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P-53 expression in complex and/or atypical endometrial hyperplasia and endometrial adenocarcinoma

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Abstract
Endometrial cancer holds fourth position after breast, colon and lung cancers. In different parts of the world endometrial carcinoma accounts for 4-8% of all cancers. The Age Standardised Rate (ASR) is approximately 4.3 cases per 1,00,000 women. Endometrial cancers are majorly observed in post menopausal women. The age group for diagnosis of endometrial cancers is around 60 years. The most common symptom in patients of endometrial carcinoma is postmenopausal bleeding. The prominent risk factors for endometrial carcinoma include obesity, nulliparity, early menarche and late menopause, and estrogen therapy. There are two types of endometrial cancers: type I endometrial cancer is associated with unopposed estrogen expression and is more common (80% of cases) whereas type II endometrial malignancies are not related to estrogen and are more aggressive tumor.P53-driven model of carcinogenesis is responsible for the rapid development and progression of type II endometrial lesions. Early stage tumors (low grade) are primarily estrogen and progesterone receptor positive and P-53 negative. In contrast the advanced stage tumors (high grade) tumors show strong positive expression for P-53 and are negative for estrogen and progesterone receptors.

Keywords: P-53, Atypical Hyperplasia, Type I and Type II endometrial cancers.

Introduction
Endometrial cancer holds fourth position after breast, colon and lung cancers. [1, 2] In different parts of the world endometrial carcinoma accounts for 4-8% of all cancers. The Age Standardised Rate (ASR) is approximately 4.3 cases per 1,00,000 women (Delhi). [3] Endometrial cancers are majorly observed in post menopausal women. The age group for diagnosis of endometrial cancers is around 60 years [4-5]. The most common symptoms in patients of endometrial carcinoma are postmenopausal bleeding and pain in abdomen with lump [7-9]. Other less important symptoms include loss of weight, loss of appetite and breathlessness [10]. The prominent risk factors for endometrial carcinoma include obesity, nulliparity, early menarche and late menopause, and estrogen therapy. The other risk factors include ovarian carcinoma, breast cancer, tamoxifen therapy, diabetes and family history [11-14]. There are two types of endometrial cancers: type I endometrial cancer is associated with unopposed estrogen expression and is more common (80% of cases) whereas type II endometrial malignancies are not related to estrogen and are more aggressive tumor [15]. P53-driven model of carcinogenesis is responsible for the rapid development and progression of type II endometrial lesions like uterine papillary serous adenocarcinoma (UPSA) [16]. 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 [17]. Early stage tumors (low grade) are primarily estrogen and progesterone receptor positive [18]. In contrast the advanced stage tumors (high grade) tumors show strong positive expression for P-53 [19-20]. It is associated with nonendometrioid histology, extrauterine metastases and negative progesterone receptor status [19]. Serous carcinomas are believed to develop from endometrial intraepithelial carcinoma [21]. P-53 expression is observed in aggressive endometrial tumors than the well differentiated and moderately differentiated endometrioid adenocarcinomas [22]. It is strongly positive in high grade endometrial tumors and tumors which have progressed to advanced stage [22].

Aim and Objectives

1. To correlate complex and/or atypical endometrial hyperplasia with P-53 expression
2. To correlate endometrial carcinoma with P-53 expression.

Material and Methods

This study titled as "P-53 expression in atypical/complex endometrial hyperplasia and endometrial adenocarcinoma" was carried out in a teaching hospital in Maharashtra. Tissues were obtained from all the specimens like biopsy and hysterectomy. This was a retrospective study. Fifty cases diagnosed as atypical endometrial hyperplasia or endometrial carcinoma were selected in retrospective manner from records of Department of Pathology. Histologically confirmed diagnosis of atypical endometrial hyperplasia or endometrial adenocarcinoma were included.

Clinical details including age, symptoms, risk factors were looked for. FIGO staging of patients was done.

Patients were excluded from the study if they had uterine malignancies other than epithelial malignancies. Hematoxylin and eosin stained slides were made and the cases were classified as endometrioid (Type I) and Nonendometrioid (Type II) malignancies. The type I malignancies were further classified as Grade I, Grade II and Grade III endometrial tumors. Immunohistochemical stain for P-53 was performed on these sections.

The evaluation of p-53 was done according to the method described by Quin *et al.* (2002). [28] The percentage of P53 positive tumor cells was scored as 0 to 3+ in P53 positive region. It was given a score of 0 when <10% of tumor cells were p-53 positive. A score of 1+ when 10-30% of tumor cells were stained, score of 2+ when31-50% tumor cells expressed p-53 positivity and 3+ when>50% were p-53 positive.

Observation and Result

The age of the patients ranged from 30 to 80 years. Majorly the patients were present in 50-59 years age group. The second most common age group ranged from 40-49 years. The mean age of presentation of type I endometrial carcinoma was 55.5 years. The type II endometrial malignancies were limited to seventh decade and were less common as compared to type I endometrial malignancies. As shown in Table 1.

Table 1

Age	Atypical Hyperplasia	%	Type I Endometrial Cancer	%	Type II Endometrial Cancer	%
<30	0	0	0	0	0	0
30-39	1	10	1	2.8	0	0
40-49	5	50	8	22.2	0	0
50-59	3	30	18	50	0	0
60-69	1	10	5	13.9	4	100
>70	0	0	4	11.1	0	0
Total	10	100	36	100	4	100

Most common clinical presentation was postmenopausal bleeding in 44 (88%) cases, followed by lump in abdomen with pain in 4 (8%) cases. Two (4%) patients were having non-specific symptoms like weight loss and loss of appetite. As shown in Table 2.

Table 2

Predominant clinical presentation	No. of cases	Percentage (%)
Postmenopausal bleeding	44	88
Pain in abdomen with lump	4	8
Others (weight loss, loss of appetite, breathlessness)	2	4
Total	50	100

We observed for presence of various risk factors and we found that the most common risk factor was obesity found in 12 (24%) cases. History of nulliparity and late menopause was given by 10 cases (20%) each. Estrogen intake was found in 7 (14%) patients. Endometrial cancer was associated with ovarian cancer in 3 (6%) cases and 2 (4%) of the patients had previous history of breast cancer. As shown in Table 3.

Table 3

Risk Factors	Number of cases	Percentage (%)
Obesity	12	24
Nulliparity	10	20
Late menopause	10	20
History of estrogen intake	7	14
Presence of ovarian cancer	3	6
Presence of breast cancer	2	4
Early menarche	2	4
Family history	2	4
History of tamoxifen intake	1	2
Diabetes	1	2

We found that endometrioid adenocarcinoma cases were more common. (36 cases, 90%). Only four (10%) cases of non-endometrioid adenocarcinoma were reported. In the non-endometrioid adenocarcinoma two (5%) cases of serous carcinoma were observed. A single (2.5%) case each of clear cell variant and mucinous variant was observed. As shown in

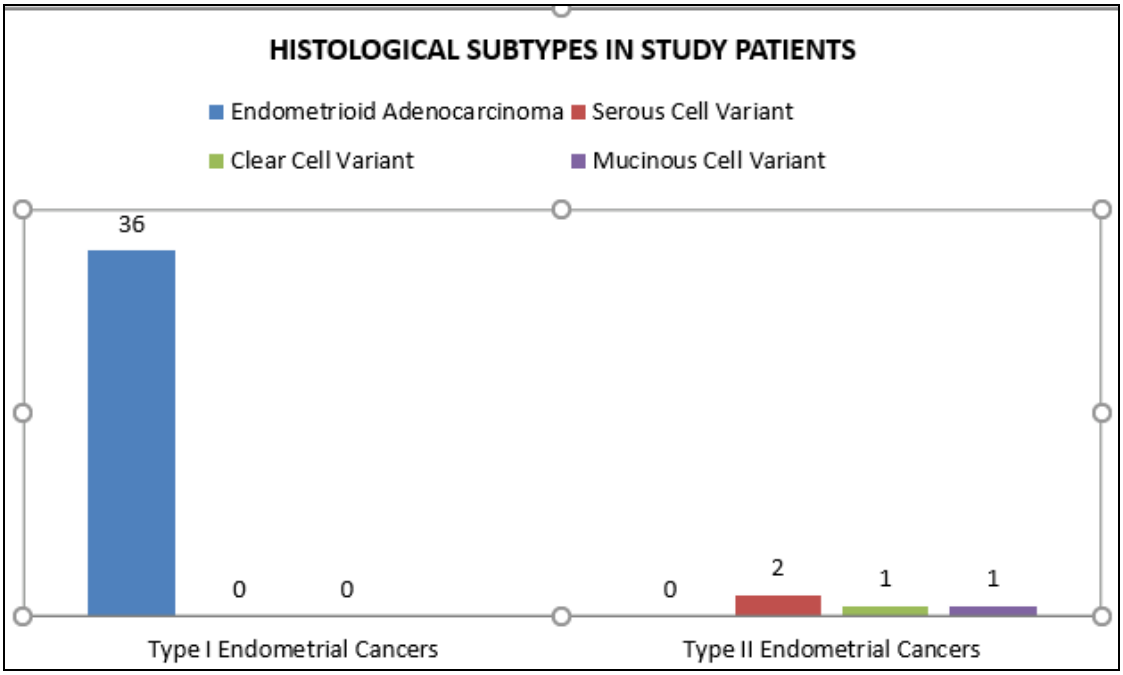

Fig 1

Table 6

Type of endometrial cancer	Number of cases	p-53 Positive		p-53 Negative	
	No.	No.	%	No	%
Type I	36	22	61.1	14	38.9
Type II	04	04	100	0	0
Hyperplasia	10	0	0	10	100
Total	50	26	52	24	48

P= 0.00038

In our study we observed that p-53 expression was absent in all the 14(100%) cases of well differentiated endometrioid adenocarcinoma. However, 3 (100%) cases of moderately differentiated endometrioid adenocarcinoma expressed p-53 with a score of 1+. Whereas all the 19(100%) cases of poorly differentiated endometrial carcinoma expressed p-53 and 13 out of 19 (68.4%) cases of poorly differentiated endometrial carcinoma over expressed p-53 with a score of 3+. The type II endometrial cancer showed over expression of p-53 in all its 4 (100%) cases with a score of 3+. It was found to be stastically significant. As shown in Table No.7 (Figure2, Figure3)

Table 7

P- 53 score	Well diff		Mod diff		Poorly diff		Type II	
	No.	%	No.	%	No.	%	No.	%
0	14	100	0	0	0	0	0	0
1+	0	0	3	100	1	5.3	0	0
2+	0	0	0	0	5	26.3	0	0
3+	0	0	0	0	13	68.4	4	100
Total	14	100	3	100	19	100	4	100

P= 0.000

It was also observed that P-53 expression was less in low grade (early stage) cases as only 3 out 17 cases showed P-53 expression whereas all 23 cases of high grade tumors were strongly positive for P-53 expression. The vale was found to be statistically significant. As shown in table 8.

Table 8

Histological Grade	P-53 Positive	(%)	P-53 Negative	Total
Low Grade (Early Stage)	3	17.64	14	17
High Grade (Advanced Stage)	23	100	0	23

P=0.000

3 plus positivity for p-53 in poorly differentiated endometrial adenocarcinoma. (IHC X 100) As shown by figure 2

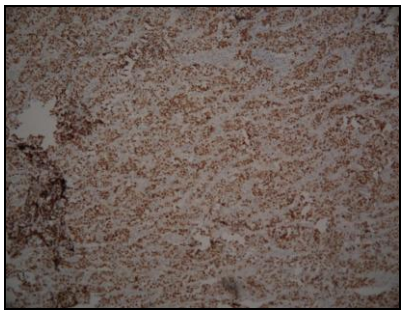

Fig 2

3 + positivity for p-53 in poorly differentiated endometrial adenocarcinoma.
(IHCX400) As shown by Figure 3

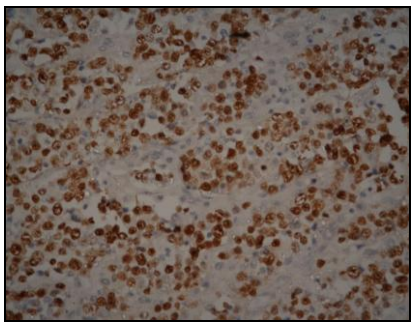

Fig 3

Discussion

In our study we found that median age for type I endometrial malignancies was 55.5 years. Whereas type II endometrial malignancies were seen in seventh decade. (Table1.)

In a study done by Kounelis *et al.* (2000) [4] it was observed that out of 61 cases of endometrial cancers the average age at presentation for type I endometrial cancer was 64.5 years and for type II endometrial cancer (uterine papillary serous adenocarcinoma) was 69.6 years respectively. The observation was consistent with our findings.

We also found that type I endometrial malignancies were more common as compared to type II endometrial malignancies. Many previous studies have also observed similar results.

The predominant clinical presentation in our study was post-menopausal bleeding which was reported in 44 (88%) cases (Table No. 2, 3).

Berek *et al.* (1994) [8] reported that ninety percent of patients with endometrial cancer presented with abnormal vaginal bleeding as the most common symptom. Colombo *et al.* (2013) [7] also reported that abnormal uterine bleeding was the presenting symptom in 90% cases of endometrial cancers. Pakish *et al.* (2016) [9] in a case control study on endometrial cancer associated symptoms observed that 84.8% of women with endometrial carcinoma presented with the complaint of postmenopausal bleeding.

The observation in our study was similar to these studies that postmenopausal bleeding was the most common clinical symptom in patient of atypical hyperplasia and carcinoma of endometrium.

In present study we included 50 consecutive cases of endometrial lesions, 10(20%) cases were of atypical hyperplasia and 40(80%) cases were of endometrial cancers. We observed that the most common risk factors observed in patients of atypical endometrial hyperplasia and endometrial carcinoma in present study were obesity (24%) and nulliparity (20%) and late menopause (20%) as shown in Table No.3

A case control study was conducted by Vecchia *et al.* (1984) [12] in Milan, Italy, on 283 women with endometrial cancer. It was observed that obesity was a major risk factor of endometrial cancer both in premenopausal and postmenopausal elderly women. The risk estimates being 20.3 and 7.7 respectively for the heaviest categories. Thus, concluding that obesity is the major cause of endometrial cancer in Northern Italy. According to the study early onset of menarche and nulliparity are also prominent risk factors of endometrial cancer in premenopausal women. The point estimate for nulliparity was 35.1. The use of noncontraceptiveestrogens was also associated with an increased risk of endometrial cancer. It was found to be greater in perimenopausal women with relative risk of 5.1 for more than 2 years of use and decreased progressively after menopause. It was also observed that late menopause was related to endometrial cancer. The risk estimates for late menopause were more raised in women older than or equal to 65 years. Austin *et al.* (1991) [13] conducted a study on 168 cases of endometrial cancer. They observed that a strong relationship between obesity and endometrial cancer existed. The relative rate of endometrial carcinoma for patients in the upper 90th percentile of a body mass index compared to those below the median was estimated to be 5.5 with 95% confidence limits of 3.2–9.6.Yang*et al.* (2015) [14] conducted astudy on 8153 cases of endometrial cancer.They observed that nulliparous women had a greater risk to develop endometrial cancer as compared to parous women (OR=1.76; 95% CI: 1.59-1.94). We also observed that risk factors commonly associated with endometrial hyperplasia and carcinoma like obesity, infertility and late menopause. However, as our study did not include any control group relative risk of these factors could not be calculated. However, this was not the primary aim of our study.

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. (Table4).

Kounelis *et al.* (2000) [4] 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.

In our study we observed that all the 10(100%) cases of endometrial hyperplasia were p-53 negative, 14 out of 36 type I endometrial cancer cases (38.9%) were p-53 negative and all the 4 type II endometrial carcinoma cases were p-53 positive (P = 0.00038). We also observed that all poorly differentiated cases and all type II endometrial cancers were p-53 positive. (Table No. 6, 7, 8).

In a study conducted by Sherman *et al.* (1995) [24] immunostaining for p53 protein was detected in 24 out of 28 (86%) type II endometrial carcinoma (serous carcinomas) compared with 9 out of 45 (20%) type I endometrioid carcinomas (*P*<.001). Strong P-53 positivity was also noticed in two clear cell carcinomas, 5 out of 6 mixed endometrioid/serous carcinomas and 7 out of 10(70%) malignant mixed mesodermal tumors. Benign endometrial tissue and 12 cases of atypical endometrial hyperplasia were p-53 negative. The 27 out of 34 (79%) tumors of endometrial intraepithelial carcinoma (EIC) were p53 positive. They concluded that mutation of p53 was unrelated to the development of endometrioid carcinoma from atypical endometrial hyperplasia but was significantly correlated to development of type II endometrial cancers. Geisler *et al.* (1999) [25] conducted a study on cases in which 103 patients had endometrioid adenocarcinoma; 6 patients were of adenosquamous carcinoma; 14 cases were of papillary serous carcinoma; 10 cases of clear cell carcinoma and 4 cases were of undifferentiated carcinoma. P-53 expression ranged from 0.0 to 58.2% positive nuclear area with a mean of 11.5%. In patients with endometrioid carcinoma, the mean p53 expression was 7.1% whereas in nonendometrioidtumors it was 24.6% *(P*<0.001). They observed that 59 out of 103 (57.3%) endometrioidtumors stained positive for p53 while 32 out of 34 (94.1%) nonendometrioidtumors stained p-53 positive (*P*<0.001). They postulated that increasing histologic grade correlated with an increasing p53 expression (P = 0.003). The percentage of tumors expressing p53 was found to be higher in FIGO stage III, and IV than in FIGO stage I and II cancer (P = 0.003).

These observations were similar to findings observed in present study that p-53 positivity is commonly seen in Type II tumors and high grade tumors confirming the role of p-53 in carcinogenetic model of type II tumors and also probably responsible for higher aggressiveness of tumor

Conclusion

All the 10 cases of endometrial hyperplasia were p-53 negative. Poorly differentiated tumors (68.4%) and all type II endometrial cancer cases (100%) were strongly positive for p-53.

Endometrial hyperplasia cases were p-53 negative. Whereas poorly differentiated tumors were strongly positive for p-53 as compared to well differentiated tumors.

Hence suggesting that p-53 strong expression signifies tumor in advanced stage Type II endometrial cancers strongly expressed p-53 and hence showing the advanced stage of the disease and also suggesting the evolution of tumor through p-53 gene mutation.

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