of AR antigen rabbit monoclonal antibody (Clone : EP120) was used. AR staining was evaluated using regular light microscope at the magnification of 40x. Nuclear staining was evaluated. AR expression is interpreted using Liverpool endometrial steroid quick score with a final score out of 12 calculated by proportion of positive tumor nuclei by the staining intensity .

Data Entry and Analysis

Data thus obtained was entered in Microsoft office excel sheet 2016. This was then analysed using SPSS software version 20.0. The statistical test used is the Fisher's exact test. P value < 0.05 was considered statistically significant. The findings are presented in appropriate charts and tables.

III. RESULTS

The study was conducted in the Department of Pathology at Government Medical College, Thrissur between January 2020 to June 2021. 85 cases of endometrial adenocarcinoma of uterus were taken, Hematoxylin and Eosin staining was done. In this study, cases with 5% or less than 5 % of solid growth pattern is taken as grade 1 endometrioid adenocarcinoma. Cases with 6-50% of solid growth pattern is taken as grade 2. Cases with more than 50% of solid growth is taken as grade 3 endometrioid adenocarcinoma . Cases of serous carcinoma, clear cell carcinoma and undifferentiated carcinoma were also included. This was followed by immunohistochemical staining for AR. In this study 1% nuclear positivity was considered positive for AR expression .

Age distribution

In our study, 14 (16.5%) cases were in the age group of 41-50, 35 (41.2%) were in the age group of 51-60, 29 (34.1%) were in the age group of 61-70 and 7 (8.2%) were in the age group of 71-80.

International Journal Dental and Medical Sciences Research
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Distribution of Parity
Out of 85 cases, 5 (5.9%) were nulliparous and 80 (94.1%) were multiparous.

Distribution of Menopause Status
In this study, 69 (81.2%) were attained menopause and 16 (18.8%) were not attained menopause.

Distribution of Myometrial Invasion
Out of 85 cases, 37 (43.5%) had more than half of myometrial invasion and 48 (56.5%) had less than half of myometrial invasion.

Proportion of AR Expression
Out of 85 cases, 26 (30.6%) showed positive AR expression and remaining 59 (69.4%) showed negative AR expression.

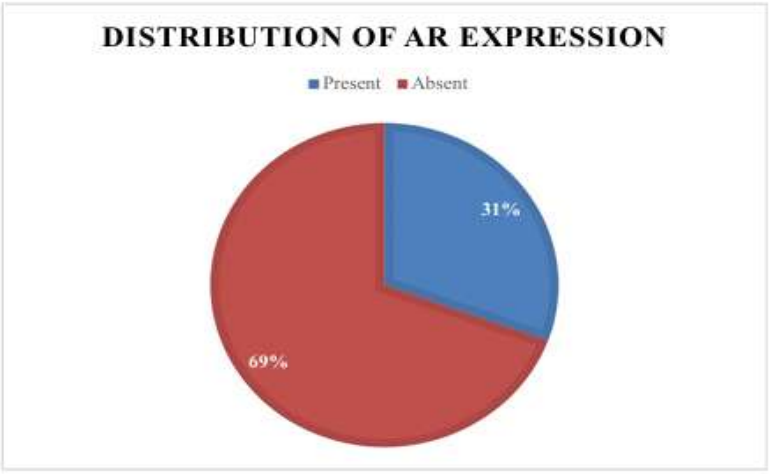

Figure 1: Pie diagram of AR expression

Out of 85 cases, high, moderate and low AR expression was noted in 7 (8.2%), 11 (12.9%) and 8 (9.4%) cases respectively. Remaining 59 cases (69.4%) showed no AR expression

AR Intensity	Frequency	Percentage
Absent	59	69.4
Low	8	9.4
Moderate	11	12.9
High	7	8.2
Total	85	100.0

Table 1: Distribution of AR intensity

Age	AR expression				Total	χ^2 Value	p Value
	Present		Absent				
	n	%	N	%			
41-50	5	35.7	9	64.3	14	1.064	0.786
51-60	9	25.7	26	74.3	35		
61-70	9	31.0	20	69.0	29		
71-80	3	42.9	4	57.1	7		

Table 2 : Association between AR expression and Age

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Positive AR expression showed in 5 (35.7%) cases in the age group of 41-50, 9 (25.7%) in the age group of 51-60 years, 9 (31.0%) in the age group of 61-70 years and 3 (42.9%) in the age group of 71-80 years. It was statistically not significant (p=0.786).

The study variables parity, menopause status, clinical feature and myometrial invasion were correlated with AR expression. Only clinical feature showed significant association with AR expression. Out of 80 cases presented with bleeding per vagina, 22 (27.5%) were showed positive AR expression and 4 (80.0%) positive cases were presented with abdominal pain.

Variables	AR expression				Total	χ^2 Value	p Value
	Present		Absent				
	n	%	n	%			
Parity							
Nulliparous	2	40.0	3	60.0	5	0.222	0.639
Multiparous	24	30.0	56	70.0	80		
Menopause Status							
Attained	19	27.5	50	72.5	69	0.935	0.334
Not attained	7	43.8	9	56.3	16		
Clinical Feature							
Bleeding per Vagina	22	27.5	58	72.5	80	3.887	0.049
Abdominal Pain	4	80.0	1	20.0	5		
Myometrial Invasion							
More than Half	13	35.1	24	64.9	37	0.315	0.575
Less than Half	13	27.1	35	72.9	48		
T Stage							
T1	14	29.8	33	70.2	47	0.167	1.000
T2	7	30.4	16	69.6	23		
T3	5	33.3	10	66.7	15		
Lymph node Involvement							
Present	3	37.5	5	62.5	8	0.192	0.661
Absent	23	29.9	54	70.1	77		
WHO type							
Endometrioid	20	28.2	51	71.8	71	5.171	0.238
Serous	1	20.0	4	80.0	5		
Clear Cell	0	0.0	1	100.0	1		
Carcinosarcoma	4	57.1	3	42.9	7		
Dedifferentiated	1	100.0	0	0.0	1		
FIGO Grade							
Grade I	14	27.5	37	72.5	51	0.628	0.817
Grade II	4	26.7	11	73.3	15		
Grade III	2	40.0	3	60.0	5		

Table 3: Association between AR expression and study variables

International Journal Dental and Medical Sciences Research
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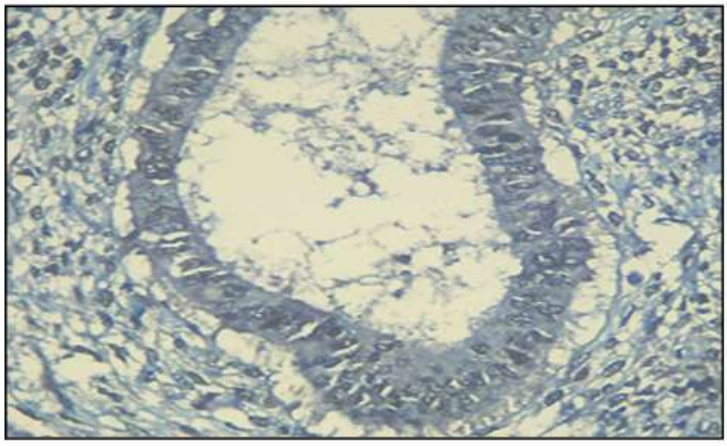

Figure 2: Picture showing weak AR expression in IHC

IV. DISCUSSION

Uterine carcinoma is one of the common cancers in women with increasing incidence and mortality(4). In India, the total number of new cases of endometrial adenocarcinoma in 2018 is 13,328 with an estimated 5010 deaths. The age standardized incidence rate of endometrial adenocarcinoma in India is 2.1/100,000 women . This increase is attributed to the changing trends in the lifestyle and reproductive profile of women and also due to urbanization(5). Majority of women with endometrial carcinoma will present at an early stage with bleeding symptoms. Most of them have a favorable histologic subtype and good prognosis. But around 20% of women have high grade endometrial carcinoma(6) and thus poor outcome. Histopathologic grading of endometrioid carcinomas into FIGO grade 1,2 and 3 is done by assessing the percentage of solid areas. Grade 1 with 5% or less than 5% of solid growth, grade 2 with 6% to 50% of solid growth and grade 3 with more than 50% of solid growth(7,8). Non endometrioid endometrial carcinomas like serous, clear cell, dedifferentiated and carcinosarcomas are generally considered to be high grade and it is not recommended to assign a histologic grade to these tumor types. Human endometrium changes morphologically and biochemically during various phases of menstrual cycle, influenced by not only estrogen and progesterone, but probably also by androgens. The purpose of this study was to investigate the androgen receptor expression in endometrial carcinoma and its clinicopathologic correlation(9,10,11). In this study 85 cases of endometrial adenocarcinoma were included. Sections were taken for H&E to assess the tumor grade and histological type. AR expression in all 85 cases were found out immunohistochemically and its association with age, parity , menopausal status, clinical features, tumor grade, histological type ,myometrial invasion, T stage and lymph node status were analysed. Nuclear staining of AR was evaluated and immunohistochemical scoring was based on Liverpool endometrial steroid quick score. Similar to the studies conducted by Atif Ali et al and Zadeh S L et al this study also considered AR expression positive with 1% nuclear positivity . 49 Age group of patients in this study ranged from 41-80 years. Majority of patients in this study were in the age group of 51-60 years. The mean age was 59 years which was similar to the age group in the study conducted by Atif Ali et al . In their study of 103 patients the average age was 56 years. Among the 85 patients in this study, 5 were nulliparous and 69 were post-menopausal women. Most of the patients presented with complaints of post-menopausal bleeding (80%). More than half of myometrial invasion was noted in 37 cases (43%). Whereas in the study conducted by Atif Ali et al out of 103 cases, 59 (57%) cases showed more than half of myometrial involvement . Out of 85 cases,15 cases (17.6%) were T3 stage and 8 cases (9.4%) showed lymph node involvement. In this study, most common histologic subtype was endometrioid 71 (83.5%), followed by carcinosarcoma 7 (8.2%), serous 5 (5.9%), clear cell (1 (1.2%) and dedifferentiated 1 (1.2%) and out of 71 cases of endometrioid carcinomas, 51 cases (71.8%) were FIGO grade I, 15 (21.1%) were grade II and 5 (7.0%) were grade III. Among 85 cases, 26 (30.6%) showed positive AR expression and remaining 59 (69.4%) showed negative AR expression. High, moderate and low intensity AR expression was noted in 7 (8.2%), 11 (12.9%) and 8 (9.4%) cases respectively. The study variables age, parity, menopausal status, clinical feature and myometrial invasion , T stage and Lymph node involvement were associated with AR expression.

Only clinical feature showed significant association with AR expression (p=0.049). Among 85 cases, 20/71 endometrioid (28.2%), 1/5 serous (20.0%), 4/7 carcinosarcoma (57.1%) and 1/1 dedifferentiated carcinoma (100.0%) showed positive AR expression. Considering the FIGO grade, 14/51 grade I (27.5%), 4/15 grade II (26.7%) and 2/5 grade III tumors (40.0%) showed AR expression .However high intensity AR expression noted only in endometrioid(7%) and carcinosarcoma cases(29%). 50 Variable expression of AR was seen in previous studies. Sasaki et al reported 21% expression of AR, on the other hand, as high as 54% AR expression was detected in Zadeh SL et al study . Kato J, Seto reported degree of differentiation/grade of endometrial carcinoma to be inversely associated with AR expression . However, no such association was noted in this study. In the prior studies most of the work focused on endometrioid EC, as it seems to arise as a result of hormonal drive. In the Zadeh SL et al study(12) it was noted that 70% of serous cancers and 50% of carcinosarcoma also showed AR expression and high levels of AR expression was noted in half of serous carcinoma while in this study high AR expression was noted in endometrioid carcinoma and carcinosarcoma cases. Mahdi Z et al study(13,14) revealed association of AR expression with good prognostic features and better disease free survival , however, present study did not show any significant association of AR expression with various pathologic parameters like tumor stage and nodal metastasis. From a clinical view point, it is important to know if AR expression can identify a subset of EC that can benefit from anti-androgen therapy. Recent evidence supports this speculation that androgen receptor antagonism can be a therapeutic option in EC(15) . This becomes especially important in high grade endometrioid and serous cancers in which endocrine (ER/PR) therapeutic option is not available. This study showed high frequency of grade III endometrioid carcinoma and carcinosarcoma to express AR.

V. CONCLUSION

In this study 85 cases of endometrial adenocarcinoma were studied, of which 71 cases were endometrioid carcinomas, 5 cases were serous carcinomas, 7 cases were carcinosarcomas and one case each of clear cell and dedifferentiated carcinoma. Most of the patients were in the age group of 51-60 years. Among the 85 cases 5 were nulliparous and 69 were postmenopausal women. Most of the patients presented with complaints of postmenopausal bleeding (80%). More than half of myometrial invasion was noted in 37 cases (43%). Out of 85 cases,15 cases (17.6%) were in T3 stage and 8 cases (9.4%) showed lymph node involvement. Among 85 cases, 26 (30.6%) showed positive AR expression and remaining 59 (69.4%) showed negative AR expression and high, moderate and low intensity AR expression were noted in 7 (8.2%), 11 (12.9%) and 8 (9.4%) cases respectively. Out of 85 cases 20/71 endometrioid cancer (28.2%), 1/5 serous (20.0%), 4/7 carcinosarcoma (57.1%) and 1/1 dedifferentiated carcinoma (100.0%) showed positive AR expression. Considering the FIGO grade, 27.5% of grade I , 26.7% grade II and 40% grade III endometrioid carcinomas showed AR expression. Except for clinical feature, no significant association of AR expression was noted with other pathologic variables of this study (p=0.049). No significant association of AR expression with tumor grade or histological type was noted

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SPT and LJconceived the idea.
SPT and LJdesigned the study and laid the framework for data collection.
SPT and LJ did data collection and data entry
SPT , PPH and LJ supervised data entry and did data analyses.
SPT laid down the framework for the paper and supervised data analysis.
SPT and LJ awrote the manuscript.
SPT and LJhelped review literature.
SPT PPH and LJhelped in editing and formation of the final draft.

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