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IMMUNOHISTOCHEMICAL EXPRESSION OF PTEN IN ENDOMETRIAL HYPERPLASIA AND ENDOMETRIAL CARCINOMA IN A TERTIARY CARE CENTRE OF NORTH INDIA

Pathology

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ABSTRACT

PTEN is a tumor suppressor gene frequently altered in endometrial carcinogenesis and is considered an early molecular event in the progression of endometrial hyperplasia to carcinoma. **Aim:** To evaluate the immunohistochemical expression of PTEN in endometrial hyperplasia and endometrial carcinoma and compare its expression with normal endometrium. Methods: This prospective observational study included 50 endometrial specimens comprising 10 normal endometria, 40 cases of endometrial hyperplasia, and endometrial carcinoma. PTEN immunohistochemistry was performed on formalin-fixed paraffin-embedded tissue sections. PTEN expression was categorized as positive, negative, or heterogeneous and correlated with histopathological and clinicopathological parameters. **Results:** PTEN immunohistochemical expression demonstrated a significant association with histopathological diagnosis (χ^2=44.271, p<0.001). PTEN expression was retained in normal endometrium and most non-atypical hyperplasia, whereas loss of expression was observed in atypical hyperplasia and endometrioid carcinoma. Heterogeneous staining was restricted to carcinoma cases. Histopathological diagnosis was significantly associated with age (p=0.022), menstrual history (p<0.001), and endometrial thickness (p<0.001). PTEN expression showed a significant association only with endometrial thickness (p<0.001). **Conclusion:** PTEN expression decreases progressively from normal endometrium and non-atypical hyperplasia to atypical hyperplasia and endometrioid carcinoma. PTEN immunohistochemistry may serve as a useful adjunct marker for identifying premalignant and malignant endometrial lesions and supports the role of PTEN loss as an early event in endometrial carcinogenesis.

KEYWORDS

PTEN, Endometrium, Hyperplasia, Carcinoma.

INTRODUCTION

Endometrial carcinoma (EC) is one of the most common gynaecological malignancies worldwide and represents the most frequently diagnosed cancer of the female reproductive tract in developed countries. Due to increased rates of obesity, diabetes mellitus, metabolic syndrome, and longer life expectancy, its incidence has been gradually rising. Even while India's illness burden is still smaller than that of Western countries, there has been a slow rise in occurrence in recent years, highlighting the need for better methods for risk assessment and early detection.[1]

The main cause of endometrial hyperplasia (EH), which is identified as a precursor lesion for endometrioid-type endometrial cancer, is chronic estrogenic stimulation that is not countered by progesterone. The World Health Organization (WHO) presently divides EH into two categories: hyperplasia without atypia and atypical hyperplasia/ endometrioid intraepithelial neoplasia (EIN). EH is histologically defined by an elevated gland-to-stroma ratio. At the time of diagnosis, the latter may coexist with invasive malignancy and has a significantly higher probability of developing into carcinoma.[2,3]

Hormonal, environmental, and molecular variables interact intricately in the pathophysiology of endometrial cancer. Mutations and loss of expression of the phosphatase and tensin homolog (PTEN) gene are among the first and most common genetic changes linked to Type I endometrial cancer. By inhibiting the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway, the tumor suppressor gene PTEN, which is found on chromosome 10q23, regulates cellular proliferation, survival, apoptosis, and genomic stability.[4]

When PTEN function is lost, the PI3K/AKT pathway is constitutive activated, which promotes cell proliferation, resistance to apoptosis, and the development of neoplastic transformation. PTEN's function as an early molecular event in endometrial carcinogenesis has been supported by studies showing its inactivation in normal endometrium, endometrial hyperplasia, and endometrial cancer. Additionally, PTEN expression has been shown to gradually decrease from normal endometrium to hyperplasia and carcinoma, indicating that it may be useful as a biomarker for detecting lesions that are more likely to undergo malignant transformation.[5,6]

In practice, immunohistochemistry (IHC) offers a useful and affordable way to measure PTEN protein expression. Assessing PTEN expression may help differentiate benign from premalignant lesions, enhance diagnostic reliability in situations with ambiguous morphology, and support prognostic evaluation. Furthermore, the therapeutic relevance of PTEN status in endometrial neoplasia has been further underlined by new targeted medicines that target the PI3K/AKT/mTOR pathway.[7]

The current study was conducted to assess the immunohistochemical expression of PTEN in endometrial hyperplasia and endometrial carcinoma and to compare these results with normal endometrial tissue, given the critical role of PTEN in endometrial carcinogenesis and the paucity of data from North Indian populations. In order to evaluate the possible diagnostic and prognostic importance of PTEN expression, the study also sought to link it with certain clinicodemographic factors and histological features.

METHODOLOGY

This prospective observational study was conducted in the Department of Pathology in collaboration with the Department of Obstetrics and Gynaecology, Government Medical College, Amritsar. A total of 50 endometrial specimens were included, comprising 40 histopathologically confirmed cases of endometrial hyperplasia and endometrial carcinoma and 10 cases of normal endometrium serving

as controls. Specimens were obtained through endometrial curettage, Pipelle endometrial aspiration biopsy, or hysterectomy.

Age, body mass index, menstrual history, menopausal state, and radiographic endometrial thickness were among the many clinical and demographic details that were documented. Sections stained with hematoxylin and eosin were examined, and cases were categorized using accepted histological standards. Using conventional procedures, formalin-fixed, paraffin-embedded tissue slices were subjected to PTEN immunohistochemical staining. Based on the staining pattern in glandular epithelial cells, PTEN expression was evaluated and classified as positive, negative, or heterogeneous; internal positive controls were stromal and endothelial cells.

Patients with endometrial hyperplasia or endometrial carcinoma who had undergone surgery, endometrial curettage, or Pipelle biopsy and provided written informed consent were included. Patients who had received prior chemotherapy, radiotherapy, or hormonal therapy before tissue sampling and those unwilling to participate were excluded.

ETHICAL APPROVAL

Ethical clearance was obtained from the Institutional Ethics Committee, and written informed consent was obtained from all participants before enrolment. Patient confidentiality was maintained throughout the study.

DATA ANALYSIS: Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 28. Categorical variables were expressed as frequencies and percentages. Associations between PTEN expression and clinicopathological parameters were evaluated using the Chi-square test or Fisher's exact test, as appropriate. A p-value of <0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

Table 1: Sociodemographic And Clinical Characteristics Of Study Participants

Sociodemographic Characteristics		Frequency (n=50)	Percentage (%)
Age group (years)	20-30	4	8
	31-40	6	12
	41-50	18	36
	51-60	10	20
	61-70	9	18
	>70	3	6
BMI categories	Normal	5	10
	Overweight	20	40
	Obesity class I	17	34
	Obesity class II	8	16
Personal history	Alcohol intake		
	No	50	100
	Yes	0	0
	Smoking		
	No	49	98
	Yes	1	2
Past history	Diabetes mellitus		
	No	43	86
	Yes	7	14
	Hypertension		
	No	43	86
	Yes	7	14
	Hypothyroidism		
	No	48	96
	Yes	2	4

Table 1 presents Sociodemographic and Clinical Characteristics of study participants. The study included 50 patients, with the majority belonging to the 41–50 years age group (36%), followed by 51–60 years (20%) and 61–70 years (18%). Most participants were either overweight (40%) or obese (50%), while only 10% had a normal body mass index. Alcohol consumption was not reported in any participant, and only one patient (2%) had a history of smoking. Comorbidities included diabetes mellitus and hypertension in 14% of patients each, whereas hypothyroidism was present in 4% of cases.

Table 2: Gynaecological Characteristics And Radiological Findings Of Participants

Gynaecological Characteristics And Radiological Findings		Frequency (n=50)	Percentage (%)
AGE OF MENARCHE	< 13 years	44	88
	> 13 years	6	12
MENOPAUSAL STATUS	< 45yrs	3	6
	45-55 yrs	21	42
	> 55yrs	0	0
	Pre-menopausal	26	52
MENSTRUAL HISTORY			
Premenopausal AUB	Regular cycles	8	16
	Irregular cycles	18	36
Post menopausal bleeding	24	48	
ENDOMTERIAL THICKNESS (ET) ON RADIOLOGY in mm			
Premenopausal females	> 12 mm	7	14
	5-12 mm	19	38
Postmenopausal females	> 4 mm	24	48

According to table 2, most participants attained menarche before the age of 13 years (88%). More than half of the study population was premenopausal (52%), while 42% of women had attained menopause between 45 and 55 years. Postmenopausal bleeding was the most common clinical presentation (48%), followed by irregular menstrual cycles among premenopausal women (36%). On radiological evaluation, ET greater than 4 mm in postmenopausal women was observed in 48% of cases, whereas 38% had an ET of 5–12 mm and 14% had a thickness exceeding 12 mm.

Table 3 Association Of Pten Expression With Histopathological Diagnosis

PTEN IHC EXPRESSION	HISTOPATHOLOGY REPORT					Total	Chi square value	p value
	Proliferative endometrium	Secretory endometrium	EH without atypia	EIN	Endometrioid EC			
Heterogenous staining	0	0	0	0	5	5	44.27 1a	<0.001
Negative	0	0	3	4	11	18		
Positive	7	3	17	0	0	27		
Total	7	3	20	4	16	50		

In our study, Positive PTEN expression was predominantly observed in benign conditions, including endometrial hyperplasia without atypia (17 cases) and controls i.e. normal endometrium (proliferative and secretory patterns). Loss of PTEN expression (negative staining) was more frequently associated with premalignant and malignant lesions which included all cases of atypical endometrial hyperplasia (4 cases) and in majority of cases of endometrioid endometrial carcinoma (11 of 16 cases). Heterogeneous staining of PTEN was seen exclusively in endometrial carcinoma (5 cases). On comparing the PTEN expression status in all the cases and controls in our study, the results came out to be statistically highly significant ($\chi^2 = 44.271$, $p < 0.001$), indicating a strong correlation between PTEN expression and progression from benign to malignant endometrial lesions. (Table 3)

Table 4: Association Of Histopathological Diagnosis With Clinicopathological Parameters

		HISTOPATHOLOGY REPORT					Total	Chi square	p value
		Proliferative endometrium	Secretory endometrium	Endometrial hyperplasia without atypia	Atypical Endometrial Hyperplasia	Endometrioid Endometrial carcinoma			
Age	20-30	1	0	2	1	0	4	34.661a	0.022
	31-40	1	2	2	1	0	6		
	41-50	5	1	5	0	7	18		
	51-60	0	0	4	2	4	10		
	61-70	0	0	7	0	2	9		
	>70	0	0	0	0	3	3		
Body mass index (BMI)	Normal	1	0	2	1	1	5	15.101a	0.232
	Overweight	4	3	9	0	4	20		
	Obesity Class I	2	0	6	3	6	17		
	Obesity Class II	0	0	3	0	5	8		
Menarche	< 13 Years	6	3	16	4	15	44	2.702a	0.609
	> 13 Years	1	0	4	0	1	6		
		Menstrual history							
Pre-menopausal AUB	Regular cycles	6	1	0	0	1	8	35.999a	< 0.001
	Irregular Cycles	1	2	9	2	4	18		
Postmenopausal bleeding		0	0	11	2	11	24		
Menopausal status	< 45 years	0	0	1	0	2	3	13.206a	0.102
	45-55 Years	0	0	10	2	9	21		
	> 55 Years	0	0	0	0	0	0		
	Premenopausal	7	3	9	2	5	26		
		ET thickness							
Pre-menopausal	5-12 mm	7	2	8	2	0	19	27.32	<0.01
	> 12 mm	0	1	1	0	5	7		
Post-menopausal	> 4 mm	0	0	11	2	11	24		
Total		7	3	20	4	16	50		

Histopathological diagnosis showed significant associations with age (p=0.022), menstrual history (p<0.001), and endometrial thickness (p<0.001). No significant association was observed with body mass index, age at menarche, or menopausal status. (Table 4)

Table 5: Association Of Pten Ihc Expression With Clinicodemographic Parameters

CLINICODEMOGRAPHIC PARAMETERS		PTEN EXPRESSION			Total	Chi square	p value
		Positive	Heterogenous staining	Negative			
Age groups	20-30	3	0	1	4	13.059a	0.22
	31-40	4	0	2	6		
	41-50	11	2	5	18		
	51-60	4	3	3	10		
	61-70	5	0	4	9		
	>70	0	0	3	3		
BMI category	Normal	2	0	3	5	12.527a	0.051
	Overweight	16	0	4	20		
	Obesity Class I	7	3	7	17		
	Obesity Class II	2	2	4	8		
Age at menarche	<13	12	4	10	26	2.279a	0.32
	≥13	15	1	8	24		
Menopausal status	< 45 years	1	1	1	3	6.892a	0.142
	45-55 Years	8	2	11	21		
	Premenopausal	18	2	6	26		
Menstrual history							
Pre-menopausal AUB	Regular cycles	7	0	1	8	6.885a	0.142
	Irregular Cycles	11	2	5	18		
Postmenopausal bleeding		9	3	12	24		
ET thickness							
Premenopausal	5-12 mm	16	0	3	19	13.28	<0.001
	>12 mm	2	2	3	7		
Postmenopausal	> 4 mm	9	3	12	24		
Total		27	5	18	50		

PTEN expression was significantly associated only with endometrial thickness on radiology (p<0.001). No statistically significant association was observed between PTEN expression and age, body mass index, age at menarche, menopausal status, or menstrual history. (Table 5)

FIGURE 1

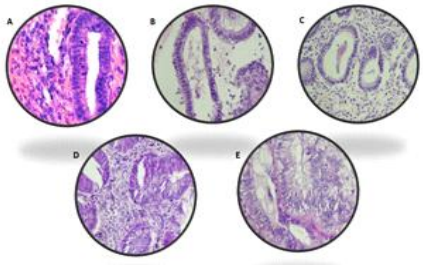

Figure 1: H&E images (A) Proliferative Endometrium (B) Secretory Endometrium, (C) Endometrial hyperplasia without atypia; (D) Atypical Endometrial Hyperplasia; (E) Endometrioid endometrial carcinoma.

FIGURE 2

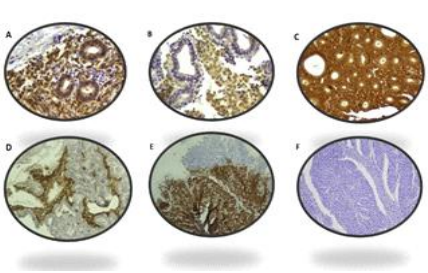

Figure 2: PTEN immunohistochemical (IHC) Expression in (A) Proliferative Endometrium- Positive expression; (B) Secretory Endometrium- Positive expression; (C) Endometrial hyperplasia without atypia- Positive expression; (D) Atypical Endometrial Hyperplasia- Negative expression; (E) Endometrioid Endometrial Carcinoma- Heterogenous staining; (F) Endometrioid Endometrial Carcinoma- Complete loss of expression.

DISCUSSION

The present study evaluated the clinicopathological spectrum of endometrial lesions and the immunohistochemical expression of PTEN in endometrial hyperplasia and endometrial carcinoma. The findings were compared with previously published studies to assess the role of PTEN in endometrial carcinogenesis.

The majority of patients in the present study belonged to the 41–50 years age group, followed by the 51–60 years age group. A statistically significant association was observed between age and histopathological diagnosis, with malignant lesions being more frequent in older women. These findings are consistent with studies by Prat and Braun et al., who reported increasing incidence of endometrial carcinoma with advancing age.[8,9]

A high prevalence of overweight and obesity was observed in the study population, with 90% of patients having a body mass index above the normal range. Obesity is a well-established risk factor for endometrial pathology because of increased peripheral conversion of androgens to oestrogens, resulting in prolonged endometrial stimulation.[10] However, despite the high prevalence of obesity, no significant association was observed between BMI and histopathological diagnosis or PTEN expression. Similar findings have been reported by Yang et al.[11]

With regard to gynaecological characteristics, most patients attained menarche before 13 years of age, and more than half were premenopausal. Although early menarche is associated with prolonged estrogen exposure, no significant association was observed between age at menarche and either histopathological diagnosis or PTEN expression. Similar observations have been reported by Yang et al. and Chhabra.[10-12]

Postmenopausal bleeding was the most common presenting complaint, followed by irregular menstrual cycles in premenopausal women. Menstrual history demonstrated a significant association with histopathological diagnosis, highlighting the importance of abnormal uterine bleeding as an indicator of underlying endometrial pathology. These findings are in agreement with previous studies by Braun et al. and Montgomery et al.[9,13]

Endometrial thickness showed a significant association with histopathological diagnosis. Premalignant and malignant lesions were more frequently observed in women with increased endometrial thickness. Similar observations have been reported by Goldstein and Taylor et al., who emphasized the importance of endometrial thickness as a predictor of significant endometrial pathology.[14,15]

Histopathological evaluation revealed that endometrial hyperplasia without atypia was the most common lesion, followed by endometrioid endometrial carcinoma and atypical endometrial hyperplasia. This distribution supports the well-recognized hyperplasia–carcinoma sequence described by Kurman and Mutter, in which prolonged estrogenic stimulation leads to progressive transformation from hyperplasia to carcinoma.[16,17]

The most important finding of the present study was the significant association between PTEN expression and histopathological diagnosis. PTEN positivity was preserved in all cases of proliferative and secretory endometrium and in the majority of cases of endometrial hyperplasia without atypia. In contrast, complete loss of PTEN expression was observed in all cases of atypical endometrial hyperplasia and in most cases of endometrioid endometrial carcinoma. Furthermore, heterogeneous staining was observed exclusively in carcinoma cases, suggesting intratumoral heterogeneity.

These findings are comparable to those reported by Mutter et al., Sarmadi et al., and Tantbirojn et al., who demonstrated progressive loss of PTEN expression from normal endometrium to hyperplasia and carcinoma and proposed PTEN inactivation as an early molecular event in endometrial tumorigenesis.[18,19] The complete loss of PTEN

expression in atypical hyperplasia observed in the present study further supports its role as a precursor lesion with increased malignant potential.

When PTEN expression was correlated with clinicopathological variables, no significant association was observed with age, BMI, age at menarche, menopausal status, or menstrual history. Endometrial thickness was the only parameter significantly associated with PTEN expression. These findings suggest that PTEN loss is primarily related to disease progression rather than demographic or hormonal factors and support its role as a molecular marker of endometrial carcinogenesis.[11,18]

Overall, the present study demonstrates a progressive reduction in PTEN expression across the spectrum of endometrial lesions, from normal endometrium to atypical hyperplasia and carcinoma. The findings support the utility of PTEN immunohistochemistry as an adjunct diagnostic marker for identifying premalignant and malignant endometrial lesions and reinforce the role of PTEN loss as an early event in endometrial carcinogenesis.

CONCLUSION

The present study demonstrates a progressive reduction in PTEN expression across the spectrum of endometrial lesions, from normal endometrium and endometrial hyperplasia without atypia to atypical endometrial hyperplasia and endometrioid endometrial carcinoma. Preserved PTEN expression was predominantly observed in benign endometrial lesions, whereas loss of expression was characteristic of premalignant and malignant lesions. A highly significant association was observed between PTEN immunohistochemical expression and histopathological diagnosis, supporting the role of PTEN loss as an early molecular event in endometrial carcinogenesis.

Among the clinicopathological parameters evaluated, endometrial thickness showed a significant association with both histopathological diagnosis and PTEN expression, while age, body mass index, age at menarche, menopausal status, and menstrual history did not demonstrate significant associations with PTEN expression. Clinically, abnormal uterine bleeding, particularly postmenopausal bleeding, remained an important indicator of underlying endometrial pathology.

The findings of the present study highlight the utility of PTEN immunohistochemistry as an adjunct diagnostic marker in the evaluation of endometrial lesions. Assessment of PTEN expression may aid in identifying premalignant lesions with increased malignant potential and improve the diagnostic accuracy of morphologically equivocal cases. Larger multicentric studies incorporating molecular analysis are recommended to further validate the diagnostic and prognostic significance of PTEN in endometrial tumorigenesis.

Conflict of Interest: NIL
Fundings: NIL

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