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Original Research Article

Immunohistochemical study of ER, PR, p53 and Ki67 expression in patients with endometrial adenocarcinoma and atypical endometrial hyperplasia

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ABSTRACT

Objective: To study Immunohistochemistry pattern of ER, PR, p53 and Ki67 expression in patients with endometrial adenocarcinoma (EC) and endometrial hyperplasia.

Materials and Methods: A retrospective study of 78 cases were studied for a period of 02 year from June 2018 to May 2020, where in the clinical data included age, presenting complaints, menopausal status, history of hormonal treatment, ultrasound examination.

Histopathological parameters were analysed as per WHO 2014 classification of endometrial hyperplasia into typical and atypical endometrial hyperplasia / Endometrial Intraepithelial Neoplasia (EIN) and endometrial carcinoma. ER, PR, p53 and Ki 67 IHC markers were done on cases diagnosed as endometrial adenocarcinoma and endometrial hyperplasia.

Results: Among 78 cases, there were 20 cases of EC and 58 cases of endometrial hyperplasia. EC was most commonly seen in sixth to seventh decade and hyperplasia was seen in fourth to fifth decade .There were 11 surgical specimens and 09 biopsies of EC. Out of total 20 cases, there were 17 cases of endometrioid adenocarcinoma and 03 cases were of papillary serous adenocarcinoma.

ER, PR expression was seen in 10 cases of grade 1 endometrial carcinomas and 5 cases of grade 2 EC. p53 expression was seen in 01 case of grade 1 EC and 03 cases grade 3 EC. ER, PR, p53 all were negative in one case. Ki67 was <10% in 11 cases, between 10-20% in 5 cases and >20% in 04 cases. We followed up 15 out of 20 cases, out of which only 01 patient died of disease who was grade 1 endometrial carcinoma. Rest 14 had progression free survival (PFS) till date.

All 58 cases of endometrial hyperplasia were reclassified complex and simple hyperplasia to typical and atypical hyperplasia (as per WHO Classification 2014). Out of 58 cases, 56 cases were typical hyperplasia and 02 cases atypical hyperplasia. ER, PR expression was positive in all the cases of typical and atypical hyperplasia. p53 expression was absent in typical and atypical hyperplasia with low Ki 67 index (<10%).

Conclusion: High ER, PR expression along with low p53 was seen in type 1 endometrial carcinomas compared to low or absent ER, PR along with strong p53 expression in papillary serous carcinoma (Type 2). The expression of ER, PR was high in typical hyperplasia as against high p53 expression observed in atypical hyperplasia.

1. Introduction

Endometrial carcinoma (EC) is the second most common gynecologic malignancy with an incidence of 5.9 per 100,000 women in the developing countries. In India, the incidence is 4.3 per 100,000 women.[1] Endometrial hyperplasia (EH) implies an overgrowth of the endometrium. It constitutes a spectrum of irregular morphological alterations, due to which abnormal proliferation of the endometrial glands occurs resulting in an increase in gland to stroma ratio when compared to endometrium from the proliferative phase of the cycle.[2]

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WHO 2014 classification differentiates endometrial hyperplasia into typical hyperplasia and atypical hyperplasia/endometrial intraepithelial neoplasia (EIN).[3] EH is one of the most frequent causes of abnormal uterine bleeding, which leads to EC if left untreated. In 10% of premenopausal women with abnormal uterine bleeding, histological findings show endometrial hyperplasia and in 06% of postmenopausal women with uterine bleeding EC are found.[4]

Despite of these facts the general population is not aware of EC which is reflected by increased use of endogenous and exogenous estrogen in the treatment of post menopausal symptoms there by resulting in EC.[5–7] The two types of EC, Type-1 and Type-2 which are different in their etiology, clinical behavior and treatment modalities were originally described by Bokhman JV et al. in 1983.[8] High grade serous carcinoma are found to be less or non-responsive to usual chemotherapy.[9] One study shows that serous carcinoma forms 10% of all EC.[10]

Estrogenic action unopposed by progesterone induces sequential malignant changes in the endometrium by atypical hyperplasia. Decreased expressions of estrogen receptor (ER) and progesterone receptor (PR) are observed in EC which increases in both grade and stage when compared to atypical hyperplasia. Therefore absence of ER and PR expression is important in the progression of type 1 EC.[11,12] In type II EC, p53 mutation is common phenomenon.

Traditional histopathological classification system of endometrial hyperplasia exhibited variable degree of diagnostic reproducibility. WHO classifications 2014 have simplified the categorization and improve the reproducibility which clearly distinguishes between clinic-pathologic entities that are managed differently. The aim of this study was to assess the role of immunohistochemical expression of ER, PR, Ki67 and p53 in EC and atypical hyperplasia.

2. Materials and Methods

This retrospective study included total 78 cases of which 58 cases were endometrial hyperplasia (atypical hyperplasia and typical hyperplasia) and 20 cases of EC between June to May 2020.

Ethical clearance was obtained from the Institutional Ethical Committee (Letter number: BVDUMC/IEC/78E). The tissues for histopathology (surgical specimens, dilatation and curettage, biopsies) were received in the Department of Pathology. All routinely processed paraffin embedded tissue blocks and Hematoxylin and Eosin (H&E) stained slides of these 78 cases were retrieved. The slides were reviewed. Hyperplasias were re- classified as typical and atypical as per WHO classification.

IHC was performed on all cases of EC and atypical hyperplasia. The primary antibodies used were ER (Clone EP1; Dako), PR (Clone PgR636; Dako), p53 (Clone DO-7; Dako) and Ki-67 (Clone MIB-1; Dako). Section from normal breast tissue was used as positive control for ER and PR. Section from and skin and tonsil was used as positive control for p53 and Ki67 respectively. Scoring of ER, PR in EC and hyperplasia were done as positive and negative while percentage labeling index was followed for p53 and Ki67.

3. Results

Total 78 cases were studied for a period of 01 year from June 2019 to May2020. There were 20 cases of EC and 58 cases of endometrial hyperplasia as seen in Table 1. EC was most commonly seen in sixth to seventh decade and hyperplasia was seen in fourth to fifth decade (Table 2).

There are 11 surgical specimens and 09 biopsies of EC. Out of total 20 cases, there were 17 cases of endometrioid adenocarcinoma and 03 cases were of papillary serous adenocarcinoma. ER, PR expression was seen in 10 cases of grade 1 endometrial carcinomas and 5 cases of grade 2 EC. p53 expression was seen in 01 case of grade 1 EC and 03 cases grade 3 EC (Table 3) ER, PR, p53 all were negative in one case. Ki67 was <10% in 11 cases, between 10-20 % in 5 cases and >20% in 04 cases (table 4). We followed up 15 out of 20 cases, out of which only 01 patient died of disease who was grade 1 endometrial carcinoma. Rest 14 had progression free survival (PFS) till date.

All 58 cases of endometrial hyperplasia were reclassified complex and simple hyperplasia to typical and atypical hyperplasias (as per WHO Classification 2014). Out of 58 cases, 56 cases were typical hyperplasia and 02 cases atypical hyperplasia. ER, PR expression was positive in all the cases of typical and atypical hyperplasia. p53 expression was absent in typical and atypical hyperplasia with low Ki 67 index (<10%) (Tables 4 and 5).

Table 1: Table showing different endometrial lesions (n =78)

Type of lesion	Number of cases	Percentage
Typical hyperplasia	56	71.79
Atypical hyperplasia	02	2.56
Endometrioid carcinoma	17	21.79
Papillary serous carcinoma	03	3.84
Total	78	100

4. Discussion

The molecular classification of EC that has emerged from the Cancer Genome Atlas (TCGA) study provides additional potentially superior prognostic information to traditional histologic typing and grading. This classifier does not, however, replace clinicopathologic risk assessment based on parameters other than histopathology type and grade.[15,16]

Table 2: Age wise distribution of endometrial carcinoma, atypical and typical hyperplasia

Age range (total number of cases)	Number of cases of Endometrial carcinoma	Number of cases of atypical hyperplasia/EIN	Number of cases of typical hyperplasia
21-30 (n =6)	0	0	6
31-40 (n= 18)	2	0	16
41-50 (n= 30)	2	1	27
51-60 (n=12)	6	1	5
61-70 (n = 9)	7	0	2
>70 (n= 3)	3	0	0
Total	20	2	56

Table 3: Grade wise distribution ofimmunohistochemical markers in EC

Endometrial carcinoma	ER , PR positive	p 53 positive	P value
Grade 1(n=11)	10 (90.9%)	01 (9.09%)	
Grade 2 (n= 5)	05 (100%)	0	P value = 0.005
Grade 3 (n = 3)	0	03 (100%)	

Table 4: Ki67 index in various lesions of endometrium

Lesions	Ki 67 <10	Ki 67 10-20	Ki67 >20	P value
Typical Endometrial hyperplasia (n=56)	56	0	0	
Atypical Endometrial hyperplasia (n=2)	0	02	0	
Grade 1 EC (n= 11)	7	4	0	P value < 0.001
Grade 2 EC (n= 5)	4	1	1	
Grade 3 EC (n= 3)	0	0	3	
Total	67	07	04	78

Table 5: Distribution of ER, PR and p53 in variousendometrial lesions

Lesion Type (Number)	ER	PR	p53
Typical Endometrial hyperplasia (n= 56)	56	56	00
Atypical endometrial Hyperplasia(n = 02)	02	02	00
Endometrioid adenocarcinoma (n= 17)	15	15	01
Papillary serous carcinoma (n = 03)	0	0	03

Table 6: Comparison studies of various variables in EC:

Various studies	N [number of cases]	Age range (mean age)	Endometriod type	Serous type	Grade 1	Grade 2	Grade 3
Our study	78	31-70 (50.5)	17	03	11	06	03
Somsubhra Goswami et al[9]	34	35-58 (60)	32	2	16	7	11
Trovik et al[10]	1192	28-94 (66)	954	107	458	343	143
Amany Salama et al[11]	109	37-79 (59.8)	89	12	36	39	30
Geoffroy et al[12]	69	58-77 (67.5)	56	02	43	6	17

Table 7: Comparison studies of expression ofImmunohistochemical markers in EC:

Various studies	ER expression	PR expression	p 53 expression
Our study	15	15	04
Trovik et al[10]	492	492	150
Nayar et al[13]	17	18	27
Suthipintawong C et al[14]	50	47	31

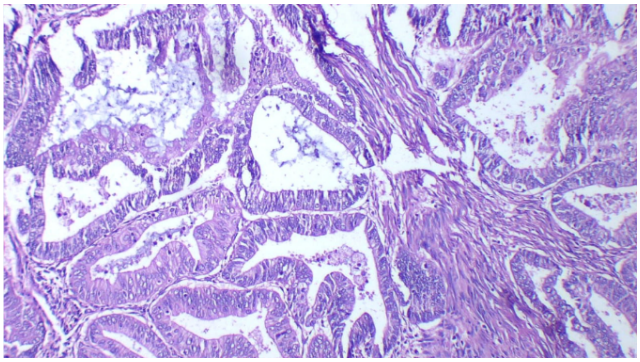

Fig. 1:

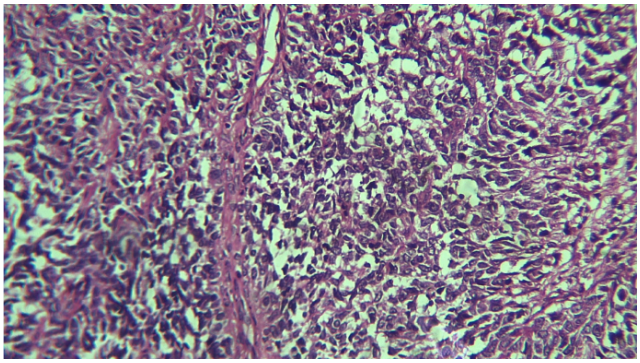

Fig. 2:

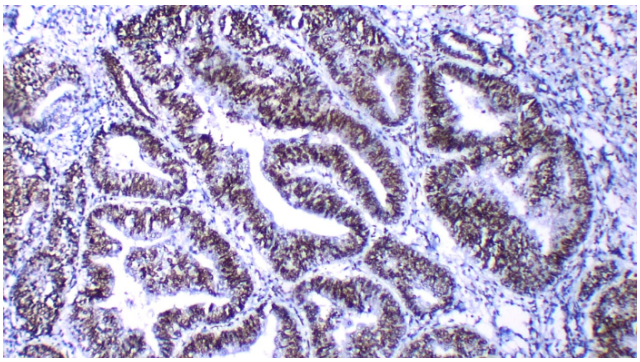

Fig. 3:

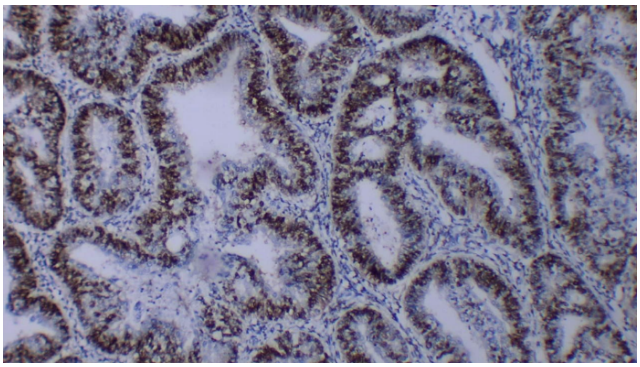

Fig. 4:

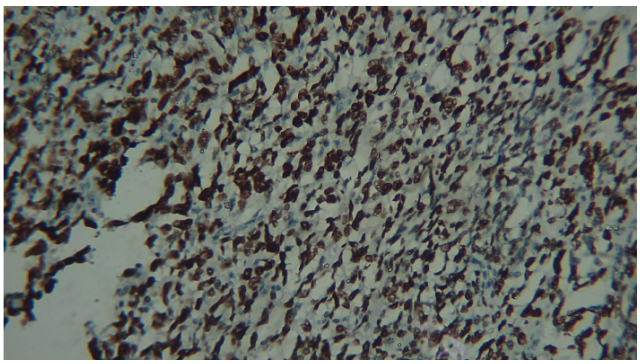

Fig. 5:

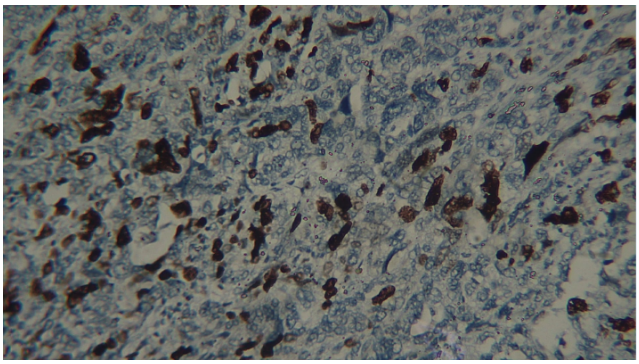

Fig. 6:

4.1. ER and PR receptors and functions

ER and PR belong to the nuclear receptor superfamily. They are ligand-dependent transcriptional factors, which can bind to different DNA sites to initiate the expression of specific genes. ER exists in 2 isoforms, ER-α and ER-β which have a distinct pattern of expression in the tissues,[13] that varies during cellular proliferation and differentiation.[14,17]

Progesterone receptor (PR) also has 2 isoforms PR-A and PR-B which are functionally distinct transcription factors.[18] According to the literature the transcription of PR gene is induced by estrogen and inhibited by progesterone in the majority of estrogen responsive cells, so the expression of ER and PR is considered to be coordinated.[19,20]

4.2. ER and PR in endometrial carcinoma

The expression of steroid receptors in EC has been quantitatively associated with histologic differentiation.[21,22] The loss of steroid receptors is an early event in EC has a lower level of steroid receptors than does normal endometrium or EH.[23] ER-α expression is decreased in EC.[24] in both glands and stroma in relation to EH and is further decreased as EC grading advances.[23–25]

PR-A is associated with a cell and promoter specific repression of PR-B[26] and imbalance in PR-A to PR-B ratio is frequently associated with carcinogenesis.[27]

4.3. ER and PR status relationship with disease progression and prognosis

Molecular tumor classification, which includes PR and ER expression, is an integral part of the EC. Five-year survival rate (stage I) and median survival time (stages II-IV, recurrences) for patients with ER+/PR+ and ER-/PR+ EC i.e. PR+ were reported to be significantly better than for ER-/PR- and ER+/PR- i.e. PR- patients.[28] Thus, PR/ER immunohistochemistry appears to be a reliable means for predicting survival in EC, independent of other clinicopathological parameters.[29]

In the present study, 58 cases of EH and 20 cases of EC were distributed in the age range of 21-81 years. It is observed that peak incidence of endometrial hyperplasia was in fourth to fifth decade and that of EC was in the sixth decade. Commonest histomorphology was endometrioid type of adenocarcinoma in 17 cases followed by papillary serous carcinomas in 3 cases.

Our study correlates with various studies as seen in table number no 6 in all the variables described.[30–33] Our study show that grade 1 and 2 endometrial carcinomas have different ER, PR, Ki67 and p53 immunostaining profiles compared with grade 3, as also shows a significant p value of less than 0.005. Out of 20 cases of endometrial carcinomas, 15 cases showed strong expression of ER and PR indicating type 1 pathogenetic mechanism and 4 cases showed strong p53 expression which had serous papillary morphology confirming the pathogenesis of type 2 EC.[34,35]

The expression of ER, PR, p 53 was compared and correlated with other studies in the literature as shown in Table 7.[31,36,37] One case of endometrial carcinoma in present study was negative for ER, PR and p53 (aberrant expression). These findings are clinically important, because ER/PR loss may help identify high-risk patients from presumed low-risk group for in-time and treatment. In our study, grade 1 and 2 endometrial carcinomas showed lower Ki67 index (<10- 20%) than grade 3 tumors thus Ki 67 labeling index can be closely associated with tumor grade. This fact also correlates with Canlorbe G et al.[12] In study by Sirijaipracharoen et al., which included 108 patients, ER, PR and HER-2/neu expression were positive in 59.3%, 65.7% and 2.8% respectively.[38]

ER PR expression was seen equally in typical and atypical hyperplasia. Ki67 index was minimal in hyperplasia and its expression increased as disease progressed from atypical hyperplasia to carcinoma which also correlates with studies by Masjeed et al.[37]

The p value for expression in our study for ER, PR, p53 and Ki67 was statistically significant for hyperplasia versus EC (Tables 6 and 7).

5. Conclusion

Distinguishing between hyperplasia and true precancerous lesions has significant clinical implications because distinct endometrial precancerous conditions require appropriate intervention. EH, especially atypical, increases the risk for EC and their early detection becomes mandatory under cancer prevention.

High ER, PR expression along with low p53 was more in type 1 endometrial carcinomas compared to low or absent ER, PR along with strong p53 expression in papillary serous carcinoma (Type 2) confirming the different pathogenetic mechanism for both.

6. Source of Funding

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7. Conflict of Interest

The authors declare they have no conflict of interest.

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