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Progesterone receptors in complex and/or atypical endometrial hyperplasia and endometrial adenocarcinoma

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Abstract
Endometrial carcinoma is second most common malignancy of female genital tract with an incidence of 5.9 per 100,000 women in the developing counties. In India the incidence id 4.3 per 100,000 women. Endometrial adenocarcinoma are categorised into type I and type II histological types. Type I endometrial adenocarcinomas comprise of 80% of the cases which results due to unopposed estrogen stimulation. It is associated with lesions like Endometrial Intraepithelial Neoplasia (EIN)/Atypical Hyperplasia. Type I endometrial tumors present with a low tumor grade. Endometrial tumors of type II are also called as non endometrioid tumors. It includes serous, clear cell, mucinous and mixed tumors. These tumors account for approximately 10% of cases. Early stage and well differentiated tumors are primarily progesterone positive. Whereas poorly differentiated tumors and type II endometrial cancers are progesterone positive.

Keywords: Progesterone Receptors, Atypical Hyperplasia, Type I and Type II endometrial carcinoma

Introduction
Endometrial carcinoma is second most common malignancy of female genital tract with an incidence of 5.9 per 100,000 women in the developing counties. In India the incidence id 4.3 per 100,000 women. Creaseman *et al.* (2007) [1] reported in the year 2007 that 75% patients are postmenopausal and only 3-10% are less than 40 years of age. Endometrial adenocarcinoma are categorised into type I and type II histological types. Type I endometrial adenocarcinomas comprise of 80% of the cases which results due to unopposed estrogen stimulation. It is associated with lesions like Endometrial Intraepithelial Neoplasia (EIN)/Atypical Hyperplasia. Type I endometrial tumors present with a low tumor grade. They present with mutations in PTEN, PAX2 and k-ras. Endometrial tumors of type II are also called as non-endometrioid tumors. It includes serous, clear cell, mucinous and mixed tumors. These tumors account for approximately 10% of cases. They are less associated with estrogen stimulation and present with higher tumor grade and stage [2-4]. Prognosis of endometrial carcinoma depends on multiple factors like age of the patient, histological type and grade, vascular invasion, FIGO stage, estrogen and progesterone receptor, proliferation index (Ki-67), p53 tumour suppressor gene and over expression of oncogene c-erbB-2 [5]. Early stage and well differentiated tumors are primarily estrogen and progesterone positive [6]. Low grade tumors usually present in early stage and high grade tumors usually present in advanced stage [10].

The progesterone receptor is expressed inside cells. Progesterone receptor is encoded by a PGR gene located on chromosome 11q22 [7]. Progesterone receptors have two main forms A and B [8]. PR-A isoform's function is to oppose estrogen-induced proliferation as well as PR-B-dependent proliferation. Progesterone induces the progesterone receptors. In the absence of binding hormone the carboxyl terminal inhibits transcription. When the receptor binds to a hormone it induces a structural change which removes the inhibitory action. When progesterone binds to the receptor restructuring with dimerization takes place and the complex enters the nucleus and thereby binds to DNA [7, 8] as the transcription takes place there is formation of messenger RNA that is translated by ribosomes to produce distinct proteins. Early-stage, well differentiated endometrial carcinomas usually express for estrogen and progesterone receptors. As the tumor progresses to advanced stage, poorly differentiated

tumors do not express these receptors [9]. Loss of PR expression is observed in well and in poorly differentiated endometrial carcinoma and related to PR-A [9]. Estrogenand progesterone receptors are expressed more in endometrioid than in serous tumors. The expression of these tumors is associated with low-grade and early-stage tumors [10].

Pieczynska *et al.* (2011) [11] conducted a study on 98 cases of endometrial hyperplasia. They found that PR expression decreased in order from disordered proliferative endometrium, endometrial hyperplasia to atypical endometrial hyperplasia.

Srijaipracharoen *et al.* (2010) [12] concluded in their study that positive progesterone and estrogen receptor expression is linked with endometrioid histology, grade I-II tumor, less myometrial invasion (MI) and no lymph node involvement. They concluded in their study that progesterone and estrogen receptor expression is a good prognostic factor.

Meng *et al.* (2001) [13] conducted a study on 37 specimens of endometrial lesions. There were12 cases of endometrial hyperplasia. All the 12 (100%) cases were strongly positive for estrogen and progesterone receptors.

Aim and Objectives

1. To correlate complex and/or atypical endometrial hyperplasia with tissue progesterone receptor status.
2. To correlate histology of endometrial carcinoma with tissue progesterone receptor status.

Material and Methods

Study setting

This study titled as "Progesterone receptor expression in atypical/complex endometrial hyperplasia and endometrial adenocarcinoma" was done in a teaching hospital in Maharashtra. The specimens included biopsy and hysterectomy. This was a retrospective study. It was a pilot exploratory study. 50 cases diagnosed to have atypical endometrial hyperplasia or endometrial carcinoma were included in retrospective manner from records of Department of Pathology. Patients were excluded from the study if they had uterine malignancies other than epithelial malignancies.

Study procedure

The study protocol was approved by Institutional ethical committee before the commencement of study. Hematoxylin and eosin stained slides were retrieved and the cases were categorised as atypical hyperplasia, endometrial type I tumors were classified into Grade I, Grade II and III endometrial tumors. The endometrial type II tumors were categorised into Serous/Clear Cell/Mucinous and mixed variant. IHC staining for progesterone recptors was conducted.

The evaluation of ER and PR was performed according to the method described by Carcangiu *et al.* (1990) [137] According to the percentage of stained cells and the intensity of nuclear stain. The percentage of PR positive cells was graded as follows

1. if 0 to 25% of the nuclei stained
2. when 26 to 75% of nuclei stained
3. if more than 76% of the nuclei stained.

The staining intensity was scored as follows:

1. as absent or weak
2. as strong
3. as very strong.

The sum of percentage and intensity gave an immunohistochemical score.

Tumors were categorised as follows:

Category I asigned of 2,

Category II was scored as ¾

Category III was scored as 5/6.

Category I tumors were immunonegative and Category II and III tumors were immunopositive.

Observation and Results

This was a retrospective study entitled as "Progesterone Receptors expression in Complex and/or Atypical Endometrial Hyperplasia and Endometrial Adenocarcinoma" in which we selected 50 cases diagnosed to have either complex/atypical hyperplasia or endometrial adenocarcinoma on histopathology for expression progesterone receptors.

The age of the patients ranged from 38 years to 80 years. Peak of patients (21 cases, 42%) were seen in 6th decade. Next highest number of cases were in 5th decade (13 cases, 26%). In the seventh decade 10 cases (20%) were seen. There were only 4 cases (8%) in eithh decade. Whereas there were no cases seen in less than 30 years age group. (Figure 1)

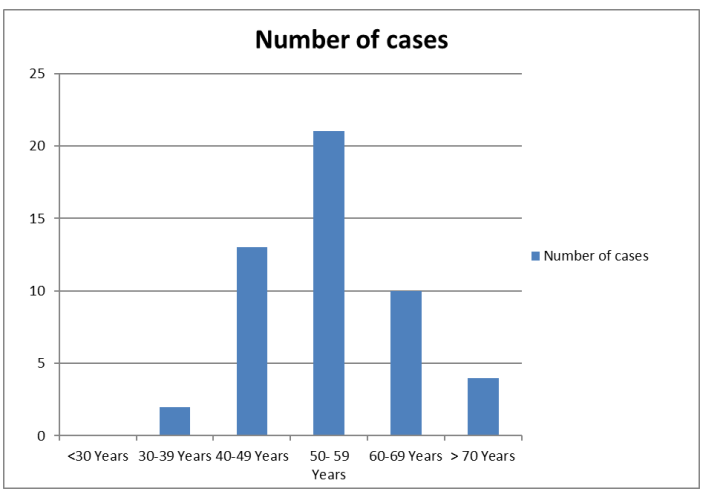

Fig 1

It was observed that there were 10 cases of atypical endometrial hyperplasia and 40 cases of endometrial adenocarcinoma. As shown in Table 1

Table 1

Cases	Number	%
Atypical Hyperplasia	10	20
Endometrial Carcinoma	40	80
Total	50	100

We found that type I endometrial tumors cases (36 cases, 90%) were more than type II endometrial malignancies (4 cases, 10%). As shown in Figure 2.

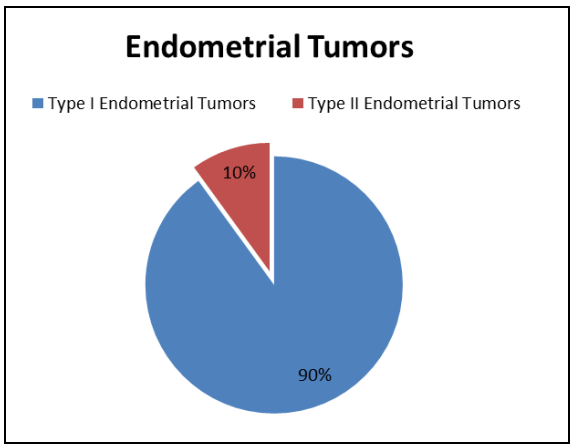

Fig 2

In type II endometrial malignancies out of 4 cases we observed that there were 2 cases (5%) of serous carcinoma, one case each of clear cell and mucinous variants of non endometrioid malignancies.

In our study we found that there were 14 cases (35%) of well differentiated endometrioid adenocarcinoma. There were 3 cases (7.5%) of moderately differentiated endometrioid adenocarcinoma. Together they were categorised as low grade (early stage) tumors accounting to 17 cases. Whereas the poorly differentiated endometrial adenocarcinoma cases were 19 (47.5%). The poorly differentiated endometrial malignancies along with type II non endometrioid tumors accounted for the high grade (advanced stage) tumor cases (23 cases). As shown in Table 2.

Table 2

Histological Grade	Histological Subtypes	Percentage (%)	
Low Grade (Early Stage)	Well differentiated (Grade I)	14	35
	Moderately Differentiated (Grade II)	3	7.5
High Grade (Advanced Stage)	Poorly Differentiated (Grade III)	19	47.5
	Non Endometrioid (Type II)	4	10
Total		40	100

In our study we found that 32 (64%) cases were progesterone receptor (PR) positive. All the 10 (100%) cases of atypical endometrial hyperplasia strongly expressed for progesterone receptor. In the type I endometrial cancers 22 (61.1%) cases were PR positive. All the 4 (100%) cases of type II endometrial cancer were PR negative. The difference was found to be statistically significant as shown in Table 3. (Figure 3, 4, 5)

Table 3

Type of endometrial cancer	Number of cases		PR Positive		PR Negative	
	No.	%	No.	%	No	%
Type I	36	(100)	18	50	18	50
Type II	04	(100)	0	0	4	100
Hyperplasia	10	(100)	10	100	0	0
Total	50	(100)	28	56	22	44

P= 0.001

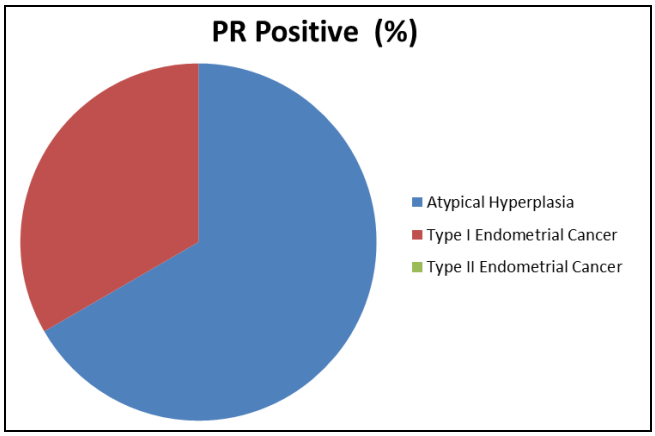

Fig 3

Based on the intensity of Progesterone Receptor (PR) staining and percentage of cells involved we observed that in atypical hyperplasia there was strong positivity for progesterone receptor. Out of 10 cases, 8 (80%) cases were in category three and 2 (20%) cases showed moderate positivity for PR receptors. None of the cases of atypical hyperplasia were immunonegative for PR. In well differentiated endometrioid adenocarcinoma 12 out 14 cases were immunopositive for PR and 9 (64.3%) cases strongly expressed for progesterone receptors. All the 3(100%) moderately differentiated tumors were immunopositive for progesterone receptor. Whereas the intensity and percentage of nuclear stain reduced from moderately differentiated tumors, poorly differentiated tumors to type II non endometrioid tumors. In poorly differentiated carcinoma cases 16 out of 19(84.2%) tumors were PR negative. All (4, 100%) type II endometrial tumors were PR negative. The difference was found to be statistically significant. As shown in Table 4. (Figure3, 4)

Table 4

PR Category	Atypical Hyperplasia		Well differentiated endometrial carcinoma		Moderately differentiated endometrial carcinoma		Poorly differentiated endometrial carcinoma		Type II endometrial cancers	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Category 1/Negative	0	0	2	14.3	0	0	16	84.2	4	100
Category 2	2	20	3	21.4	2	66.7	2	10.5	0	0
Category 3	8	80	9	64.3	1	33.3	1	5.3	0	0
Total	10	100	14	100	3	100	19	100	4	100

P= 0.00008

It was observed that out of 17 low grade cases 10 (58.8%) cases strongly expressed for progesterone receptor. Moderate expression of progesterone receptor was seen in 5 (29.4%) cases hence 15 out 17 low grade tumors were PR positive and only 2 (11.8%) cases were immunonegative for PR. Whereas in high grade tumors 20 out of 23(86.9%) tumors were PR negative. The difference was found to be statistically significant as shown in Table No. (Figure 4,5)

Table 5

Histological grade	PR Category 3		PR Category 2		PR Category 1 /Neg		No. of cases	
	No.	(%)	No.	(%)	No.	(%)	No.	%
Low Grade	10	58.8	5	29.4	2	11.8	17	(100)
High Grade	1	4.4	2	8.7	20	86.9	23	(100)
Total	1 1		7		22		40	(100)

P= 0.00001

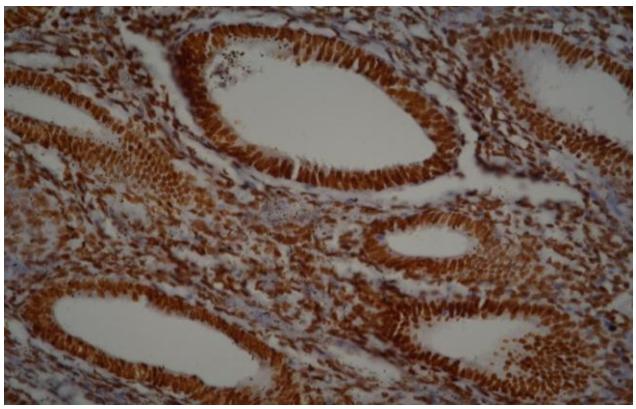

Fig 4: Category 3 positivity for progesterone receptor in atypical endometrial hyperplasia. (IHCX400)

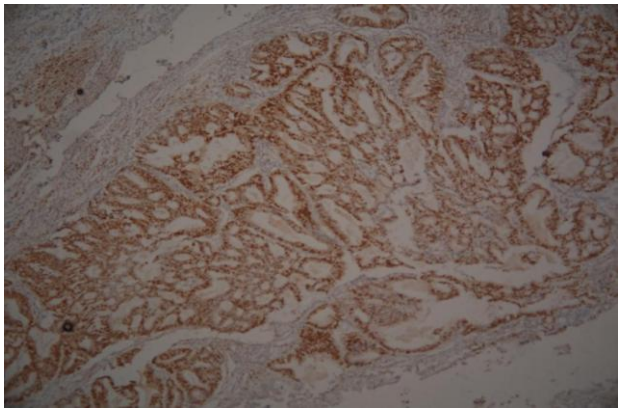

Fig 4: Category 3 positivity for progesterone receptor in well differentiated endometrial adenocarcinoma. (IHCx 100)

Discussion

This study titled as as "Progesterone Receptors expression in Complex and/or Atypical Endometrial Hyperplasia and Endometrial Adenocarcinoma." was conducted in department of Pathology of a rural hospital in Central India. The study included a total of 50 cases of atypical endometrial hyperplasia and endometrial adenocarcinoma.

In our study we found that atypical endometrial hyperplasia and endometrial cancer were more common after 40 years. It peaked in sixth decade.

Byun*et al.* (2015)[38] reported that average age of women with endometrial lesions was 46.8±10.0 years. In a study conducted by Malik*et al.* (2016) [39] it was found that the mean age of the patients was 56.6(SD±10.51) years in type I endometrial carcinoma cases while it was 61.08 (SD±6.69) in type II endometrial cancer cases. The observation in our study was similar to these studies. In our study we observed that there were 90% cases (36 patients) of type I endometrial carcinoma where as there were only 10% cases (4 patients) of type II endometrial carcinoma. Talhouk *et al.* (2016) reported that type I endometrial carcinomas constitute around 70-80% cases. In contrast the type II endometrial cancers are around 20-30%, type I endometrial tumors being more common. Our results also showed similar observation. In our study it was observed that all well differentiated endometrial carcinoma were limited to the uterus (Stage I and Stage II) and were in early stage. Whereas the poorly differentiated tumors and type II endometrial tumors were in advanced stage and were either in stage III or IV. (Table 2)

Kounelis *et al.* (2000) [10] conducted a study on 61 cases of endometrial tumors. The twenty-seven type I endometrial lesions were of low grade and included the well differentiated and moderately differentiated endometrial lesion and 13 were high grade which were the poorly differentiated endometrial carcinoma cases. The 20 cases with FIGO stage I and II were in early-stage and 20 patients lying in FIGO stage III and IV were in advanced-stage tumors. Majority of type II endometrial carcinoma (18/21) cases were in advanced-stage. The observations were similar to our study that low grade tumors usually present in early stage and high grade tumors usually present in advanced stage. We observed that all the endometrial atypical hyperplasia cases (10,100%) were strongly positive for PR. It was noticed that 18 out of 36 (50%) type I endometrial cancer cases were positive for PR (P= 0.0011) Whereas all 4 cases of type II endometrial carcinoma were negative for progesterone receptors. The difference was found to be

statistically significant (Table No.3-5).

Kounelis *et al.* (2000) [10] reported in a study on Immunohistochemical Profile of Endometrial Adenocarcinoma conducted on 61 cases that in 27 cases of low grade tum ors 88.8% were ER positive and 85.2% were PR positive. Out of the 13 cases of high grade endometrial tumours including poorly differentiated and type II endometrial carcinoma cases 30.8% were ER positive and 46.2% were PR positive. Willson *et al.* (2015) concluded that well-differentiated tumors expressed for estrogen receptors (8/9) more often than poorly differentiated tumors (5/9). Meng *et al.* (2001) conducted a study on 37 specimens of endometrial lesions. There were12 cases of endometrial hyperplasia. All the 12 cases were strongly positive for estrogen and progesterone receptors.

Conclusion

1. Endometrial lesions including atypical endometrial hyperplasia and endometrial cancer are more common in fifth, sixth and seventh decade.
2. Type I endometrial cancer are more than type II endometrial cancers.
3. Well differentiated endometrial carcinoma were mostly in early stage. Whereas the poorly differentiated tumors and type II endometrial tumors usually presented in advanced stage.
4. Endometrial atypical hyperplasia cases were strongly positive for progesterone receptors.
5. In type I endometrial cancers are positive for progesterone receptors in contrast to type II endometrial carcinomas which are negative for progesterone receptors.
6. The intensity of expression of PR reduced as the tumor progressed from well differentiated tumors to poorly differentiated tumors.

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