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Research Article

EXPRESSION OF CYCLIN D1 IN NORMAL, HYPERPLASTIC AND NEOPLASTIC ENDOMETRIUM

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ABSTRACT

Background: Overexpression of Cyclin D1, a positive cell cycle regulator, may lead to uncontrolled cell proliferation. ***Aim:*** The present study was undertaken to examine the expression profile of Cyclin D1 in normal, hyperplastic and neoplastic endometrium and to evaluate the possibility of its role in the genesis of endometrial neoplastic and preneoplastic lesions. ***Settings and Design:*** A cross sectional study conducted during a 1 year period in a tertiary referral centre. ***Materials and Methods:*** We evaluated and compared the expression profile of Cyclin D1 in 50 endometrial samplings that were diagnosed as simple hyperplasia without atypia (n=12), complex hyperplasia without atypia (n=7), complex hyperplasia with atypia (n=4), endometrial carcinoma (n=7) and proliferative (n=10) and secretory (n=10) endometrium. ***Results:*** An increasing gradient of Cyclin D1 expression was noted in endometrial glands from normal endometrium to hyperplasia to carcinoma ***Conclusion:*** Cyclin D1 overexpression is an early event in endometrial carcinogenesis.

INTRODUCTION

Endometrial carcinoma is one of the most common malignancies of female genital tract.[1] accounting for 7 % of all invasive cancers in women. Studies have shown that unopposed estrogen intake exceeding two years has a two to three fold greater risk of endometrial cancer. Clinicopathologic studies and molecular analysis support the classification of endometrial carcinoma into two broad categories referred to as Type 1 and Type 2 endometrial carcinoma. Type 1 carcinoma / Endometrioid carcinoma is the most common type accounting for approximately 80 % of cases. It typically arises in the setting of endometrial hyperplasia and is seen in 55-65 years age group. Type II /Serous Carcinoma occurs in women who are about a decade older than those with Type I carcinoma and does not arise in the background of estrogen overexposure.

Cyclin D1 (also known as BCL1) is a proto-oncogene located on chromosome 11q13. D-cyclins selectively control cell-cycle progression by activating their cdk partners, 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.[2]

Cyclin D1 is often over expressed in human neoplasia e.g. in situ and infiltrating ductal breast carcinoma, colorectal carcinoma, bladder carcinoma, head and neck, lung and prostate cancers.[3] Nikaido *et al*[4] reported that about 40 % of endometrial carcinomas overexpress Cyclin D1 and proposed that Cyclin D1 dysregulation may have role in endometrial carcinogenesis.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of Pathology at Adesh Institute of Medical Sciences and Research, Bathinda for a period of one year, from 1st April 2015 to 31st March 2016 after getting approval from Research Committee, AIMSR, Bathinda and Ethical Committee, Adesh University, Bathinda.

A total of 50 endometrial samples in the form of either endometrial curetting or hysterectomy specimens that were diagnosed as simple hyperplasia without atypia (n=12), complex hyperplasia without atypia (n=7), complex hyperplasia with atypia (n=4), endometrial carcinoma (n=7) and proliferative (n=10) and secretory (n=10) endometrium were taken up for the study.

Study procedure: Immunohistochemical staining was performed using monoclonal rabbit anti –human Cyclin D1 antibody by streptavidin-peroxidase-biotin method on specimens of formalin- fixed, paraffin embedded tissue sections to evaluate the extent of Cyclin D1 expression. Immunoreactivity was regarded as positive when brown staining was localized in the nuclei or cytoplasm. The extent was estimated as percentage by counting at least 50 nuclei and

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then taking the ratio of immunoreactive nuclei to total number of nuclei multiplied by 100 and rounded off to the nearest 10%. <10% staining was considered as negative for Cyclin D1.11-30% cell positivity was scored 1 +;31-60% positivity was scored 2 + and >60 % positive cells was labelled 3 +.[5]

RESULTS

Demographics: In our study, 50 patients were selected in the age group of 26 to 75 years. The 12 patients diagnosed with simple hyperplasia without atypia had an age range of 33 to 64 years with mean age of 43.50±8.74 years and a maximum numbers of 5 cases (45.83%) were in the age group of 41-45 years. The 7 patients diagnosed with complex hyperplasia without atypia had an age range of 38-65 years with mean age of 47.14±10.35years and a maximum number of 3 cases (30%) were in the age group of 36-40 years. The 4 patients diagnosed with complex hyperplasia with atypia had an age range of 31-73 years with mean age of 50.50±19.07years. The 7 patients diagnosed with endometrial carcinoma had an age range of 38-65 years with mean age of 51.86±10.32years and a maximum number of 2 cases (28.57%) were in the age group of 61-65 years.

Cyclin D1 expression profile (Table 1.): 3 out of the 10 cases (30%) of proliferative endometrium showed Cyclin D1 positivity ranging in extent from 11-30% and the remaining 7 cases (70%) were negative. 4 out of the ten cases (40%) of secretory endometrium were positive amongst which, 2 cases showed an extent of 11-30% (20%) and remaining 2 cases showed an extent of 31-60% (20%).

Rest of the 6 cases (60%) were negative. 6 out of the 12 cases (50%) of simple hyperplasia without atypia showed positivity with an extent of 11-30% and remaining 6 cases (50%) were negative. 3 out of the 7 cases (42.86%) of complex hyperplasia without atypia showed Cyclin D1 positivity with an extent of 11-30% and remaining 4 cases (57.14%) were negative. All 4 cases (100%) of complex hyperplasia with atypia were positive for Cyclin D1 with 11-30% and 31-60% as extent of positivity in 2 cases each. Thus, overall, 63.63% of all the cases of complex hyperplasia showed positivity for Cyclin D1. 6 out of the 7 cases (85.71%) of endometrial carcinoma were found to be positive for Cyclin D1amongst which 4 cases (57.13%) showed an extent of 31-60%, 1 case (14.28%) showed an extent of 11-30% and another case (14.28%) showed an extent of >60%.

Comparison of extent of Cyclin D1: Table 2 shows the comparison of expression profile of Cyclin D1 in paired groups. A statistically significant difference was observed between the results of proliferative phase vs. complex hyperplasia without atypia (p=0.017), proliferative phase vs. complex hyperplasia with atypia (p= 0.014), proliferative phase vs. endometrial carcinoma (p = 0.021), secretory phase vs. complex hyperplasia without atypia (p =0.020), secretory phase vs. complex hyperplasia with atypia (p =0.039), secretory phase vs. endometrial carcinoma (p =0.036), simple hyperplasia without atypia vs. complex hyperplasia without atypia (p = 0.039), simple hyperplasia without atypia vs.

Table 1 Distribution of total cases with Cyclin D1 (n=50)

Diagnosis	No. of Cases (n)	Percentage (%)	Cyclin D1 Positive	Percentage (%)
Proliferative Phase	10	20%	03	30%
Secretory Phase	10	20%	04	40%
Simple Hyperplasia without atypia	12	24%	06	50%
Complex Hyperplasia without atypia	07	14%	03	42.86%
Complex Hyperplasia with atypia	04	08%	04	100%
Complex Hyperplasia (with without atypia)	11	22%	07	63.63%
Endometrial Carcinoma	07	14%	06	85.71%
Total	50	100	26	52%

Table 2 Comparison of extent of Cyclin D1

Parameter a vs Parameter b	Positives (Parameter a)	Positives (Parameter b)	X^2 value	P value	Significance
Proliferative phase vs. Secretory phase	03/10	04/10	1.79	0.182	Non Significant
Proliferative phase vs. Simple Hyperplasia without Atypia	03/10	06/12	1.24	0.260	Non Significant
Proliferative phase vs. Complex Hyperplasia without Atypia	03/10	03/07	6.11	0.017	Significant
Proliferative phase vs. Complex Hyperplasia with Atypia	03/10	04/04	6.92	0.014	Significant
Proliferative phase vs. Endometrial carcinoma	03/10	06/07	5.88	0.021	Significant
Secretory phase vs. Simple Hyperplasia without Atypia	04/10	06/12	5.41	0.033	Non Significant
Secretory phase vs. Complex Hyperplasia without Atypia	04/10	03/07	6.43	0.020	Significant
Secretory phase vs. Complex Hyperplasia with Atypia	04/10	04/04	4.59	0.039	Significant
Secretory phase vs. Endometrial carcinoma	04/10	06/07	4.53	0.036	Significant
Simple Hyperplasia without Atypia vs. Complex Hyperplasia without Atypia	06/12	03/07	4.27	0.039	Significant
Simple Hyperplasia without Atypia vs. Complex Hyperplasia with Atypia	06/12	04/04	5.24	0.035	Significant
Simple Hyperplasia without Atypia vs. Endometrial carcinoma	06/12	06/07	5.20	0.036	Significant
Complex Hyperplasia without Atypia vs. Complex Hyperplasia with Atypia	03/07	04/04	4.16	0.040	Significant
Complex Hyperplasia without Atypia vs. Endometrial carcinoma	03/07	06/07	6.29	0.013	Significant
Complex Hyperplasia with Atypia vs. Endometrial carcinoma	04/04	06/07	5.47	0.039	Significant

complex hyperplasia with atypia (p = 0.035), and simple hyperplasia without atypia vs. endometrial carcinoma (p = 0.036), complex hyperplasia without atypia vs. complex hyperplasia with atypia (p =0.040), complex hyperplasia without atypia vs. endometrial carcinoma (p =0.013) and complex hyperplasia with atypia vs. endometrial carcinoma (p =0.039) using Chi square test. There was no statistical difference in extent between proliferative phase vs. secretory phase (0.182), proliferative phase vs. simple hyperplasia without atypia (0.260), and secretory phase vs. simple hyperplasia without atypia (0.133).

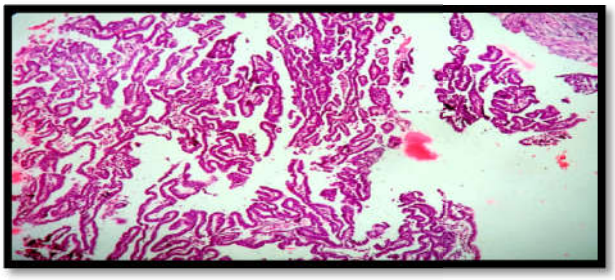

Figure 1 Low power view showing endometrioid carcinoma (H & E; X100)

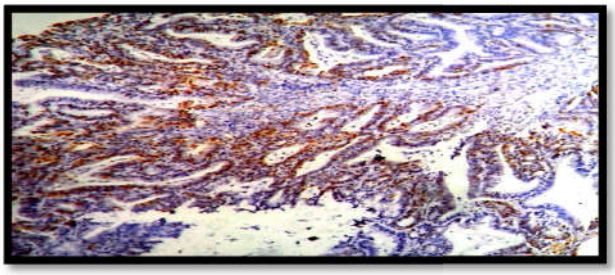

Figure 2 Low power view showing endometrioid carcinoma Positive for Cyclin D1. Extent- 2+ (50%). (X100)

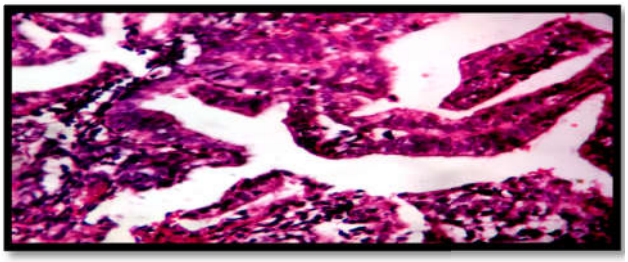

Figure 3 High power view showing complex hyperplasia of endometrium with atypia(H& E; X400)

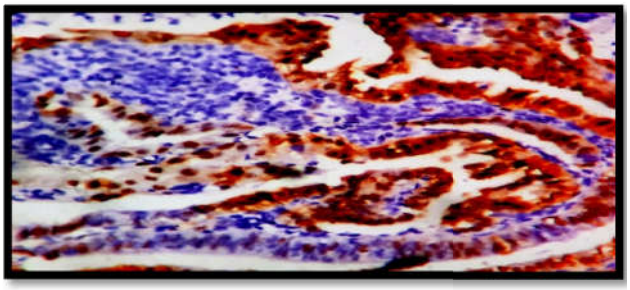

Figure 4 High power view showing complex hyperplasia of endometrium with atypia. Positive for Cyclin D1 expression., Extent- 3+ (70-80%). (X400)

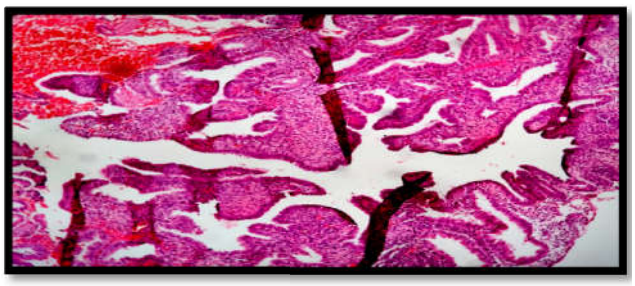

Figure 5 Low power view showing complex hyperplasia of endometrium without atypia (H& E; X100)

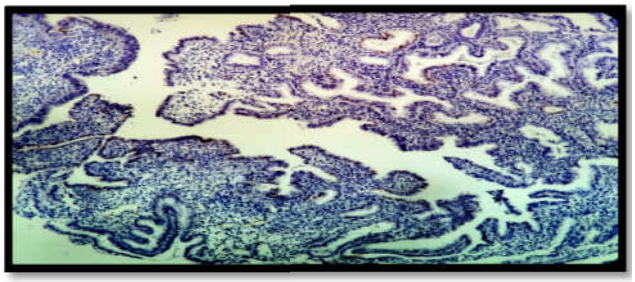

Figure 6 Low power view showing complex hyperplasia of endometrium without atypia. Negative for Cyclin D1 expression. Extent- 0 (5-10%). (X100)

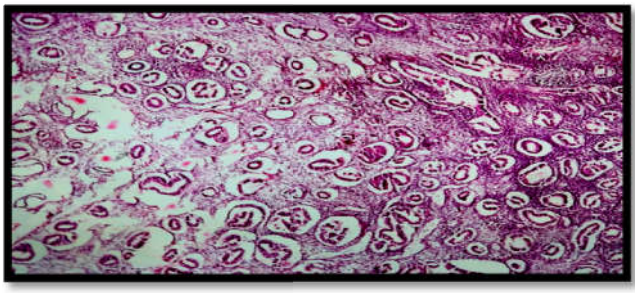

Figure 7 Low power view showing simple hyperplasia of endometrium without atypia (H & E; X100)

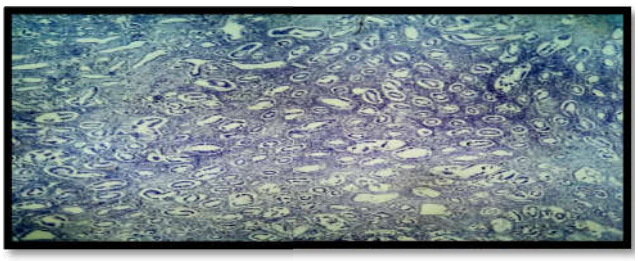

Figure 8 Low power view showing simple hyperplasia of endometrium without atypia. Negative for Cyclin D1 expression. Extent- 0(<5%). (X100)

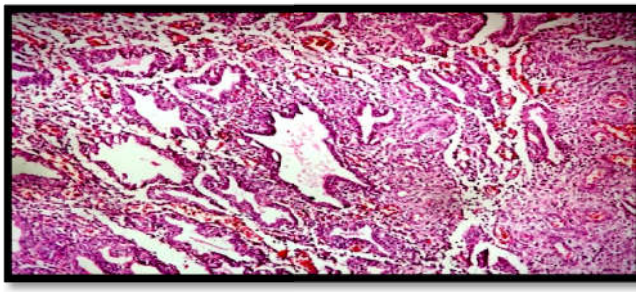

Figure 9 Low power view showing endometrial glands and stroma in secretory phase (H & E; X100)

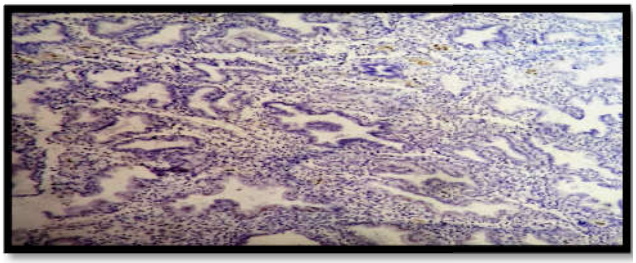

Figure 10 Low power view showing normal secretory phase of endometrium. Negative for Cyclin D1 expression (X100)

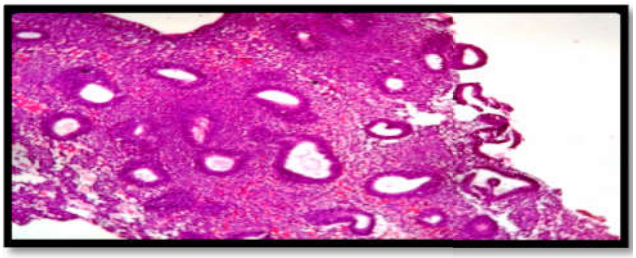

Figure 11 Low power view showing normal proliferative endometrium (H & E; X 100)

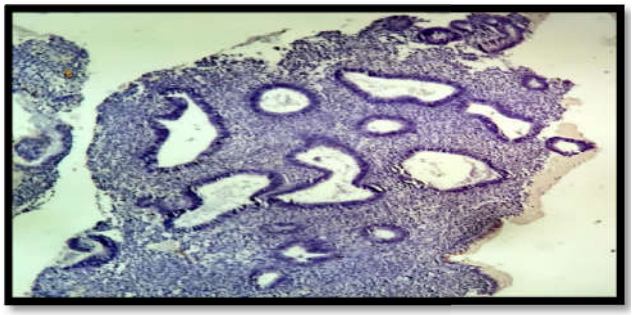

Figure 12 Low power view showing normal proliferative endometrium. Negative for Cyclin D1 expression (X100)

DISCUSSION

Over expression 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.

In the current study, cyclin D1 expression is negative in 70% of proliferative endometrium and positive in 30% of proliferative endometrium. In secretory phase cyclin D1 is positive in 40% of cases and negative in 60% of cases. Difference between the expression of cyclin D1 in proliferative and secretory phase is statistically insignificant.

In previous studies, the positivity of Cyclin D1 ranges from 0 % to 36 % in normal endometrium.In a study by M Ruhul Quddus *et al*[6], cyclin D1 expression in proliferative endometrium is 36% positive and remaining 64% is negative. In secretory phase, 34% is positive and 66% is negative. This study correlates well with our study. In a study by Sema Ozuysal *et al*[7] (2005) only 3.3% cases of proliferative endometrium are positive. This study shows very low positivity when compared with our results. Nishimura *et al*[2] (2004) reported no expression in the secretory phase and focal staining in proliferative phase.

In our study, expression of Cyclin D1 in simple hyperplasia (50%), in complex hyperplasia without atypia (42.86%), in complex hyperplasia with atypia (100%), overall in complex hyperplasia (63.63%) and in endometrial carcinoma (85.7 %) has the closest resemblance with the results in the study done by Quddus *et al*.[6] Quddus *et al* reported Cyclin D1 positivity as 57% in simple, 71% in complex hyperplasia and 68% in endometrial carcinoma. In our case, the positivity for complex hyperplasia was less than the positivity for carcinoma endometrium.

In previous studies, the positivity of Cyclin D1 in endometrial hyperplasia ranges from no positivity as reported by Tsuda *et al*[8] to 83% reported by Cao *et al*.[9] Nikaido *et al*[4] studied the role of Cyclin D1 in the development of endometrial carcinoma. He found that Cyclin D1 expression was limited to only few cells of hyperplastic endometrium, whereas 40% of endometrioid carcinoma showed Cyclin D1 expression. Nishimura *et al*[2] found 25% positivity in endometrial hyperplasias and 46.1% in endometrioid carcinomas.

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. 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

Cyclin D1 expression in endometrial glands increases progressively in extent from normal endometrium to hyperplasia to carcinoma. It appears that the dysregulation is maximal at the complex hyperplasia state and that cyclin D1 overexpression may be an early event in endometrial carcinogenesis. Our findings support the significance of complex hyperplasia as a premalignant lesion. Intensity and extent of Cyclin D1 expression on immunohistochemistry should be used as an adjuvant to histopathological diagnosis for the cases of complex hyperplasia with high malignant potential for the benefit of patients.

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