Original Article

DOI: 10.7860/JCDR/2022/55445.16783

Pathology Section

Study of ER, PR and VEGF Expression in Endometrial Epithelial Neoplasms and its Association with Histological Stage and Grade of Endometrial Carcinoma

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ABSTRACT

Introduction: Exogenous or endogenous oestrogen induces hyperplastic endometrium which presents with abnormal uterine bleeding. Atypical endometrial hyperplasia is the precursor for endometrial carcinoma. In case of invasive carcinoma, oestrogen Receptor (ER) and Progesterone Receptor (PR) expressions are commonly diminished but their expressions are generally increased in high grade and high stage endometrial carcinomas. Vascular Endothelial Growth Factor (VEGF), a crucial promoter of angiogenesis in endometrial carcinogenesis, is associated with poor prognosis. This study is needed for assessment of biological behaviour of endometrial epithelial neoplasms and application of targeted antiangiogenic therapy.

Aim: To analyse the expression of ER, PR, and VEGF in normal endometrium, hyperplastic endometrium and endometrial carcinoma by immunohistochemistry and to find the association between immunohistochemical expression with grade and stage of endometrial carcinoma.

Materials and Methods: The present cross-sectional, non interventional, retrospective study was conducted in the Department of Pathology along with Department of Obstetrics and Gynaecology of NRS Medical College, Kolkata, from 1st January 2018 to 30th June 2019 comprising of 51 cases. In the present study, histopathological diagnosis was made for each endometrial lesion with grading and staging of endometrial carcinoma followed by immunohistochemical evaluation, performed on the representative sections using monoclonal antibody. Chi-square test and Z-test were used to observe the association of different study variables and to see the significant difference between two proportions. The p-value of<0.05 was taken as statistically significant.

Results: Out of 51 endometrial samples, eight cases had proliferative endometrium, 14 cases had endometrial hyperplasia without atypia, five cases had atypical endometrial hyperplasia and 24 cases had endometrial carcinoma. ER and PR expression was seen less in endometrial hyperplasia and endometrial carcinoma than in benign proliferative endometrium and there was statistically significant association present between PR expression and histopathological diagnosis. All cases of grade 1 endometrial carcinoma showed ER and PR positivity and decreasing expression in higher grades-2 and 3, but were not statistically significant. Expression of VEGF in the groups of endometrial carcinoma (91.7%) and atypical hyperplasia (80%) was significantly increased in comparison with the groups of normal proliferative endometrium (37.5%) showing a significant statistical association (p-value <0.0001). VEGF expression had no statistical association with grade and stage of endometrial carcinoma.

Conclusion: ER, PR and VEGF were effectively associated with prognosis in patients with endometrial carcinoma.

Keywords: Oestrogen receptor, Progesterone receptor, Vascular endothelial growth factor

INTRODUCTION

Endometrial hyperplasia stratifies hyperplastic endometrium based on cytological features into atypical endometrial hyperplasia and endometrial hyperplasia without atypia [1]. Patients with endometrial hyperplasia experience abnormal uterine bleeding in the perimenopausal or postmenopausal age group; rarely, adolescents show signs of atypical hyperplasia [2,3]. The oestrogen accountable for this process may be either endogenous or exogenous. The risk of endometrial hyperplasia as well as endometrial carcinoma is commonly associated with exogenous administration of tamoxifen [4-7]. The risk of progression to carcinoma in cases of atypical endometrial hyperplasia and non atypical hyperplasia was 23% and 2% respectively [8]. The most common malignant epithelial tumour of uterine corpus is endometrial adenocarcinoma. They are classified into endometrioid endometrial adenocarcinoma (most common type) and other special types [1,8]. More than 80% of endometrial adenocarcinomas are of the endometrioid type [8]. Endometrial cancer accounts for 4-8% of all cancers, and approximately 7,400 die from the disease [9,10]. The incidence of endometrial carcinoma in India is 4.3/1,00,000 women [11]. Endometrial biopsy remains an imperative tool to diagnose endometrial premalignant and malignant lesions.

Angiogenesis plays a crucial role in endometrial carcinoma development and progression. The most important molecule that is responsible for angiogenesis is VEGF. It is expressed not only in endometrial carcinoma but also in normal endometrium and associated with poor prognosis. During the development of endometrial carcinoma, oestrogen and progesterone play the most important role. In case of invasive carcinoma, ER and PR expressions are commonly diminished but their expressions are generally increased in high grade and high stage endometrial carcinomas compared to atypical endometrial hyperplasia [12]. Therefore absence of ER and PR expression may be important in the progression of endometrial carcinogenesis [13]. PR expression is associated with better survival in patient with endometrial carcinoma. The study aims to analyse the expression of ER, PR and VEGF in normal endometrium, hyperplastic endometrium, and endometrial carcinoma by immunohistochemistry and to find the association of VEGF, ER, PR expressions with grades and stages of endometrial carcinoma.

MATERIALS AND METHODS

This cross-sectional, non interventional, retrospective study was conducted in the Department of Pathology along with Department of Obstetrics and Gynaecology of NRS Medical College, Kolkata, West Bengal, India from 1st January 2018 to 30th June 2019 (total 18 months duration) after obtaining a permission letter from Institutional Ethics Committee (IEC) vide No/NMC/7847 dated 07.12.2017.

Total 75 endometrial samples were taken from 75 patients attending Gynaecology Outpatient Department (OPD) after taking informed consent, were taken into consideration by purposive sampling technique during this 18 months period.

Inclusion criteria: Out of 75 cases, 51 cases with clinical or sonographical suspicion of endometrial pathology were included in the study.

Exclusion criteria: Total 24 patients with history along with signs and symptoms suggestive of cervical and adnexal pathology were excluded.

Morphological diagnosis and categorisation of endometrial biopsies, presence/absence of hyperplastic changes, presence or absence of atypia, final histopathological diagnosis, subtyping, grading and pathological staging of endometrial carcinoma were done during gross and microscopic examination in the resected samples. Grading of endometrial carcinoma was done by International Federation of Gynaecology and Obstetrics (FIGO), three tier grading system and pathologic staging was done by American Joint Committee on Cancer (AJCC), Cancer Staging Manual, 8th edition [14]. Immunohistochemistry was performed on the representative sections using a monoclonal antibody. Lobular capillary haemangioma was taken as positive control for VEGF and normal breast tissue for ER and PR. Following parameters were studied during immunohistochemical evaluation: location of these immunomarkers, percentage of cells positive for markers and intensity of IHC staining. The criteria for positive VEGF immunoreaction is granular membranous or/and cytoplasmic positivity.

To calculate the immunostaining grade and intensity of VEGF, a semi-quantitative scoring system was used depending on two parameters: 1. colour intensity and 2. percentage of cytoplasmic positive cells. Those parameters were expressed by numbers from 0 to 3 as below:

Staining intensity: 0=negative, 1=weak, 2=moderate and 3=strong.

Percentage of cytoplasmic positive cells:

- 0=negative, 1 ≤25% positive cells, 2=26-50% positive cells, 3 ≥50% positive cells.

A final score was obtained after adding the two parameters with the following interpretation for the immunohistochemical reaction:

- 0-2=negative immunoreaction,
- 3-4=slightly positive immunoreaction,
- 5-6=strongly positive immunoreaction.

ER and PR status were evaluated according to the following method: percentage (P) of stained cells:

- 1=0-25%, 2=26%-75%, 3 >75%.

Intensity (I) of nuclear staining:

- 1=Absent-to-weak, 2=Strong, 3=Very strong.

Category of ER and PR scoring was determined by summation of percentage and intensity scores (P+I) as described:

- Category 1=Scores 1-2,
- Category 2=Scores 3-4,
- Category 3=Scores 5-6.

Category 1 was considered negative, Category 2 was slightly positive and Category 3 was strongly positive.

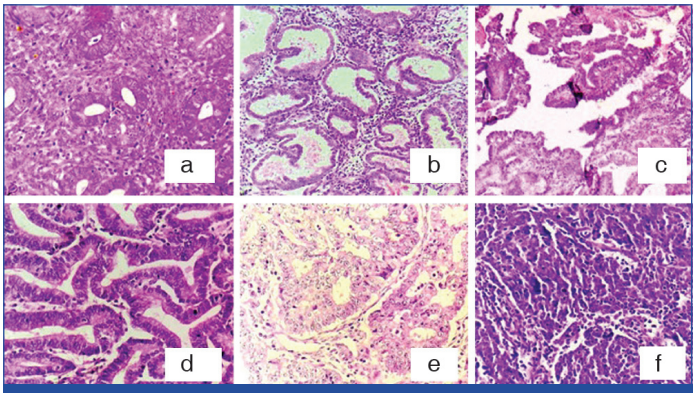
STATISTICAL ANALYSIS

Epi Info (TM) 238 7.2.2.2 software system was used for statistical analysis of the data. Chi-square test and Z-test (Standard Normal Deviate) was used to observe the association of different study variables and to see the significant difference between two proportions respectively. To compare the study mean, t-test was used. The p-value of <0.05 was taken as statistically significant.

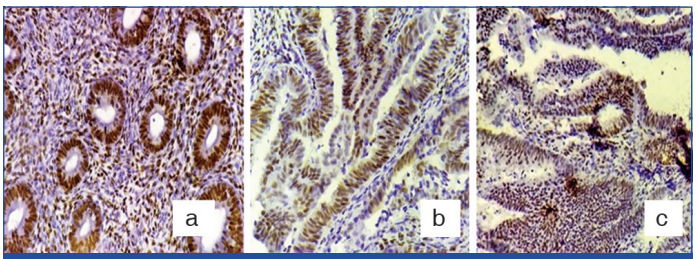
RESULTS

The mean age, age range and median age were 48.29 years, 30-60 years and 49 years respectively, having suspected endometrial pathology whereas the mean age, age range and median age were 59.08 years, 47-68 years and 60 years respectively were of endometrial carcinoma and most of the patients were more than 50 years (87.5%), that was comparatively greater than other age group (Z=9.66; p-value <0.0001). Hyperplasia without atypia (78.6%) and atypical endometrial hyperplasia (60.0%) were most prevalent in the fourth and fifth decades respectively. Total 50% (12/24) of the cases of endometrial carcinoma was found in the 5th and 6th decades of life and 37.5% (9/24) of cases in the 6th to 7th decades.

Microscopic examination [Table/Fig-1] revealed that most of the cases were of endometrial carcinoma: 24 cases (47%) followed by hyperplasia without atypia: 14 cases (27.5%), proliferative endometrium: eight cases (15.7%) and atypical endometrial hyperplasia: five cases (9.8%). A 43.1% of the patients presented with postmenopausal bleeding per vagina, which was significantly higher (Z=2.94; p-value <0.0001) than other complaints like menorrhagia, abnormal non cyclical vaginal bleeding, menometrorrhagia, metrorrhagia etc. Hyperplasia without atypia (92.9%) was most prevalent among the premenopausal patients. All cases of atypical endometrial hyperplasia and endometrial carcinoma were mostly prevalent among the postmenopausal patients. Total 17 (89.5%) out of 19 cases of endometrial hyperplasia, 21 (87.5%) out of 24 cases of endometrial carcinoma and all cases of benign proliferative endometrium showed ER expression [Table/Fig-2].

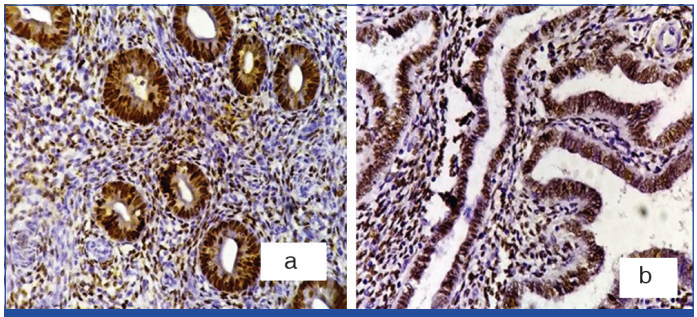


[Table/Fig-1]: Photomicrograph showing; 1a) Proliferative endometrium, (H&E, magnification 400X); 1b) Endometrial hyperplasia without atypia (H&E, magnification 200×); 1c) Atypical endometrial hyperplasia (H&E, magnification 200X); 1d) Grade 1 endometrial carcinoma (H&E, magnification 400X); 1e) Grade 2 endometrial carcinoma, (H&E, magnification 400X); 1f) Grade-3 endometrial carcinoma (H&E, magnification 200X).

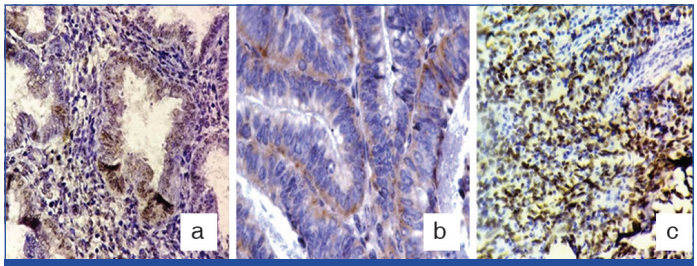


[Table/Fig-2]: Photomicrograph of immunohistochemical staining showing nuclear expression of ER in (2a) Proliferative endometrium, (diaminobenzidine immunohistochemical stain, magnification 400X), (2b) Grade-1 endometrial carcinoma, (diaminobenzidine immunohistochemical stain, magnification 400X), (2c) Grade-3 endometrial carcinoma (diaminobenzidine immunohistochemical stain, magnification 400X).

Endometrial carcinoma was most prevalent among the patients with positive ER expression. Corrected Chi-square test (χ^2=9.69) showed no significant association between status of ER expression and histopathological findings. Positive PR expression [Table/Fig-3] was seen less in endometrial hyperplasia (16/19, 84.2%) and endometrial carcinoma (19/24, 79.2%) than proliferative endometrium (8/8,100% cases). Corrected Chi-square test (χ^2=12.97) revealed a significant association between PR expression status and histological diagnosis (p-value=0.043). Endometrial carcinoma was significantly prevalent among the patients with positive PR expression whereas atypical endometrial hyperplasia was seen among PR negative cases. Expression of VEGF [Table/Fig-4] in the groups of endometrial carcinoma (22/24, 91.7%) and atypical endometrial hyperplasia (4/5, 80%) was significantly increased in comparison with the groups of normal proliferative endometrium (3/8, 37.5%). Corrected Chi-square test (χ^2=33.56) showed a significant association between VEGF score and histological diagnosis (p<0.0001). There were 17 cases (70.8%) of high grade (grade 2 and grade 3) endometrial carcinoma which were significantly higher than the low grade (29.2%) (Z=9.66; p-value <0.0001). Total 14 cases (58.3%) of endometrial carcinoma were of the stage 1 which was significantly higher than other stages (41.7%) (Z=2.64; p-value <0.01). Corrected Chi-square (χ^2=0.97) test revealed insignificant association between ER immunoreactivity score and FIGO stage of endometrial carcinoma (p-value=0.61).



[Table/Fig-3]: Photomicrograph of immunohistochemical staining showing nuclear expression of PR in (3a) Proliferative endometrium, (diaminobenzidine immunohistochemical stain, magnification 400X), (3b) Endometrial hyperplasia (diaminobenzidine immunohistochemical stain, magnification 400X).



[Table/Fig-4]: Photomicrograph of immunohistochemical staining showing cytoplasmic expression of VEGF in (4a) Endometrial hyperplasia (Diaminobenzidine immunohistochemical stain, magnification 400X), (4b) Grade 1 endometrial carcinoma,(diaminobenzidine immunohistochemical stain, magnification 400X), (4c) Grade 2 endometrial carcinoma (diaminobenzidine immunohistochemical stain, magnification 200X).

Endometrial carcinoma with early stages (stage 1, 92.3%, 13/14) compared to higher stages (stage 2 and 3, 8/10, 80%) showed higher expression of ER. Corrected Chi-square (χ^2=1.37) test showed that there was expressed more in higher stages (stage 2 and 3, 8/10, 80%) than stage 1(11/14, 78.9%) of endometrial carcinoma. Corrected Chi-square (χ^2=0.14) test revealed insignificant association between status of VEGF and FIGO stage of endometrial carcinoma (p-value=0.93). The quantification of VEGF expression according to the stage showed slightly different values for FIGO stage 1 (92.9%, 13/14) as compared to FIGO stage 2 and 3 (90.0%, 9/10) [Table/Fig-5].

All cases of grade 1 (7/7 cases, 100%) endometrial carcinoma showed ER positivity and decreasing expression of ER in higher grades 2 and 3 (82.4%, 14/17 cases). Corrected Chi-square (χ^2=1.87) test does not show a significant association between status of ER and grade of endometrial carcinoma (p-value=0.39). All cases of grade -1 endometrial carcinoma (7/7, 100%) showed PR positivity and decreasing expression of PR in higher grades (70.6%, 12/17 cases). Total 3 out of 7 (42.9%) grade-3 cases and 2 out of 10 (20%) grade 2 cases showed negative PR expression. Corrected Chi-square (χ^2=2.63) test revealed insignificant association between the status of PR and grade of endometrial carcinoma (p-value=0.26). VEGF expression was 85.7% (6 out of 7 cases) in grade 1 endometrial carcinoma and 94.1% (16/17 cases) in grade 2 and 3 endometrial carcinoma. Corrected Chi-square (χ^2=0.52) test revealed insignificant association between VEGF immunoreactivity score and grade of endometrial carcinoma (p-value=0.77) [Table/Fig-6].

DISCUSSION

The second most common gynaecological malignancy is endometrial carcinoma. The incidence of this carcinoma in India is 4.3 per 1,00,000 women [11]. Various studies have investigated about the roles of endometrial immunohistochemical markers like ER, PR and VEGF which could directly affect prognostication [15]. In case of invasive carcinomas, ER and PR expressions are commonly diminished, but their expressions are generally increased in high grade and high stage carcinomas, compared to atypical endometrial hyperplasia [12]. So, absent ER and PR expressions might be an important issue during the endometrial carcinogenesis [13].

VEGF expression in endometrial hyperplasia is significantly upregulated compared to normal endometrial mucosa, with a further increase during the development of endometrial carcinoma [16]. Total 78.6% of the cases (11/14) diagnosed as endometrial hyperplasia without atypia were in the fourth decade of life and 60% of the cases (3/5) of atypical endometrial hyperplasia were in the fifth decade of life. About

ER status	FIGO stage (EC)		Total	PR status	FIGO stage (EC)		Total	VEGF status	FIGO stage (EC)		Total
	I	II and III			I	II and III			I	II and III	
-ve	1	2	3	-ve	3	2	5	-ve	1	1	2
+ve	4	3	7	+ve	4	1	5	+ve	2	1	3
++ve	9	5	14	++ve	7	7	14	++ve	11	8	19
Total	14	10	24	Total	14	10	24	Total	14	10	24

[Table/Fig-5]: Association of ER, PR and VEGF immunoreactivity with FIGO Stage of endometrial carcinoma (EC) (n=24).

ER status	Grade of EC		Total	PR status	Grade of EC		Total	VEGF status	Grade of EC		Total
	1	2 and 3			1	2 and 3			1	2 and 3	
-ve	0	3	3	-ve	0	5	5	-ve	1	1	2
+ve	3	4	7	+ve	2	3	5	+ve	1	2	3
++ve	4	10	14	++ve	5	9	14	++ve	5	14	19
Total	7	17	24	Total	7	17	24	Total	7	17	24

[Table/Fig-6]: Association of ER, PR and VEGF immunoreactivity with grade of endometroid endometrial carcinoma (EC) (n=24).

50% of the cases of endometrial carcinoma were found to occur in the 5th and 6th decades and 37.5% in the 6th to 7th decades of life. In the present study, all the cases of endometrial carcinoma were in postmenopausal age group. Creaseman W et al., have reported that 75% women of endometrial carcinoma were in postmenopausal age group [17]. In the present study, 6/19 (31.6%) cases of endometrial hyperplasia and 22/24 (91.7%) cases of endometrial carcinoma presented with postmenopausal bleeding. Gull B et al., included 394 women in their study having postmenopausal bleeding and documented the relative risk of endometrial carcinoma was 63.9% in contrast to 22.7% in the corresponding age groups [18]. ER expression was seen less in endometrial hyperplasia (17/19, 89.5%) and endometrial carcinoma (21/24, 87.5%) than in benign proliferative endometrium (8/8,100.0%). PR expression was also seen less expressed in endometrial hyperplasia (16/19, 84.2%) and endometrial carcinoma (19/24, 79.2%) than proliferative endometrium. This shows that ER and PR expression has inverse association with the severity of endometrial lesion. This was parallel to the studies of Orejuela F et al., and Bozdoğan O et al., [19,20]. Hormone receptors have been found positive in 35-90% of endometrial carcinomas according to some literatures, and in some advanced diseases these receptors might be absent [21].

In the present study, there were 87.5% (21/24) ER positive cases, 79.2% (19/24) PR positive cases and 75.0% (18/24) of cases were both ER and PR positive. In case of well-differentiated tumours the hormone receptors are frequently positive compared to poorly differentiated tumours [22], which corroborate with present study findings. In present study, all cases of grade 1 carcinoma showed ER (100%) and PR (100%) positivity and decreasing expression in higher grades, grade 2 and 3 (ER 82.4%, 14/17 and PR 70.6%, 12/17). 3 out of 7 grade 2 (42.9%) and 2 out of 10 grade 3 (20%) cases showed negative PR expression. Endometrial carcinoma with early stages (stage 1) compared to higher stages (stage 2 and 3) showed higher expression of ER (13/14, 92.3%) but PR is expressed more in higher stages (8/10, 80%) than stage 1(11/14, 78.9%).

Study of Fanning J et al., did not reveal direct relationship between hormone receptor expressions to stage and grade of the tumour which associated with present study [23]. Expression of VEGF in endometrial carcinoma (22/24, 91.7%) and atypical hyperplasia (4/5, 80%) were significantly increased in comparison with the groups of normal proliferative endometrium (3/8, 37.5%). There was significant association between status of VEGF and histopathological findings (χ^2=33.56; p<0.0001). Studies by Holland C et al, Fine B et al., and Yokoyama Y et al., observed that increased expressions of VEGF in carcinoma of endometrium and endometrial hyperplasia compared to normal endometrium [24-26]. The association between the obtained VEGF score and tumour grade was statistically insignificant (χ^2=0.52; p-value=0.77). The expression rate for VEGF were 85.7% (6 out of 7 cases) in grade 1 and 94.1% (16/17 cases) in the grade -2 and 3 endometrial carcinoma which is consistent with study performed by Sanseverino F et al., and Hirai M et al., [27,28]. Regarding VEGF expression during the FIGO staging, authors found different values for stage 1 FIGO (92.9%) in contrast to stage 2 and 3 FIGO (90%), which was not statistically significant (χ^2=0.14; p-value=0.93).

Every pathologist should include the ER and PR status during reporting of endometrial carcinoma for the better understanding of the tumour behaviour and may help tailor individual treatment strategies. VEGF expression is increased during the development of endometrial carcinoma and its expression correlates with vascular density, aggressiveness, prognosis, recurrence and metastasis.

Limitation(s)

The limitations of the present study comprise a small study population of 51 patients who attended a tertiary care hospital and the duration (18 months) for data collection and data analysis. It is recommended that inclusion of a larger study population and a multicentric study design for a longer duration in near future may add a better tool for validation of results generated in present study.

CONCLUSION(S)

ER, PR and VEGF were effectively associated with prognosis in patients with endometrial carcinoma. Increased expressions of ER and PR are observed in high grade and high stage endometrial carcinomas whereas decreased expressions have been found in case of invasive carcinomas. During progression of endometrial carcinogenesis absence of ER and PR expressions may be an important factor. So the study of both the hormonal receptors (ER and PR) could be an important marker to look for the high risk category patients of endometrial adenocarcinoma. VEGF plays an important role in neoangiogenesis and tumour progression thus providing a promising target for antiangiogenic therapy against endometrial carcinoma.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 07, 2022
- Manual Googling: May 11, 2022
- iThenticate Software: Jul 30, 2022 (7%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Feb 03, 2022**
Date of Peer Review: **Apr 01, 2022**
Date of Acceptance: **May 24, 2022**
Date of Publishing: **Aug 01, 2022**