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Study of Pten Immunohistochemical Expression in Endometrial Biopsies From Patients With Endometrial Hyperplasia and Endometrial Carcinoma

Medical Science

KEYWORDS :

Uma Singh	Professor, Department of Obstetrics and Gynecology, King George's Medical University, Chowk, Lucknow – 226003
*** Dr Sabuhi Qureshi**	Professor, Department of Obstetrics and Gynecology, King George's Medical University, Chowk, Lucknow – 226003 * Corresponding Author
Shivani Mishra	Post graduate student, Department of Obstetrics and Gynecology, King George's Medical University, Chowk, Lucknow – 226003
Prachi Srivastava	Senior resident, Department of Obstetrics and Gynecology, King George's Medical University, Chowk, Lucknow – 226003
Madhumati Goel	Professor, Department of Pathology, King George's Medical University Chowk Lucknow – 226003

ABSTRACT

Loss of PTEN, an early event in endometrial carcinogenesis can be used as an immunohistochemical biomarker for premalignant disease. This study was done to find PTEN expression in endometrial hyperplasia and carcinoma and to study clinicopathological correlation of such cases for PTEN expression or non expression .Study included women > 40 years of age with abnormal uterine bleeding excluding women with coagulopathies, iatrogenic bleeding per vaginum, malignancy other than endometrial carcinoma and not willing to participate. Relevant data was collected. Biopsies were send for histopathology and immunohistochemistry. Out of 28 cases with endometrial hyperplasia and 1 case with endometrial carcinoma, loss of PTEN was seen in 11 cases with endometrial hyperplasia, more with atypical hyperplasia. No significant association was seen with age, parity, BMI, diabetes, hypertension, various clinical complaints, uterine size and endometrial thickness. PTEN immunohistochemistry could be used for early diagnosis of premalignant and malignant endometrial lesions.

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in developed countries with an incidence of 12.9 per 100,000 women and a mortality rate of 2.4 per 100,000 women.[1] Endometrial hyperplasia represents a spectrum of morphologic and biological alterations of endometrial glands and stroma, ranging from exaggerated physiological state to carcinoma in situ.

Recognition of biomarkers for endometrial hyperplasia or carcinoma are some of the newer techniques to diagnose premalignant lesions. The tumor suppressor gene phosphatase and tensin homologue (PTEN) is one such biomarker, being abnormally turned off in approximately 2/3 rd of lesions and evaluated by PTEN immunohistochemistry. Loss of PTEN expression tends to be diffuse in endometrial carcinomas but also occurs in morphologically normal endometrial tissue, which suggests that PTEN abnormalities occur early in sporadic endometrial carcinomas.[2]

Loss of PTEN function by mutational or any other mechanism is an early event in endometrial tumorigenesis that may occur in response to known endocrine risk factors and offers an informative immunohistochemical biomarker for premalignant disease. Various studies[3, 4] have been conducted in this regard on endometrial samples including normal, hyperplastic and malignant endometrium and have suggested that loss of PTEN protein expression plays a key role in the process of neoplastic transformation of endometrial hyperplasia and adenocarcinoma development.

This study was planned to find the PTEN immunohistochemical expression in endometrial biopsies in cases with endometrial hyperplasia and carcinoma. Clinicopathological correlation of such cases was studied with respect to presence of or loss of PTEN expression in these lesions.

MATERIALS AND METHODS

This was a prospective cohort study conducted in Department of Obstetrics and Gynecology of King George's Medical University, Lucknow from July 2013- August 2014.

At an expected prevalence of 33% of endometrial pathology the sample size was 85 at 10% precision and after adding contingency of 20% sample size was calculated as 102, which was taken approximately as 100.

Inclusion criteria was premenopausal and postmenopausal women >40 years of age with abnormal uterine bleeding. Women with abnormal uterine bleeding due to coagulaopathies, with iatrogenic bleeding per vaginum, patients diagnosed with malignancy other than endometrial carcinoma and patients not willing to participate were excluded from the study. Informed consent was taken from the patients. A detailed history including age, parity, menopausal status, risk factors such as diabetes, hypertension, infertility, HRT, unopposed estrogen exposure, tamoxifen therapy, smoking, socio economic status, dietary habits etc was taken. General and systemic examination was done. Ultrasonographic examination for uterus and adnexa was performed. Endometrial biopsies were taken either by endometrial aspiration, dilatation and curettage, hysteroscopy guided biopsy or hysterectomy specimens. Biopsy tissue was sent for histopathological examination. Samples testing positive for endometrial hyperplasia and carcinoma were further analyzed for PTEN immunohistochemistry.

28 specimens (27 cases of endometrial hyperplasia and 1 case of endometrial carcinoma) were evaluated for PTEN status.

RESULTS

Total of 100 patients were included in the study. On histopathology 28 cases of endometrial hyperplasia and 1 case of endometrial carcinoma was diagnosed. These cases were evaluated for PTEN immunohistochemical expression.

Loss of PTEN is significant rather than expression. PTEN was not expressed in 11 patients with endometrial hyperplasia while it was expressed in remaining 16 patients with endometrial hyperplasia and 1 patient with endometrial carcinoma. On analyzing the association of PTEN expression or non expression with different types of endometrial hyperplasia individually, the difference was not significant statistically, however, the loss of PTEN expression was maximum in cases with atypia. PTEN analysis was done in one case of endometrial adenocarcinoma where it was expressed. (Table 2)

On studying correlation of PTEN expression with different demographic and clinical profile, there was loss of PTEN expression in postmenopausal women and association was found to be statistically significant. PTEN expression or non expression showed no significant association with age, parity, BMI, diabetes, hypertension, various clinical complaints, uterine size and endometrial thickness. (Table 1)

Table 1 – Correlation of PTEN expression with endometrial hyperplasia (n=27)

	PTEN expressed (n=16)		PTEN not expressed (n=11)		P value
	n	%	n	%	
Simple hyperplasia without atypia	12	70.5	5	29.4	0.223
Simple hyperplasia with atypia	1	33.33	2	66.66	0.548
Complex hyperplasia without atypia	2	50	2	50	1.00
Complex hyperplasia with atypia	1	33.33	2	66.66	0.548

Table 2 – correlation of PTEN expression with different demographic and clinical variables in patients with endometrial hyperplasia and endometrial carcinoma

Demographic and clinical variables	PTEN expressed(n=17)	PTEN not expressed(n=11)	Statistical significance
Mean age(yrs)	44.88±5.64	46.18±7.21	P=0.598
Mean parity	1.53±0.71	1.64±0.50	P=0.671
Menopausal status			
premenopausal	17(100%)	7(63.6%)	P=0.007
postmenopausal	-	4(36.4%)	-
Mean age at menopause	-	48.0±5.7	-
Mean duration of menopause	-	5.0±4.1	-
Mean BMI	31.36±2.59	31.73±2.15	P=0.703
Diabetes	1 (5.9%)	1 (9.1%)	P=0.747
Hypertension	2(11.8%)	3 (27.3%)	P=0.295
Presenting complaints			
Menorrhagia	15 (88.2%)	6 (54.5%)	P=0.083
Menorrhagia and polymenorrhea	0(0%)	1 (9.1%)	
polymenorrhea	1 (5.9%)	0 (0%)	
PMB	1 (5.9%)	4 (36.4%)	
Mean uterine size	144.8±51.1	185.0±135.2	P=0.273
Mean ET	13.6±2.9	12.9±2.9	P=0.547

DISCUSSION

PTEN is a tumor suppressor gene that plays a significant role in inducing cell cycle arrest and programming apoptosis and in cell physiology, including the regulation of cell adhesion, migration and differentiation. It is one of the most frequently altered genes in endometrial carcinoma and in precursor lesion hyperplasia.

In present study PTEN evaluation was done in 28 cases (27endometrial hyperplasia and 1 endometrial carcinoma). Out of 27 cases of endometrial hyperplasia, loss of PTEN expression was found in 11 cases and was maximum in cases with atypia. However the difference was not significant stastically.1 patient diagnosed with endometrial carcinoma expressed PTEN. Erknali et al[5] suggested that loss of PTEN activity increases accordingly with architectural changes in the endometrium and cumulates most predominantly in atypical lesions. On the contrary, Kimura et al[6] found no significant difference in PTEN expression amongst subtypes of endometrial hyperplasia. Xiong etal[7] found complete loss of PTEN immunoreactivity in 20% of proliferative endometrium, 29% of benign hyperplasia, 38% of EIN, and 63% of endometrioid adenocarcinoma. Konkopa et al observed no statistically significant correlation between frequency of PTEN gene mutations and clinical stage of endometrial carcinomas. Athanassiadou et al[8] concluded in their study that PTEN positivity was correlated with decreased stage and negative lymph nodes and loss of PTEN may also be associated with a worse prognosis in patients with early stage disease. Salvesen et al[9] found a significant association between loss of PTEN expression and metastatic disease. Mutter et al [10]examined the altered PTEN expression in endometrioid endometrial carcinoma and found PTEN expression was completely absent in 61% of cases. Kapucuoglu et al[11] observed significantly higher PTEN expression in typical hyperplasia as compared to endometrioid endometrial carcinoma, while no significant difference was seen between atypical hyperplasia and endometrioid endometrial adenocarcinoma.

In the present study there was loss of PTEN expression in post menopausal women and association was also statistically significant. PTEN showed no significant association with age, parity, BMI, diabetes, hypertension, various clinical complaints, uterine size and endometrial thickness.

PTEN staining has its pitfalls. The selection of antibody is very important as studied by Pallaras et al [12]who tested four different anti PTEN commercial antibodies and found that monoclonal 6H2.1 as the only antibody that correlates statistically with phosphor- AKT and also the only one to show correlation with the presence of molecular alterations in PTEN (mutations, deletions or proper hypermethylation). In present study also this clone was used.

To summarize, loss of PTEN expression was more in complex hyperplasia with atypia as compared to simple hyperplasia without atypia. Loss of PTEN expression could be

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an important indicator of fore runner of malignancy. PTEN immunohistochemical biomarker has further pushed the detection limit of premalignant endometrial disease to a truly preclinical stage, disclosing a much higher prevalence of disease than previously suspected.

CONCLUSION

Thus, PTEN immunohistochemical expression can be used a newer diagnostic technique of premalignant and malignant endometrial diseases. Long term follow up on a larger sample size with careful selection of antibody supported with corresponding molecular alterations for detection of PTEN loss is required, before arriving at a valid, acceptable and reproducible solution.

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