

Original Research Article

Study of expression of PTEN and Cyclin D1 in endometrium at a tertiary care centre

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ABSTRACT

Background: To study the expression of PTEN (Phosphatase and Tensin homologue) and Cyclin D1 in normal, hyperplastic and neoplastic endometrium by immunohistochemistry and to corroborate the interrelationship between PTEN and Cyclin D1 in normal to neoplastic endometrial disorders including endometrial carcinoma.

Methods: Formalin fixed paraffin embedded (FFPE) sections of spectrum of endometrium in fifty different cases were taken from secretory phase to endometrial carcinoma and subjected to Immunohistochemistry using PTEN and Cyclin D1 .

Results: Immunoreactivity was regarded as positive when brown staining was localized in the nuclei or cytoplasm. The intensity of nuclear staining was graded from 0 to 3+ and the extent was semi quantitatively estimated. If less than 10% of cells were positive a score of 0 was given, 11 % to 30% cell positivity was scored as 1+, 31% to 60 % positivity was scored as 2+ and more than 60% positive cells was labelled as 3+. Statistical analysis was performed with Chi-Square test and significant differences were noted between these 3 groups (p value < 0.05).

Conclusions: The present study supports that an inverse correlation exists in the expression of PTEN and Cyclin D1 in normal, hyperplastic and neoplastic endometrium. The decreased PTEN expression is a marker of the earliest endometrial premalignant lesions, and we propose that use of PTEN immunostaining may be informative in identifying premalignant lesions that are likely to progress to carcinoma. Cyclin D1 expression in endometrial glands increases progressively in intensity and extent from normal endometrium to hyperplasia to carcinoma.

Keywords: Cyclin D1, Endometrial carcinoma, Hyperplastic, Neoplastic, Normal, PTEN

INTRODUCTION

Endometrial carcinoma is one of the most common malignancies of female genital tract.¹ It accounts for 7 % of all invasive cancers in women.² Development of endometrial carcinoma involves stepwise acquisition of several genetic alterations in tumour suppressor genes and oncogenes. Studies have shown that unopposed estrogen intake exceeding two years has a two to three fold greater risk of endometrial cancer.³ Cyclin D1 also known as BCL1 belonging to a family of three closely

related D-type cyclins, Cyclin D1 , D2 and D3, is a proto-oncogene located on chromosome 11q13.^{4,5} Cyclins are key components in the regulation of the cell cycle in combination with their respective cyclin-dependent kinases (CDKs) CDK4 and CDK6, which phosphorylate retinoblastoma (RB) protein that leads to the release of associated proteins like E2F. These proteins have the capability to activate genes necessary for cell progression into the S-phase through G1-phase.⁶ Studies done in past have stated that there is increased cellular proliferation co-existing with progressive derailment of Cyclin D1 ,

leading to the progression of hyperplasia to endometrioid endometrial carcinoma and also increase in expression of Cyclin D1 from normal endometrium to hyperplasia to carcinoma. There are studies conducted that have found correlation of Cyclin D1 expression in endometrial carcinoma with histological grade, stage and other clinicopathological parameters.⁷⁻⁹ The PTEN tumor suppressor gene is located on chromosome 10 (10q23) that acts through an AKT-dependent pathway to suppress cell division and enable apoptosis.^{10,11} It negatively regulates the Phospho Inositol 3 Kinase-AKT (Protein Kinase B)/PI3K-AKT signalling pathway, which is implicated in the pathogenesis of endometrial carcinoma.¹² Endometrial expression of normal PTEN in menstrual cycle changes in response to the hormonal environment with expression always present in estrogenic proliferative phase.

In secretory phase its expression is variable with a post ovulatory secretory phase showing an increased PTEN expression relative to the estrogenic proliferative phase. In mid secretory phase there is loss of PTEN expression in the epithelial cells and in increased expression by the stromal cells. In late secretory phase there is loss of PTEN expression. Endometrium stimulated for abnormally long intervals with estrogen begin to display clonal outgrowth of PTEN-depleted epithelium, which eventually assumes the configuration diagnostic of a precancerous state.¹³ PTEN mutations occur at the earliest detectable stage of endometrial carcinogenesis and are found in approximately 20% of precancerous hyperplastic lesions and 50% of endometrial carcinomas.

The current study was designed to study the pattern of PTEN/Cyclin D1 expression in normal, hyperplastic, and neoplastic endometrium and corroborate their interrelationship and thereby evaluate the possibility of a role in the genesis of endometrial neoplastic and preneoplastic lesions.^{2,3}

METHODS

The study was a cross sectional study carried out in the Department of Pathology, Adesh Institute of Medical Sciences and Research, Bathinda over a period of one year from February 2015 to March 2016. 50 cases were taken with 10 cases of proliferative phase of endometrium, 10 cases of secretory phase, twelve cases of simple hyperplasia without atypia, seven cases of complex hyperplasia without atypia and four cases of complex hyperplasia with atypia and seven cases of endometrial carcinoma.

Immunohistochemical procedure was employed on formalin fixed paraffin embedded (FFPE) tissue sections to study the expression of PTEN and Cyclin D1. A mouse anti-PTEN monoclonal antibody (Biogenex, USA) and mouse monoclonal anti-Cyclin D1 antibody (Dako, Japan) were used.

Scoring system

Immunoreactivity was regarded as positive when brown staining was localized in the nuclei or cytoplasm. The intensity of nuclear staining was graded as no staining (0), weak nuclear staining (1+), moderate nuclear staining (2+) and marked nuclear staining (3+). The extent was semi quantitatively estimated by counting at least 50 nuclei and then establishing the ratio of immunoreactive nuclei to total number of nuclei multiplied by 100. When less than 10% of cells were positive a score of 0 was used, 11 % to 30% cell positivity was scored as 1+, 31% to 60 % positivity was scored as 2+, and more than 60% positive cells was labelled as 3+.¹⁴

Statistical analysis

Calculation of association using chi square test and a level of $p < 0.05$ was considered as statistically significant.

RESULTS

In our study, the age of the patients ranged from 27-73 years with a median age being 45.62 ± 11.07 years. A total of 50 cases were considered with 10 cases each (20%) were there in proliferative and secretory phase (Figure 1A and B). 12 cases (24%) were found in the group Simple Hyperplasia without atypia (Figure 1C). None of the cases belonged to group simple hyperplasia with atypia. 7 cases (14%) were reported in the group complex hyperplasia without atypia (Figure 1D) and 4 cases (8%) were there in the complex hyperplasia with atypia group (Figure 1E). 7 cases (14%) belonged to endometrial carcinoma group (Figure 1F).

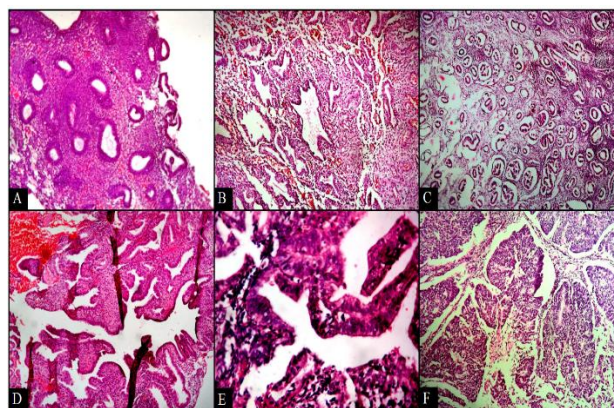


Figure 1: Hematoxylin and eosin (H and E) pictures of endometrium. (A) The normal proliferative endometrium. (B) Endometrial glands and stroma in secretory phase. (C) Simple hyperplasia without atypia. (D) Low power view showing complex hyperplasia without atypia. (E) Complex hyperplasia with atypia. (F) Endometrial carcinoma.

The immunostaining for PTEN was assessed. In 10 cases of Proliferative Phase, two cases (20%) showed 3+

intensity, seven cases (70%) cases showed 2+ intensity and one case (10%) showed 1+ intensity (Figure 2A). In the 10 cases of secretory phase, one case (10%) showed 3+ intensity, eight cases (80%) cases showed 2+ intensity and one case (10%) showed 1+ intensity (Figure 2B). Overall 100% of cases of proliferative and secretory endometrium were positive for PTEN. In the 12 cases of Simple Hyperplasia without Atypia, one case (8.33%) showed 3+ intensity, six cases (50%) cases showed 2+ intensity, three cases (25%) showed 1+ intensity and 2 cases (16.67%) were negative for PTEN (Figure 2C). In a total seven cases of complex hyperplasia without Atypia, one case (14.29%) showed 2+ intensity, five cases (71.42%) cases showed 1+ intensity, one case (14.29%) was negative for PTEN (Figure 2D). In a total four cases of complex hyperplasia with atypia all cases were negative for PTEN. In a total seven cases of carcinoma endometrium, two cases (28.57%) showed 1+ intensity and the remaining five cases (71.43%) were negative for PTEN (Figure 2E). The findings are summarized in Table 1.

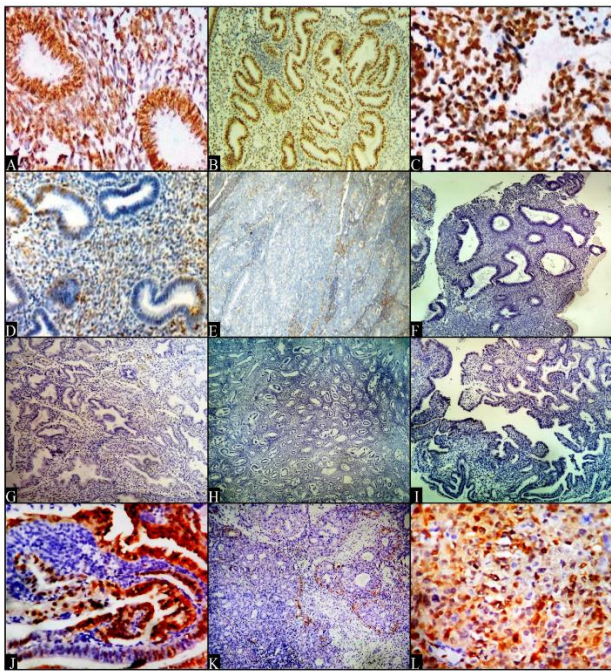


Figure 2: (A to E). PTEN immunostaining in endometrium. (A) Normal proliferative endometrium. (B) Normal Secretory phase. (C) Simple hyperplasia. (D) Complex hyperplasia. (E) Endometrial carcinoma. (F to L) Cyclin D1 immunostaining in endometrium. (F) Normal proliferative endometrium negative for Cyclin D1. (G) Normal secretory phase with negative Cyclin D1 expression. (H) Simple hyperplasia without atypia with negative Cyclin D1 expression. (I) Complex hyperplasia without atypia with negative expression of Cyclin D1. (J) Complex hyperplasia with atypia showing Cyclin D1 expression (3+). (K) Endometrioid carcinoma in glandular pattern positivity for Cyclin D1 (2+). (L) Carcinoma endometrium with Cyclin D1 expression (3+).

Table 1: Distribution of total cases with PTEN (n=50).

Diagnosis	No. of cases (n)	(%)	PTEN positive cases	(%)
Proliferative phase	10	20%	10	100%
Secretory phase	10	20%	10	100%
Simple hyperplasia without atypia	12	24%	10	83.33%
Complex hyperplasia without atypia	07	14%	06	85.71%
Complex hyperplasia with atypia	04	08%	00	00%
Endometrium carcinoma	07	14%	02	28.57%

Table 2: Distribution of total cases with Cyclin D1 (n=50).

Diagnosis	No. of cases (n)	(%)	Cyclin D1 positive	(%)
Proliferative phase	10	20%	03	30%
Secretory phase	10	20%	04	40%
Simple hyperplasia without atypia	12	24%	08	66.64%
Complex hyperplasia without atypia	07	14%	03	42.85%
Complex hyperplasia with atypia	04	08%	04	100%
Endometrium carcinoma	07	14%	06	85.71%

In a total of 10 cases of proliferative phase, three cases (30%) showed 1+ expression of Cyclin D1 expression whereas seven cases (70%) showed no staining for Cyclin D1 (Figure 2F). In a total of 10 cases of secretory phase two cases (20%) showed a 2+ expression of Cyclin D1 expression whereas two cases (20%) showed 1+ expression. Six cases (60%) showed no staining for Cyclin D1 (Figure 2G). In the 12 cases of simple hyperplasia, six cases (50%) showed a 1+ expression of Cyclin D1 expression whereas six cases (50%) were negative for Cyclin D1 (Figure 2H). In the 7 cases of complex hyperplasia without atypia, three cases (42.86%) showed a 1+ expression of Cyclin D1 expression whereas four cases (57.14%) were negative for Cyclin D1 (Figure 2I). In a total of 4 cases of complex hyperplasia with atypia one case (25%) showed a 3+ expression of Cyclin D1 expression whereas three cases (75%) showed 2+ expression of Cyclin D1 with an average expression of 63.63 in complex hyperplasia (Figure 2J). In the 7 cases

of endometrial carcinoma one case (14.28%) showed a 3+ expression of Cyclin D1 whereas four cases (57.14%) showed 2+ expression with one case (14.28%) showing a 1+ immunostaining (Figure K and L). One case was negative for Cyclin D1. The findings are summarized in Table 2.

DISCUSSION

Endometrial cancer is the most common malignancy of the female genital tract. Development of endometrial carcinoma involves stepwise acquisition of several genetic alterations in tumour suppressor genes and oncogenes. Due to the ability of estrogen and its metabolites to cause DNA damaging events, they are associated with greater risk of developing endometrial cancers.⁸ Excessive cellular proliferation is induced by loss of PTEN function and Cyclin D1 overexpression which is a feature of many types of cancers, including endometrial cancers.^{15,16} PTEN, a negative regulator of phospho inositol 3 kinase/AKT growth regulatory pathway with its loss leading to over activation of PI3K/AKT pathway. Hyperplasia comprises a heterogenous group of lesions, considered by some to be reversible and others, to be truly neoplastic, so attempts have been made to sub classify them in a biologically and clinically useful way in order to predict their precancerous behavior.¹⁷ The aim of our study was to study the expression of PTEN and Cyclin D1 in normal, hyperplastic and neoplastic endometrium and to corroborate the interrelationship between them in normal endometrium to neoplastic endometrial disorders. The

mean age of our study is in closest resemblance to the study done by Aziz et al.¹⁸

PTEN

PTEN immunoreactivity was noted in all cases of proliferative and secretory phase. These findings agreed with Erkanli S et al and Rao et al.^{19,20} PTEN expression in simple hyperplasia without atypia is 83.33% which is slightly lower to study by Sarmadi S et al but in a study by Rao A et al PTEN expression in simple hyperplasia without atypia showed 87% positivity which correlated well with our current study.²¹ In the current study PTEN expression in complex hyperplasia without atypia is 85.71%. In a study by Anuradha et al on the study group of hyperplasias found that simple hyperplasia without atypia had the maximum number of PTEN positive glands with the number of glands reducing as the number of complex hyperplastic glands increased, the least number of PTEN positive glands was seen in complex hyperplasia with atypia. Study conducted by Lee H et al showed the percentage of PTEN loss was significantly higher in endometrial carcinoma compared with simple hyperplasia and it was also higher in complex atypical hyperplasia.²² In a study by El Sheikh SA et al PTEN immunoreactivity was noted in all normal proliferative endometrium and all simple hyperplasia cases whereas complex atypical hyperplasia 66.7% showed positive immunoreactivity. The difference was highly statistically significant.²³ In a study by Tantbirojn P et al, 70 % cases of simple hyperplasia and 47 % cases of complex hyperplasia were positive.²⁴ (Table 3).

Table 3: Comparison of PTEN expression in simple and complex hyperplasia and endometrial carcinoma.

Study	PTEN expression in simple hyperplasia	PTEN expression in complex hyperplasia	PTEN expression in endometrial carcinoma
Tantbirojin P et al ²⁴	70%	47%	40%
Sarmadi et al ²¹	100%	75% of atypical complex hyperplasia	48 %
Rao et al ²⁰	100 %	100% of ACH	-
Lee H et al ²²	76%	29% of ACH	32%
Sheikh et al ²³	100%	66.67% of ACH	-
Our study	83.33%	85.71% of ACH	28.57%

In endometrial carcinoma, loss of PTEN expression is seen in 71.43% of cases. Orbo et al, reported loss of PTEN protein expression in 55% of specimens in patients with subsequent endometrioid endometrial carcinoma.²⁵ In a study by Kanamori et al out of 98 advanced cases, 64 (65.3%) showed negative or mixed PTEN staining; their survival rate was significantly lower than that of PTEN positive cases.¹⁰

In a study by Terakawa et al, out of 98 advanced cases, 64 (65%) showed negative or heterogeneous PTEN

staining; their survival rate was significantly lower than that of PTEN-positive cases (Table 4).²⁶

CYCLIN D1

Overexpression of Cyclin D1 may be associated with actual gene amplification or transcriptional dysregulation in cancers. We have used immunohistochemistry to demonstrate that Cyclin D1 is overexpressed in hyperplastic lesions, which are considered to be the precursors of endometrioid adenocarcinoma. We conducted a study to demonstrate Cyclin D1 expression

in endometrium. 30% of proliferative endometrium, 40% of secretory endometrium, six out of twelve cases (50%) of simple hyperplasia, 71.43% of cases of complex hyperplasia and six out of seven cases of carcinoma endometrium were positive for Cyclin D1. In a study by Quddus RM et al, Cyclin D1 expression in proliferative endometrium is 36% and in secretory phase it is 34% is positive, this correlated well with our study.¹⁵ In a study by Ozuysal S et al, only 3.3% cases of proliferative endometrium are positive.²⁸ This study shows very low positivity when compared with our results. Nishimura Y et al, reported no expression in the secretory phase and focal staining in proliferative phase.⁶ In a current study Cyclin D1 expression is negative in 70% of proliferative endometrium and 60% in secretory phase with difference being statistically insignificant.

In previous studies, the positivity of Cyclin D1 in endometrial hyperplasia ranges from no positivity as reported by Tsuda et al to 83% as reported by Cao et al.^{29,30} Ozuysal et al, also found no Cyclin D1 immunoreactivity in simple hyperplasia.²⁸ Quddus et al, reported Cyclin D1 positivity as 57% in simple, 71% in complex hyperplasia and 68% in endometrial carcinoma.¹⁵ Nishimura et al found 25% positivity in endometrial hyperplasias and 46.1% in endometrioid carcinomas.⁶

As seen in Table 5, expression of Cyclin D1 in simple hyperplasia in our study (50%) has the closest resemblance to the study done by Quddus et al, (57%). Expression of Cyclin D1 in simple hyperplasia in our study (50%), complex hyperplasia without atypia is 42.85% and complex hyperplasia with atypia is 100% and the average expression of Cyclin D1 in complex hyperplasia (71.43%) and endometrial carcinoma (85.7%) has the closest resemblance with Quddus et al, and Liang et al.^{15,31}

Table 4: Comparison of loss of PTEN expression in endometrial carcinoma with other studies.

Study	Loss of PTEN expression in carcinoma
Kanamori et al ¹⁰	65.3%
Orbo et al ²⁵	55%
Bueno et al ²⁷	50%
N Terakawa et al ²⁶	64%
Erknali S et al ¹⁹	80%
Soheila Sarmadi et al ²¹	52%
Our study	71.43 %

Table 5: Comparison of Cyclin D1 expression in simple hyperplasia, complex hyperplasia and endometrial carcinoma.

Study	Cyclin D1 expression in simple hyperplasia	Cyclin D1 expression in complex hyperplasia	Cyclin D1 expression in carcinoma endometrium
Tsuda et al ²⁹	0%	0%	10%
Quddus et al ¹⁵	57%	71%	68%
Ozuysal et al ²⁸	0%	1%	26.6%
Chaudhary et al ¹⁶	0%	33%	50%
Liang et al ³¹	30%	49%	67%
Our study	50%	63.63%	85.7%

In our study, the positivity for complex hyperplasia was less than the positivity for carcinoma endometrium. Based on current study overexpression of Cyclin D1 increases from normal endometrium to hyperplasia and carcinoma, suggesting that it may play a role in endometrial carcinogenesis.

Ashton KA et al, reported Cyclin D1 expression has increased risk of developing endometrial cancer. Our findings support the significance of complex hyperplasia as a precursor lesion and to some extent simple hyperplasia is also precancerous. The mechanism of dysregulation of Cyclin D1 in endometrial neoplasia is not clearly defined, but it is likely that dysregulation plays an important role in increasing the proportion of cells in transition from G1 to S phase

CONCLUSION

The present prospective study was conducted with an aim to corroborate the interrelationship between PTEN and Cyclin D1. The present study supports the view that an inverse correlation exists in the expression of PTEN and Cyclin D1 in normal, hyperplastic and neoplastic endometrium and suggests that PTEN under expression and Cyclin D1 overexpression is an early event in endometrial carcinogenesis. Altered PTEN function is responsible for the etiology of the majority of endometrial cancers with a premalignant phase and participates in their progression to carcinoma with a decreased PTEN expression being a marker of the earliest endometrial premalignant lesions. We therefore propose that use of PTEN immunostaining in a clinical setting

may be informative in identifying premalignant lesions that are likely to progress to carcinoma.

Cyclin D1 expression in endometrial glands increases progressively in intensity and extent from normal endometrium to hyperplasia to carcinoma. It appears that the dysregulation is maximal at the complex hyperplasia state and that other alterations may be responsible for the different morphologic features and behaviour of complex hyperplasia and carcinoma. This pattern of expression suggests that Cyclin D1 overexpression may be an early event in endometrial carcinogenesis. Our findings support the significance of complex hyperplasia as a premalignant lesion. PTEN under reexpression and Cyclin D1 overexpression are early events in endometrial carcinogenesis.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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