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Pathology

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

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Abstract **Original Research Article**

Endometrium is a one of the dynamic tissue of the female genital tract. Carcinoma of endometrium is one of the leading causes of mortality in aged women.The important precursor lesions are hyperplasia with or without atypia, all are mainly influenced by unchecked hormonal imbalance between Estrogen Receptor (ER) and Progesteron Receptor (PR).As the diseases advances from hyperplasia to carcinoma there is change of expression of ER, PR and VEGF leading to changes in treatment protocol. The study was conducted in the Department of Pathology in collaboration with the Department of Obstetrics and Gynaecology, Nilratan Sircar Medical College and Hospital, Kolkata from 1st January 2018 to 30th June 2019. The study included patients attending the Department of Gynaecology and Obstetrics, with clinical and/or radiological suspicion of endometrial pathologies. Total 51 cases were included in our study. The results of ER, PR and VEGF on endometrial carcinoma and its precursor lesions have been discussed below.

Keywords: Endometrium, Hyperplasia, Carcinoma, ER, PR, VEGF.

INTRODUCTION

The term endometrial hyperplasia signifies a proliferating endometrium featuring glandular architectural abnormalities that result in glandular crowding and usually take the form of either cystic dilation of glands or glandular budding [1-3]. To qualify as endometrial hyperplasia, the glandular overgrowth must be sufficiently pronounced in order to shift the glands-to-stroma ratio to 2:1 to 3:1 [4]. The glandular fraction includes both glands (including their lumina) and villoglandular structures.

Current taxonomy stratifies hyperplastic endometria on the basis of their cytological features into atypical endometrial hyperplasia and endometrial hyperplasia without atypia [5].

The characteristic architectural features of hyperplasia include glandular enlargement and budding. Excessive budding leads to complex epithelial structures with numerous branching channels and papillary infoldings [4].

The criteria for atypical hyperplasia include nuclear enlargement (the relative size of the nuclei estimated by comparing them to the adjacent stromal cell nuclei or those of residual normal epithelial elements), nuclear rounding, varying degrees of pleomorphism, loss of nuclear polarity, and a shift in the nuclear-to-cytoplasmic ratio in favour of the nuclei [5].Other features commonly found in atypical hyperplasia include prominent nucleoli, irregularity of nuclear size and shape, and dispersed (vesicular) and clumped chromatin [5]. Numerous mitotic figures are almost always present in atypical hyperplasia; however, abnormal division figures are sparse or absent [5].

Majority of the patients with endometrial hyperplasia experience abnormal uterine bleeding. Endometrial hyperplasia generally occurs in the perimenopausal or postmenopausal age group; very rarely, adolescents show signs of atypical hyperplasia [6, 7].

Endometrial carcinoma is the second most common gynaecologic malignancy with an incidence of 5.9 per 100,000 women in the developing countries. In India, the incidence is 4.3 per 100,000 women [8] while, it is the most common gynaecologic cancer in the United States, with an incidence of 23.2/100,000 women [9, 10].

Angiogenesis plays a crucial role in endometrial carcinoma development and progression. The formation of new vessels depends on the interaction between different hormones and growth factors. The endometrium expresses several growth factors involved in angiogenesis and VEGF (vascular endothelial growth factor) is one of the most common promoters of angiogenesis, being expressed even by normal endometrium. As an angiogenic factor, VEGF stimulates the proliferation of endothelial cells and also increases vascular permeability and protein extravasations [11] and associated with poor prognosis. VEGF expression in endometrial hyperplasia is significantly upregulated compared to normal endometrial mucosa, with a further increase during the development of endometrial carcinoma [12].

The steroid hormones, estrogen and progesterone, play a significant role in the pathogenesis of endometrial carcinoma, particularly the endometrioid variant. Estrogenic action unopposed by progesterone induces sequential malignant changes in the endometrium by atypical hyperplasia changes [13]. Decreased expressions of estrogen receptor (ER) and progesterone receptor (PR) are observed in invasive tumors with increase in both grade and stage compared to atypical hyperplasia [14]. Therefore absence of ER and PR expression may be important in the progression of endometrial carcinogenesis [15]. Hormone receptor expression especially PR expression is known to be associated with better survival in patient with endometrial carcinoma.

The study aims to analyse expression of VEGF, ER and PR in normal endometrium, endometrial hyperplasia, and endometrial carcinoma by immunohistochemistry and correlate the change of VEGF, ER, PR expression with grade and stage of endometrial carcinoma.

MATERIALS AND METHODS

The study was conducted in the Department of Pathology in collaboration with the Department of Obstetrics and Gynaecology, Nilratan Sircar Medical College and Hospital, Kolkata from 1st January 2018 to 30th June 2019. The study included patients attending the Department of Gynaecology and Obstetrics, with clinical and/or radiological suspicion of endometrial pathologies. Total 51 cases were included in our study.

Inclusion Criteria

- Patients with clinical and/or sonological findings suggesting endometrial pathology.

Exclusion Criteria

- Patients with history of and/or signs and symptoms suggestive of cervical pathology
- Patients with history of and/or signs and symptoms suggestive of adenexal pathology
- Inadequate sample
- Patients not giving consent
- Study design
- Observational, non-interventional study.
- Parameters studied:
- Clinical findings of the patient (age, parity, detailed menstrual history, abnormal vaginal bleeding etc).
- Morphological diagnosis and categorization of endometrial biopsies; presence/absence of hyperplastic changes; presence or absence of atypia; final histopathological diagnosis, sub typing, grading and pathological staging of endometrial carcinoma in the resected samples.
- Analysis of ER, PR& VEGF expression by immunohistochemistry: following parameters studied-location of these immunomarker, percentage of cells expressing and intensity of expression.

RESULTS

After careful analysis of the datas we found the following results.

The mean age (Mean ± S.D) of the patients was 59.08±5.88 years with range from 47 - 68 years and the median age was 60 years.

Most of the patients were with age >50 years (87.5%) which was significantly higher than other age group ($p<0.0001$). Thus malignant cases were mostly prevalent among the patients with age >50 years.

66.7% of the specimens were resected specimen (following hysterectomy) which was significantly higher than that of small biopsy (following dilatation and curettage) (33.3%) ($p<0.001$).

Histological Spectrum of the Endometrial Lesions

Histological diagnosis	Number	%
Proliferative endometrium	8	15.7%
Hyperplasia without atypia	14	27.5%
Atypical endometrial hyperplasia	5	9.8%
Endometrioid carcinoma	24	47.1%
Total	51	100.0%

As per the biopsy findings, most of the cases were Endometrioid carcinoma (47.1%) followed by hyperplasia without atypia (27.5%) which were significantly higher than other findings ($p<0.001$).

Endometrioid carcinoma were mostly prevalent among the patients with age>50 years. 50% (12/24) of the cases of endometrial carcinoma was found to occur in the 5th and 6th decades of life and 37.5% (9/24) cases of endometrial carcinoma was found in the 6th to 7th decades.

43.1% of the patients presented with post menopausal bleeding which was significantly higher than other complaints (p<0.0001).

Corrected Chi-square (χ^2) test showed that there was no significant association between status of ER and histopathological findings of the patients (p=0.13). ER expression was seen in Endometrial hyperplasia (17/19, 89.5%) and endometrial carcinoma (21/24, 87.5%) and in benign proliferative endometrium (8/8,100.0%).

However, Endometrioid carcinoma was mostly prevalent among the patients with positive ER.

There was significant association between Status of PR immunoreactivity and histological diagnosis (p=0.043). PR positive expression was seen less in EH (16/19, 84.2%) and endometrial carcinoma (19/24, 79.2%) than proliferative endometrium (8/8,100% cases)
Endometrioid carcinoma was significantly prevalent among the patients with positive PR. Negative PR significantly found in case of Atypical endometrial hyperplasia.

Corrected Chi-square (χ^2) test showed that there was significant association between status of VEGF score and histological diagnosis of the patients (p<0.0001). Expression of VEGF in the groups of Endometrial carcinoma (22/24, 91.7%) and atypical hyperplasia (4/5, 80%) was significantly increased in comparison with the groups of normal proliferative endometrium (3/8, 37.5%).

Endometrioid carcinoma was significantly prevalent among the patients with strongly positive VEGF. Negative VEGF significantly found in case of proliferative endometrium.

70.8% of the patients were with Grade-2 and Grade-3 (87.5%) which was significantly higher 70.8% of than other grades (Z=9.66; p<0.0001). Thus endometrioid carcinoma cases were mostly with Grade-2 and Grade-3.

58.3% of the patients were with Stage-I which was significantly higher than other Stages (p<0.01). Thus malignant cases were mostly with Stage-I.

There was no significant association between ER immunoreactivity score and FIGO Stage of endometrioid carcinoma (p=0.61). Endometrial carcinoma with early stages (stage1, 92.3%, 13/14) compared to higher stage (2&3) (8/10,80%) showed higher expression of ER.

There was no significant association between PR immunoreactivity and FIGO Stage (p=0.50). PR is expressed more in higher stage (8/10, 80%) than stage 1(11/14, 78.9%) endometrioid carcinoma.

There was no significant association between Status of VEGF and FIGO Stage of EC (p=0.93). The quantification of VEGF expression according to the stage shows slightly different values for stage I FIGO (92.9%, 13/14) as compared to stage II and III FIGO (90.0%, 9/10).

There was no significant association between Status of ER and Grade of EC (p=0.39). All cases of grade-1 (7/7 cases) carcinoma showed ER (100%) positivity and decreasing expression in higher grade 2&3(ER 82.4%, 14/17 cases).

There was no significant association between Status of PR and Grade of EC (p=0.26).All cases of grade-1 (7/7cases, 100%) carcinoma showed PR positivity and decreasing expression in higher grade 2&3(PR 70.6%, 12/17 cases). 3 out of 7 G3 cases (42.9%) and 2 out of 10 G2 (20%) cases showed negative PR expression.

There was no significant association between VEGF immunoreactivity score and Grade of endometrial carcinoma (p=0.77). The expression rate for VEGF was 85.7% (6 out of 7 cases) in the well-differentiated endometrial carcinoma (grade1) and 94.1% (16/17 cases) in the moderately and poorly differentiated carcinoma (grade 2 & 3).

DISCUSSION

Endometrial carcinoma is the second most common gynaecologic malignancy with an incidence of 5.9 per 100,000 women in the developing countries. In India, the incidence is 4.3 per 100,000 women [8]. Time honored prognostic factors include patient's age, tumour grade, stage, histologic type, and the depth of myometrial invasion. Various studies have investigated the endometrial immunomarkers ER, PR and VEGF which could directly affect prognostication [16]. Numerous studies in the literature consider the stage and histopathologic tumor grade as being the most relevant features for subsequent therapeutic management [17]. Conventionally, endometrial carcinomas are divided into two types: type I tumors (about 80%) are endometrioid carcinomas, preceded by atypical hyperplasia and associated with estrogenic stimulation [18]. They occur primarily in pre or perimenopausal women and are associated with obesity, hyperlipidemia, anovulation, infertility, and late menopause. Typically, they are mostly limited to the

uterus and follow a favourable clinical course. In contrast, type II tumors (about 10%) are nonendometrioid (largely papillary serous) carcinomas, arising occasionally in endometrial polyps or from precancerous lesions that occur in atrophic endometrium (endometrial "intraepithelial" carcinoma). Type II tumors readily invade the myometrium and vascular spaces, and carry a high mortality rate. Prognosis depends on several uterine and extra-uterine factors that include various molecular markers.

Most of these risk factors are associated with the changes in levels of sexual hormones during women's lifetime. The steroid hormones, estrogen and progesterone, play a significant role in the pathogenesis of endometrial carcinoma, particularly the endometrioid variant.Estrogenic action unopposed by progesterone induces sequential malignant changes in the endometrium by atypical hyperplasia changes [13]. Decreased expressions of estrogen receptor (ER) and progesterone receptor (PR) are observed in invasive tumors with increase in both grade and stage compared to atypical hyperplasia [14]. Therefore absence of ER and PR expression may be important in the progression of endometrial carcinogenesis [15].

Solid tumors beyond 2 mm in diameter require angiogenesis for growth and nutrition [19]. Angiogenesis plays a crucial role in endometrial carcinoma development and progression. The formation of new vessels depends on the interaction between different hormones and growth factors. The endometrium expresses several growth factors involved in angiogenesis and VEGF (vascular endothelial growth factor) is one of the most common promoters of angiogenesis, being expressed even by normal endometrium. As an angiogenic factor, VEGF stimulates the proliferation of endothelial cells and also increases vascular permeability and protein extravasations [11] and associated with poor prognosis. VEGF expression in endometrial hyperplasia is significantly upregulated compared to normal endometrial mucosa, with a further increase during the development of endometrial carcinoma [12].

The present study aims to determine the correlation between ER, PR & VEGF expression to the various clinicopathological prognostic parameters.

In our study we found that 6/19 (31.6%) cases of endometrial hyperplasia (atypical hyperplasia 5/5 plus 1/14 hyperplasia without atypia) and all the cases (24/24) of endometrial carcinoma were post-menopausal. Creaseman *et al*., [20] have reported that 75% women of endometrial carcinoma were postmenopausal, and only 3-10% less than 40 years of age.

According to our current study, 6/19 (31.6%) cases of endometrial hyperplasia presented with post menopausal abnormal noncyclical bleeding and 22/24 (91.7%) cases of endometrial carcinoma presented with postmenopausal bleeding. Gull *et al*., [21] have evaluated 394 women with postmenopausal bleeding and reported relative risk for endometrial carcinoma was 63.9% compared with 22.7% in the age-matched general population.

In the present study, 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%). This was not statistically significant (χ^2=9.69; p=0.13). PR expression was also seen less expressed in EH (16/19, 84.2%) and endometrial carcinoma (19/24, 79.2%) than proliferative endometrium. This was statistically significant (χ^2=12.97; p=0.043). This shows that ER and PR expression has inverse correlation with the severity of endometrial lesion. This is parallel to the studies in literature [22, 23].

We applied modified FIGO grading system for grading of Endometriod carcinoma. Out of 24 cases of Endometrioid carcinoma, 29.2% (7/24) cases were Grade I, 41.7% cases were Grade II (10/24) and the rest were Grade III (29.2%, 7/24). According to stage, 14 cases were of Stage I and 10 cases were in stage II and III.

Literature review has shown that hormone receptors are positive in 35%-90% of endometrial carcinomas [15] and the absence of these receptors might indicate advanced disease [24]. In our study, there were 87.5% (21/24) ER positive cases, 79.2% (19/24) PR positive cases and 75.0(18/24)% of cases had combined ER and PR positivity, which supported results stated in the literature.

The well-differentiated tumours are more frequently positive for the estrogen and the progesterone receptors than the poorly differentiated lesions [25] consistent with our findings. In our study, all cases of grade-1 (7/7) carcinoma showed ER (100%) & PR (100%) positivity and decreasing expression in higher grade 2&3 (ER 82.4%, 14/17 and PR 70.6%,12/17). 3 out of 7 G3 cases (42.9%) and 2 out of 10 G2 (20%) cases showed negative PR expression. The same results were obtained by other authors, which by making a comprehensive statistical analysis showed that the ER expression is decreasing in the poorly differentiated carcinomas with a statistically significant difference to those with well differentiation [26-28].

Endometrial carcinoma with early stages (stage1) compared to higher stage (2 & 3) showed higher expression of ER (13/14,92.3%) but PR is expressed more in higher stage (8/10,80%) than stage 1(11/14,78.9%). Previous studies have failed to show a direct relationship between hormone receptor

expression to tumour grade and stage [29], which was similar to our study.

Many studies have found that the hormone dependence, and thus the response to the hormonal therapy or the chemotherapy for the endometrial carcinoma decreases in aggressive tumors, the survival rate improves at every stage in the case of the patients with receptor-positive tumors compared with tumors that are receptor-negative [30].

Analysis of VEGF Expression

In present study, expression of VEGF in the groups of Endometrial carcinoma (22/24, 91.7%) and atypical hyperplasia (4/5, 80%) was significantly increased in comparison with the groups of normal proliferative endometrium (3/8, 37.5%) and expression of VEGF in the groups of endometrial carcinoma was significantly increased in comparison with the groups of normal proliferative endometrium. There was significant association between status of VEGF and histopathological findings of the patients (χ^2 =33.56; p<0.0001). So VEGF (immunoreactions) expression is gradually increased from normal benign proliferative endometrium to endometrial hyperplasia and carcinoma. Many studies eg. Holland CM *et al.*[31], Fine BA *et al.*, [32], Yokoyama Y *et al.*, [33] sustain that there is an increased production of VEGF in endometrial carcinoma and hyperplasia of the endometrium compared to normal endometrium; the VEGF expression contributes to the role of angiogenesis in the transition towards carcinoma. Still, there are contradictory results regarding prognostic relevance of VEGF and its receptors in the evolution of endometrial carcinoma.

Current study showed a correlation between the tumour histological grade and the obtained VEGF score, but not statistically significant (χ^2 =0.52; p=0.77). The expression rate for VEGF was 85.7% (6 out of 7 cases) in the well-differentiated endometrial carcinoma (grade1) and 94.1% (16/17 cases) in the moderately and poorly differentiated carcinoma (grade 2&3). This is consistent with study performed by *Sanseverino F et al., [34], Hirai M et al., [35]. But not consistent with the study performed by* Saito M *et al.*, [36].

The quantification of VEGF expression according to the stage of the disease shows slightly different values for stage I FIGO (92.9%) as compared to stage II and III FIGO (90.0%), not statistically significant (χ^2 =0.14; p=0.93). *Sanseverino F et al., [34]* found a significant positive correlation by means of the Spearman coefficient, between VEGF expression and binary grading (0.450, p- value < 0.005) which is an architectural grading system that divide endometrioid carcinomas into low- and high-grade tumors. But not found any correlation between stage and VEGF expression (p-value > 0.005).

CONCLUSION

The important observations from our study has been enumerated below: ER, PR and VEGF are effectively correlated with prognosis in patients with endometrial carcinoma.

Decreased expressions of estrogen receptor (ER) and progesterone receptor (PR) have been observed in invasive tumors with increase in both grade and stage compared to atypical hyperplasia and benign proliferative endometrium. So absence of ER and PR expression may be important in the progression of endometrial carcinogenesis. Therefore, the analysis of both estrogen and progesterone receptors might be used as a marker to identify high risk patients only in a subset of patients with endometrioid adenocarcinoma. The ER, PR status, if included in each pathology report will pave the way for better understanding of biological behavior and may help tailor individual treatment strategies.

VEGF expression in endometrial hyperplasia is significantly upregulated compared to normal endometrial mucosa, with a further increased during the development of endometrial carcinoma and its expression correlates with invasiveness, vascular density, metastasis, recurrence and prognosis. So VEGF play an important role in neoangiogenesis and tumor progression. Thus VEGF pathway is a promising target for anti-angiogenic therapy against endometrial carcinoma.

Steroid hormones are particularly important molecules of the human endometrium, since they regulate the composition and decomposition of the endometrium, as well as cell growth and division. VEGFR also participate in cell growth and neoangiogenesis, combination of these molecules may influence the growth and metastasis of endometrial adenocarcinomas. There is a need of further study for better understanding of correlation between VEGF and steroid hormones.

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