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EXPRESSION OF P53 IN NORMAL, HYPERPLASTIC AND NEOPLASTIC LESIONS OF ENDOMETRIUM

Histopathology

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ABSTRACT

Background One of the most prevalent gynaecological cancers in developed nations is Endometrial Carcinoma. Endometrial hyperplasia, Atypical Endometrial Hyperplasia and finally fully developed, well-differentiated Adenocarcinoma are regarded to be the progression of premalignant lesions into Endometrial Carcinoma. The p53 signalling pathways are crucial in the development of Endometrial Cancer. Expression of p53 is associated with Atypical Endometrial Hyperplasia and Endometrial Carcinomas. **Aim & Objective** To study the expression of p53 as molecular biomarker in Normal, hyperplastic and neoplastic lesions of endometrium. **Material & Methods** A total of 50 cases of endometrial biopsies were collected over a period of 18 months from January 2020 to June 2021. Samples were received and reported in Department of Pathology Gandhi Medical College, Bhopal, Madhya Pradesh. **Results** A total of 50 cases of endometrial lesion were studied. p53 expression was observed in 80% cases of the Endometrial Carcinoma and 50% cases of Atypical Endometrial Hyperplasia. It was mostly negative in Normal and Endometrial Hyperplasia. Expression of p53 in Atypical Endometrial Hyperplasia and Endometrial Carcinomas helps to detect the progression and predicting the response to targeted therapies against carcinogenic pathways. **Conclusion** p53 expression is mainly seen in Endometrial Cancer and Atypical Endometrial Hyperplasia. And it is almost absent in Normal and Endometrial Hyperplasia. The dysregulation appears to be most evident in the Atypical Endometrial Hyperplasia. This expression pattern suggests that p53 over-expression could be the origin of endometrial cancer.

KEYWORDS

P53, Endometrial Carcinoma, Immunohistochemistry

BACKGROUND

One of the most prevalent gynaecological cancers in developed nations is endometrial carcinoma. Endometrial carcinoma is now the fourth most common cancer and the seventh most common cause of cancer deaths in women in India, despite the fact that the prevalence is lower than in industrialised nations.[1]

Postmenopausal women are more likely to develop endometrial carcinomas. Less than 25% of premenopausal women are affected. Endometrial cancer development and oestrogen exposure have a well-established significant correlation. Obesity, diabetes, hypertension, infertility, and nulliparity are among the risk factors.[2]

The histology of the normal endometrium is characterised by a well-controlled hormone dependant menstrual cycle.[3] The proliferative lesions of endometrium comprise of endometrial hyperplasia which may be associated with or without atypia. In many cases hyperplasia predisposes a carcinoma.[4] About 70-80% of type I endometrial adenocarcinoma cases occur on a background of endometrial hyperplasia which along with endometrial intraepithelial neoplasia is considered as a precursor lesion.[5]

Endometrial carcinomas are divided into Type 1 (estrogen-dependent) and Type 2 (estrogen-independent) subtypes, with Type 1 typically having endometrioid morphology and Type 2 having serous/clear cell morphology.[6]

Endometrial hyperplasia, Atypical Endometrial Hyperplasia and finally fully developed, well-differentiated adenocarcinoma are regarded to be the progression of premalignant lesions into endometrial carcinoma.[7]

Endometrial hyperplasia is a setting for endometrial cancer of the endometroid type, which has a favourable prognosis and primarily affects postmenopausal women. Contrarily, the non-endometroid type endometrial adenocarcinoma has a poor prognosis and develops in the context of an atrophic endometrium.[8] Recent advancements have been made in the analysis of other molecular prognostic and predictive markers, such as PTEN and P53. [8] A new area of research into the gynaecological malignancy gene profile opens up for the improvement of years of survival rates through early diagnosis and better prognosis. In the last decades, studies aimed at analysing the human genome identified additional factors, particularly in molecular and cellular level concerning the pathogenesis of endometrial carcinoma.[9]

Specifically, several DNA mutations concerning proteins involved in mechanisms of cell signal transduction and communication have been investigated.[9] The P53 protein is involved in gene transcription, DNA synthesis and repair, genomic plasticity, and apoptosis. [9,11] Mutation of P53 is commonly observed in serous papillary endometrial carcinomas, as well as 10-15% of early and 40- 50% of advanced endometrioid endometrial carcinomas. [11] Its identification is associated with poor prognosis. [13]

The P53 signalling pathways are crucial in the development of endometrial cancer. The idea that both types of endometrial carcinomas (endometroid and non-endometroid type) involve various molecular carcinogenic pathways is supported by tumour suppressor genes including PTEN, P53, and Kras. [3]

Previously studies have been done about the expression of p53. Expression of p53 is associated with atypical endometrial hyperplasia and endometrial carcinomas. Hence studying these markers will aid in early diagnosis and thereby affecting the outcome.

The aim of this study is to analyse the immunohistochemical expression of P53 in normal, hyperplastic and neoplastic lesions of endometrium.

METHODS-

This was a cross sectional study (retrospective and prospective). Fifty paraffin-embedded endometrial tissue samples diagnosed as: Normal endometrium, endometrial hyperplasia including Endometrial hyperplasia (EH) and Atypical Endometrial Hyperplasia (AEH) and Endometrial Carcinoma (ECA) were collected from Department of Pathology of Gandhi Medical College and associated Hospital, Bhopal, Madhya Pradesh.

Inclusion Criteria :

1. All the samples tissues of endometrium received in 10 % formalin with requisition form received in the department of pathology for histopathological evaluation.
2. Cases with predisposed risk factors for the Endometrial Carcinoma are considered for the study.

Exclusion Criteria:

1. Biopsies with tissue insufficient for histopathological evaluation.
2. Autolyzed samples.

The evaluation of p-53 was done according to the method described by Quin et al. (2002). [25] 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. 1+ when 10-30% of tumor cells were stained, 2+ when 31-50% tumor cells expressed p-53 positivity and 3+when>50% were p-53 positive.

P value < 0.05 was considered significant.

RESULTS-

In the present study, the age of the patients ranged from 25-70 years with a mean age being 41.5 years.

Table 1- Mean age of EH, AEH, ECA

	MEAN AGE (YEARS)
EH	39.4
AEH	44.8
ECA	57.4

Most common chief complaint was AUB (40%) followed by post menopausal bleeding and infertility. Amongst the associated risk factors, history of OCP (36%) intake was most common followed by early menarche, hypertension.

Table 2- Case wise distribution

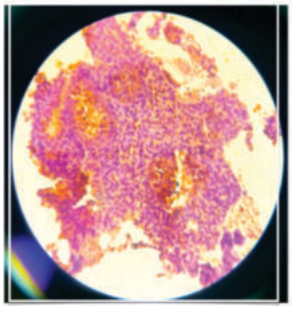
PP	16 (32%)
SP	08 (16%)
EH	15 (30%)
AEH	06(12%)
ECA	05 (10%)
TOTAL	50 (100%)

A total of 50 cases were considered with 16 cases (32%) were there in proliferative phase and 8 (16%) cases in secretory phase. 15 cases (30%) were found in the group Endometrial Hyperplasia. 6 cases (12%) were reported in the group Atypical endometrial hyperplasia 5 cases (10%) belonged to endometrial carcinoma group.

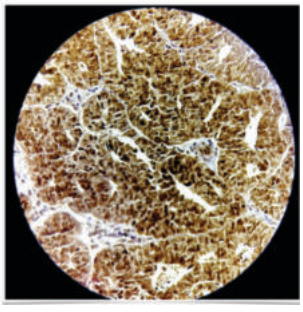
TYPE OF ENDOMETRIUM	NEGATIVE	POSITIVE
PP	15 (93.7%)	01 (6.3%)
SP	08 (100%)	00 (0%)
EH	13 (86%)	02 (14%)
AEH	03 (50%)	03 (50%)
ECA	01(20%)	04 (80%)

pValue <0.05

P53 Expression in Atypical Endometrial hyperplasia



P53 Expression in Endometrial Carcinoma



In PP 93.7% cases showed negative expression of p53 and 6.3% cases showed positive expression. In SP 100% showed negative expression of p53. In EH 86% showed negative expression of p53 and 14% showed positive expression. In AEH 50% showed negative expression and rest 50% showed positive expression. In ECA 20% showed negative expression and 80% showed positive expression.

DISCUSSION-

Endometrial carcinoma is the fifth most common cancer of women worldwide.[16] Based on clinico-pathologic observations, there are two types of endometrial carcinoma: Type-I usually arising in the background of endometrial hyperplasia and Type - 2 which is unrelated to estrogen.[17] Hyperplasia comprises a heterogenous group of lesions, considered by some to be reversible and others, to be truly neoplastic, so attempts have been made to sub classify them in a biologically and clinically useful way in order to predict their precancerous behaviour. [22] Endometrial hyperplasia is classified by the WHO into two groups, namely Endometrial hyperplasia & Atypical Endometrial hyperplasia. The pathogenesis of endometrial carcinoma and its precursor lesion is complex and involves many molecular disturbances. [18] Development of endometrial carcinoma involves stepwise acquisition of several genetic alterations in tumour suppressor genes and oncogenes. Due to the ability of estrogen and its metabolites to cause DNA damaging events, they are associated with greater risk of developing endometrial cancers. [19] Excessive cellular proliferation is induced by p53 overexpression which is a feature of many types of cancers, including endometrial cancers. [20,21]

In the present study, p53 immunoreactivity was detected in the majority of endometrial carcinoma and AEH but none in EH and normal proliferative endometrium. P53 Immunostaining was assessed and graded according to the slide area stained.

In our study all the cases of proliferative phase, secretory phase, endometrial hyperplasia were negative for p53 reaction. However, 50% cases of AEH showed expression and 80% cases diagnosed as ECA expressed p53 gene.

In a study done by Kirti et al it was 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). [14]

In a study conducted by Sherman et al. (1995) [23] 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<0.001). 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) [15] 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 non-endometrioid tumors it was 24.6% (P<0.001). They observed that 59 out of 103 (57.3%) endometrioid tumors stained positive for p53 while 32 out of 34 (94.1%) non-endometrioid tumors stained p-53 positive (P<0.001). They postulated that increasing histologic grade correlated with an increasing p53 expression (P = 0.003).

These observations were similar to findings observed in present study that p-53 positivity is commonly seen in ECA confirming the role of p-53 in carcinogenetic model and also probably responsible for higher aggressiveness of tumour.

Ellenson et al in 2019 observed that the missense mutations were found to correlate with intense, diffuse immuno histochemical staining for p53; by contrast, a complete lack of staining (null pattern) for p53 was indicative of nonsense or frame shift mutations [24]

CONCLUSION

The current study supports the notion that p53 over-expression is an early event in endometrial carcinogenesis.

p53 expression is mainly seen in endometrial cancer and atypical endometrial hyperplasia. And it is almost absent in normal and endometrial hyperplasia.Other modifications may be to blame for the unique morphological traits and behaviour of hyperplasia with atypia and carcinoma. The dysregulation appears to be most evident in the

atypical endometrial hyperplasia. This expression pattern suggests that p53 over-expression could be the origin of endometrial cancer.

To sum up, p53 is a useful marker in detecting pre-malignant lesion (Atypical Endometrial Hyperplasia) and Endometrial Carcinoma timely for early intervention and proper treatment which will increase the survival of the patient. Thereby decreasing morbidity and mortality.

Competing Interests

The authors declare that they have no competing interests.

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