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Role of Ki 67 in Normal Endometrium, Endometrial Hyperplasia and Endometrial Carcinoma: A Comparative Study

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KEYWORDS

Ki-67

Endometrium

Endometrial hyperplasia

Atypical endometrial hyperplasia

Endometrial carcinoma

ABSTRACT:

Introduction: Endometrial carcinoma is the 4th most common malignancy inwomen and its incidence is increasing both in developed and developing countries. The updated WHO classification classifies endometrialhyperplasiait as hyperplasia without atypia and atypical endometrial hyperplasia. Atypical hyperplasia has a high risk of progression to endometrial carcinoma. Ki 67 is a well-known marker of cell proliferation and its expression is upregulated in many cancers. Development of endometrial hyperplastic lesions and its transformation to endometrial carcinoma may be strongly influenced by cell proliferation markers.

Objectives: The aim of this study was to assess and compare staining of Ki 67 in the normal, hyperplastic and carcinoma endometrium which could help in understanding its role in progression to carcinoma endometrium.

Methods: The study was conducted from January 2017 to June 2018. 50 cases were included, out of which 15 cases were of normal endometrium, 10 cases were of endometrial hyperplasia without atypia, 10 cases were of atypical hyperplasia and 15 cases wereof endometrial adenocarcinoma. Immunohistochemical staining with Ki-67 was performed and the results were analyzed based on percentage positivity of the cells.

Results: Among 50 cases, 84% (n=42) showed positive Ki-67 staining. Ki 67 expression increased as the lesions progressed from normal endometrium, endometrial hyperplasia to endometrial carcinoma, which was found to be statistically significant. (p=0.000122).

Conclusions: Our findings, suggest the significance of endometrial hyperplasia as a precancerous lesion. Ki 67 may have a prognostic role in patients diagnosed as endometrial hyperplasia, and carcinoma.

1. Introduction

Endometrial hyperplasia is characterized by an increase in gland: stroma ratio along with proliferation of glands of varying shapes and sizes. [1] The exuberant proliferation of the glands in endometrial hyperplasia is associated with unopposed estrogen influence. [2]

The World Helath Organization (WHO) classifies endometrial hyperplasia as hyperplasia without atypia and atypical endometrial hyperplasia. [3]Atypical endometrial hyperplasia is composed of crowded, cytologically altered glands with little intervening stroma. [4]

The relative risk of progression of hyperplasia without atypia to endometrial carcinoma varies from 1.01- 1.03, whereas that of atypical hyperplasia to carcinoma varies from 14-45. [5]

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Endometrial carcinoma is the fourth most common cancer occurring in women after breast, bowel and lung cancers [6] and represents a spectrum of tumours which are diverse both morphologically and biologically. [7, 8]Type I endometrial carcinoma is believed to be significantly associated with unopposed estrogen therapy as well as, obesity. They usually rise in the setting of endometrial hyperplasias.[9, 10, 11]A recognized indicator of cell mitotic activity is Ki 67 and an increase in Ki 67 expression is indicative of increased cell mitotic activity and proliferation. In the menstrual cycle, its expression is usually elevated during the proliferative phase. [12]

Loss of normal cell control mechanisms that regulate cell proliferation is one of the mechanisms that characterize endometrial carcinogenesis. [13]The development of endometrial hyperplastic lesions, as well as its progression to endometrial carcinomas, is strongly influenced by cell proliferation markers.

2. Objectives

Our study was intended to compare the expression of Ki-67 in the three groups of endometrial samples, to help understand its role in evolution of endometrial hyperplasia and subsequent progression to endometrial carcinoma.

3. Methods

The cross sectional prospective study was conducted in our tertiary care hospital from January 2017- June 2018. Hysterectomy specimens, endometrial biopsy and curettage specimens received in the Department of pathology were analayzed.Cases diagnosed as normal endometrium, endometrial hyperplasias and endometrial adenocarcinomas were included. Non epithelial tumours of endometrium and cases with insufficient material were excluded.

Our total study size encompassed of 50 cases - 15normal endometrium, 10 hyperplasia without atypia, 10 hyperplasia with atypia and 15 endometrial carcinomas. Histopathological evaluation was done. The reperesentative paraffin block was taken for immunohistochemical analysis from each case. Immunohistochemical staining with Ki 67 (Clone Mib-1, DAKO) was performed. Positive control tissue sections of tonsil was used

Evaluation of immunostaining for Ki-67

Ki 67 positive cells exhibited brown nuclear staining. [12, 14]The percentage positivity of glandular cells were assessed semi quantitatively throughout the entire tissue section at40 x magnification assigned to one of the following categories. [12,14,15] (Table 1)

Table 1: Proportion scoring of Ki- 67

Scoring	Proportion of positive cells
0	< 5%
1+	5-25%
2+	25-50%
3+	50-100%

Tumours with negative immunodetection as well as those showing less than 5% positivity were considered negative. [14]

Statistical analysis was done using SPSS 23 software. Pearsons chi-square test and Fishers exact test was used to determine association between various factors.p value was < 0.05 was considered as statistically significant.

All procedures performed in the current study were approved by the institutional ethics committee. Informed consent was obtained from all individual participants included in the study.

4. Results

The ages of the pateints in the study ranged from 42- 70 years. The cases of both hyperplasia with and without atypia were seen maximally in the 4th and 5th decades (80%). All cases of endometrial carcinomas were in the between the ages of 50- 70 years. The most common clinical presentation was abnormal uterine bleeding (80%), with the second most common being pain abdomen (20%).

The 15cases of normal endometrium comprised of 10cases of proliferative endometrium and 5 cases of secretory endometrium .Among the cases of hyperplasia, hyperplasia without atypia constituted 10/20 cases with 10 casesof atypical endometrial hyperplasia .The International Federation of Gynaecology and Obstetrics (FIGO) grading system was used to grade the cases of endometrial

Journal of Chemical Health Risks

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JCHR (2023) 13(6), 839-846 | ISSN:2251-6727

carcinoma.08 cases were FIGO grade 1 , with 04 cases being FIGO grade 2 and 03 cases being FIGO grade 3, respectively.

Ki 67 Expression Status (Figure 1)

A three tier scoring system was applied (Table 1) Ki 67 positive cells showed crisp, brown nuclear staining. In the present study 84% of the cases showed positivity with Ki 67, whereas 16%, were immunonegative.Ki 67 showed a progressive increase in expression from normal endometrial samples to endometrial carcinoma.There was no significant relationship between Ki-67 expression and age (p=0.72), as well as other clinicopathological variables.

Ki 67 in normal endometrium

40% cases of normal endometrium (06/15 cases), showed negative staining (<5% of cells) with Ki 67. Among the remaining 09 cases, 06 cases were assigned score 1, and only 03 cases were assigned score 2. On comparison between proliferative and secretory endometrium, all cases of secretory endometrium wereimmunonegative for Ki 67 and proliferative endometrium showed higher scores of staining. (Figure 2, Figure 3)

Cases of normal endometrium displayed the maximum number of cases with negative staining for Ki 67, across all three categories of endometrial lesions.

Ki 67 in Hyperplastic Endometrium

Out of the 10 cases of endometrial hyperplasia without atypia , 02/10 (20%) cases were score 0 (negative), 04/10 cases (40%) cases were score 1, 03/10 cases (30%) cases were score 2(Figure 4)and 01/10 cases (10%) cases were score 3. All 10 cases of atypical endometrial hyperplasia (100%) showed postitive staining with Ki-67 out of which, 06 cases (60%)showed Score 3 staining (Figure 5), with 04(40%) cases showing Score 2 staining.

The results of Ki 67 staining varied significantly on comparison between normal endometrium and hyperplastic endometrium (p=0.0059). There was however no significant association between Ki 67 expression in hyperplasia without atypia and atypical hyperplasia (p=0.0573).

Ki 67 in Endometrial Carcinoma.

Ki 67 was positive in 100 % of the endometrial carcinoma cases, out of which 11 of 15 cases(73.33%) showed Score 3 staining(Figure 6).Of the remaining 04 cases; 01 case displayed Score 1 staining (6.66%) and 03 cases (20%) displayed Score 2 staining.

Of the 08 FIGO grade 1cases, 02 cases displayed score 2 staining, 01 case displayed Score 1 staining with the remaining displaying Score 3 staining . Of the 04 cases of FIGO grade 2 cases , 02 displayed score 2 staining. All remaining cases, including all cases of FIGO grade 3 (03/15) displayed Score 3 staining.

We did not observe any significant association with regards to the grade of carcinoma and Ki-67 staining (0.5692). However the percentage ofcases displaying Score 3 staining was increased in Grade 3 carcinoma (100%) on comparing with Grade 1 carcinoma (62.5%).

There was no significant difference on comparing cases of atypical endometrial hyperplasia and endometrial carcinoma. (p=0.666).

A significant statistical difference with p value of 0.000122 was obtained on comparing the Ki 67 staining in all three groups of normal, hyperplastic and carcinoma endometrium.

FIGURES

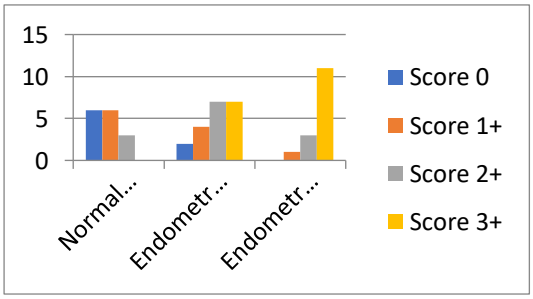

Fig. 1: Ki 67 Expression status in types of endometrium

Journal of Chemical Health Risks

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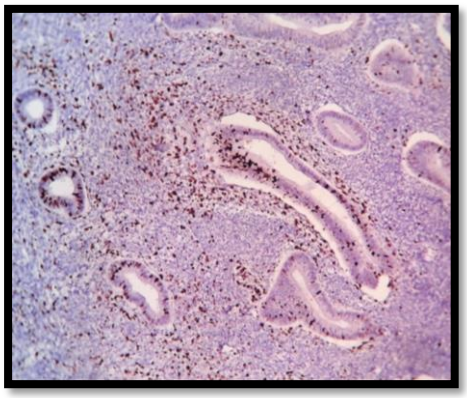

Fig. 2: Immunohistochemical staining using Ki 67 antibody showing Score 1 staining (5-25% positivity) in normal proliferative endometrium, (Ki 67, 10x).

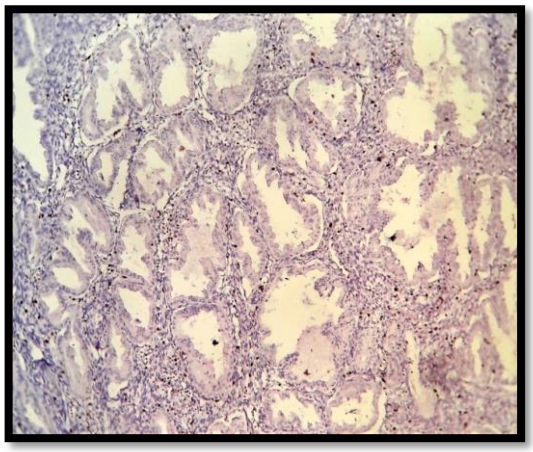

Fig. 3: Immunohistochemical staining using Ki 67 antibody showing negative staining (<5-% positivity) in normal secretory endometrium, (Ki 67, 10x).

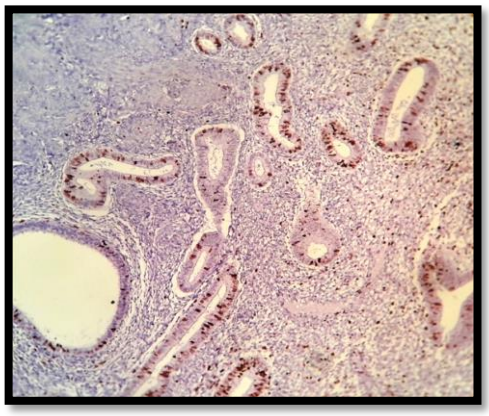

Fig. 4: Photomicrograph of Ki 67 staining in endometrial hyperplasia without atypia showing score 2 staining(25-50% positivity); (Ki 67; 10x)

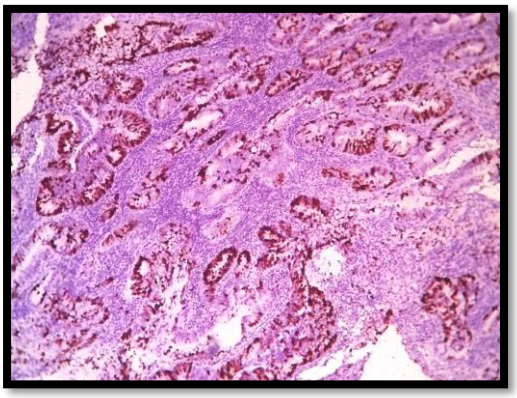

Fig. 5: Ki 67 showing score 3 staining (50-100% positive cells- dark brown) of endometrial glands in hyperplasia with atypia (Ki 67, 10x)

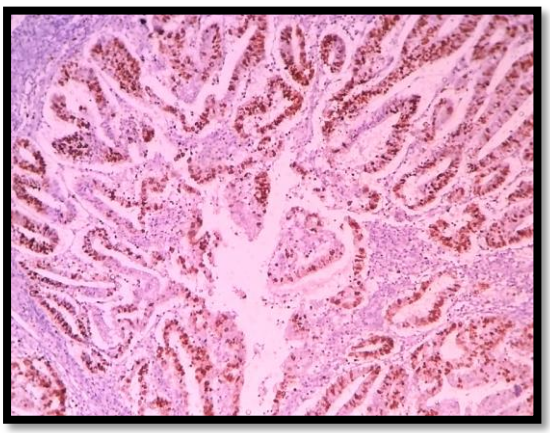

Fig. 6: Ki 67 showing score 3 staining (50-100% positive cells- dark brown) in endometrioid endometrial carcinoma (Ki 67, 10x)

5. Discussion

Endometrial hyperplasia is a fertile soil for the formation of carcinoma, and is deemed as a precancerous lesion. [2,15] Up to 60% of cases of atypical endometrial hyperplasia cases have high risk of developing invasive cancer or have coexisting invasive cancer. [16] However, hyperplasia without atypiahas a lower risk of transformation to carcinoma.[4] Cellular pathways and various genes have an important role in Type 1 carcinomas. [17] Mutations in PTEN, Beta catenin, Kras, and DNA mismatch repair defects are known to play a role in the genesis of Type 1 endometrial carcinoma. . [17]

Journal of Chemical Health Risks

www.jchr.org

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Ki 67 is a known marker of cell proliferation and is expressed in the nucleus of proliferating cells. It is strongly associated with tumour growth and is a reliable proliferation index, due to its short half-life. [18,19] The marker has an established role in various carcinomas such as breast, cervix and lung etc. and studies in the endometrium have shown a high index in endometrial carcinomas. [18-22]

The present studycomprised of 50 cases. Majority of the cases of endometrial hyperplasia (80%) were present in the 4th and 5th decades of age, which correlated with the findings reported by Raychaudhuri et al and ShaliniRao et al. [23,24] All cases of endometrial carcinoma (100%) fell in the 5th and 6th decades of age, comparable to the study by Lacey et al. [25] Similar to the study of Mutter et al, the most frequent clinical indication (80%) for curettage/hysterectomy in this study was abnormal uterine bleeding. [26]

Ki 67 staining was evaluated based on the percentage of positive cells. In cases of normal endometrium, Ki 67 showed maximum negative staining. It was also observed that on comparison between proliferative and secretory endometrium, all cases of secretory endometrium were immunonegative. These findings correlated with those of a previous study byTaylor LJ et al [12]and pointed towards, the decreased amount of cell proliferation in secretory endometrium**.**

Among cases of endometrial hyperplasia, increased number of cases showed score 3 staining compared to normal endometrium. Also, the percentage of negatively stained cases in endometrial hyperplasia progressively decreased from those of normal endometrium. Of particular interest, was that a significant majority of atypical endometrial hyperplasia cases displayed score 3 proportion of Ki 67 staining. We found a marked increase in Ki 67 scoring in the cases of endometrial carcinoma, with 100% of the cases being positively stained and majority of the cases displaying maximum Ki 67 staining. This correlated with the findings by Ioffe OB et al.[2]

With regards to the expression of cell proliferation marker Ki 67, our study has shown an increase in the percentage positivity of cells, through the continuum of normal endometrium, endometrial hyperplasia with and without atypia, and endometrial carcinoma, which was statistically significant. In response to estrogen, proliferative endometrium shows higher mitotic activity and hence a higher Ki 67 scoring. [5] The decreased levels of estrogen, may be responsible for the reduced staining of Ki 67 in the secretory phase of cyclical endometrium. Endometrial hyperplasia is associated with hyper-estrogenic states and increased cell proliferation, thereby gaining the potential to evolve into endometrioid carcinoma. [5]

Amit Pal, PriyankaMondal , SudiptaChakraborti and JayatiChakraborty found an increase in the Ki-67 levels from hyperplasia without atypia, atypical hyperplasia to endometrial carcinoma with median values of 20%, 35% and 50%, respectively. Greater than 50% cases of endometrial carcinomas showed more than 30% nuclear staining for Ki-67. A statistically significant difference was also seen with regards to Ki 67 staining in the categories of endometrial carcinoma and atypical hyperplasia (P = 0.04664), endometrial carcinoma and hyperplasia without atypia (P = 0.00003) and atypical hyperplasia and hyperplasia without atypia (P = 0.00001). (27)

Arjunan A et al reported an increase in the mean scores of Ki 67 from normal endometrium, to hyperplasia with atypia ranging from mean score- 3 in proliferative endometrium to 2.54 in hyperplasia without atypia and maximum score of 9.33 in hyperplasia with atypia. Similar to the findings in our study, they also found negative Ki 67 immunostaining in the secretory phase of normal endometrium. [5]

Salvesen HB, Iversen OE and Akslen LA assessed nuclear Ki 67 staining for the purpose of recognition of high-risk patients by assessment of. The Ki-67 expression was significantly associated with FIGO stage (P = 0.0004), histological type (P = 0.03), and histological grade (P = 0.0001). Ki-67 expression was found to be a significant prognostic indicator for endometrial carcinoma patients. [28] Similarly we also found an increased (Score 3) staining in 100% FIGO grade 3 cases in this study.

Ferradina G, Ranelletti FO, Gallotta V et al investigated, by immunohistochemistry, the relationship between Ki 67 and endometrial cancer . In this study, tumours with elevated Ki 67 expression were more frequently observed in endometrial tumours exhibiting more aggressive clinicopathological features such as advanced stage of disease, poor grade of differentiation,

Journal of Chemical Health Risks

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positive lymph node status and deeper myometrial invasion suggesting a negative prognostic role of this marker in endometrial cancer. [29]

Suthipintawong C et al, analyzed the prognostic significance of Ki 67 in endometrial carcinoma. They reported that cases with a Ki 67 staining < 35% showed better survival outcome and the marker is an independent prognostic indicator for both survival time and recurrence of tumour. [30]

CONCLUSION

The findings of our study indicate that uncontrolled cellular proliferation plays a major factor in neoplastic transformation. Ki 67 may have a significant role as a prognostic marker in cases of endometrial hyperplasia and endometrial carcinoma.It also gives weight to the role of endometrial hyperplasia as a potential precancerous lesion.

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