INTRODUCTION

Endometrial carcinoma is one of the most common malignancies of female genital tract,
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.

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. Nikaido et al 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
deformal curetting or hysterectomy specimens that were
diagnosed as simple hyperplasia without atypia (n=12),
complex hyperplasia without atypia (n=7), 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.
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 47.14±10.35 years and a maximum number of 2 cases (28.65%) 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 51.86±10.32 years 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±19.07 years. The 7 patients diagnosed with endometrial carcinoma had an age range of 38 to 65 years with mean age of 63.63% of all the cases of complex hyperplasia showed positivity for Cyclin D1.

Comparison of extent of 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 D1 amongst 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. 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%).

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 (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) | X² value | P value | Significance |
|---------------------------|-------------------------|-------------------------|----------|---------|--------------|
| Proliferative phase vs. Secretory phase | 03/10 | 06/12 | 1.79 | 0.182 | Non Significant |
| Proliferative phase vs. Simple Hyperplasia without Atypia | 03/10 | 06/07 | 6.11 | 0.017 | Significant |
| Proliferative phase vs. Complex Hyperplasia with Atypia | 03/10 | 06/07 | 5.88 | 0.021 | Significant |
| Secretory phase vs. Endometrial carcinoma | 04/10 | 06/12 | 5.41 | 0.033 | Non Significant |
| Simple Hyperplasia without Atypia vs. Complex Hyperplasia without Atypia | 04/10 | 06/07 | 4.59 | 0.036 | Significant |
| Simple Hyperplasia without Atypia vs. Complex Hyperplasia with Atypia | 04/10 | 06/07 | 5.41 | 0.033 | Non Significant |
| Simple Hyperplasia without Atypia vs. Endometrial carcinoma | 06/12 | 03/04 | 4.27 | 0.039 | Significant |
| Complex Hyperplasia without Atypia vs. Simple Hyperplasia without Atypia | 06/12 | 06/07 | 5.24 | 0.035 | 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 (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)
DISCUSSION

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. 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 to 83% reported by Cao et al. Nikaido et al 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 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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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)
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How to cite this article:
Vijay Suri., Shaffy and Karishma Sharma.2017, Expression of Cyclin D1 in Normal, Hyperplastic And Neoplastic Endometrium, *Int J Recent Sci Res. 8*(5), pp. 17003-17007. DOI: http://dx.doi.org/10.24327/ijrscr.2017.0805.0263

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