Section: Pathology

Original Research Article

EXPRESSION OF P53 AND E-CADHERIN IN ENDOMETRIAL CARCINOMA AND ITS HISTOPATHOLOGICAL CORRELATION

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Abstract

Background: Endometrial carcinoma is one of the commonest cancers in women. E-cadherin and p53 had an important role in predicting the prognosis of endometrial carcinoma. This is study to objective is to evaluate the expression of p53 and E-cadherin in all diagnosed cases of endometrial carcinoma and to correlate them histopathologically. **Materials and Methods:** We collected a total of 53 cases and subjected them to immunohistochemistry. We analysed 46 cases of endometrioid type carcinoma and 7 cases of non-endometrioid type. We assessed the significance of the association between the expression of the markers and clinicopathological parameters. **Result:** Significant association of E-cadherin overexpression with endometrioid type (P=0.001). However, neither HER2 nor p53 showed the same association. The association between P53 and high grade was significant (P=0.02). There was a statistically significant link between myometrial invasion and either P53 expression or E-cadherin expression (P=0.01, 0.03). There was a significant, considerable negative correlation between E-cadherin and p53 expression. **Conclusion:** E-cadherin expression is a better predictor of the prognosis of endometrial cancer than the proliferation marker p53. In the future, IHC testing and scoring guidelines that are specific to endometrial cancer will need to be made to reflect the unique biology and pathogenetic features of these tumours.

INTRODUCTION

Human endometrium has a tremendous proliferative and regenerative potential. Hormones from the ovaries and pituitary gland cause the endometrium to break down during menstruation, which is typical for a hormonal two-phase endometrium.[1,2] Endometrial proliferation rearrangements caused by long-term oestrogen stimulation include a lot of different problems with a lot of different shapes and sizes.[3,4] Several types of pathologic proliferation begin with slight differences from the late proliferative phase endometrium and progress to complex types that are difficult to distinguish from carcinoma.[5] The most probable hypothesis of endometrial cancer aetiology is based on prolonged oestrogen stimulation of the endometrium of genetically prone women, characterized by histopathological lesions designated as endometrial hyperplasia.[6] It is accepted that there is a continuum of changes that evolve to endometrial carcinoma. Endometrial carcinoma is the most common invasive neoplasm of the female genital tract and the fourth most frequently diagnosed cancer in women worldwide. The 14thmost common cancer overall.[7,8] There are two main types of endometrial carcinoma, which are called Type I and Type II.[9] These are based on clinical, pathological, and molecular genetics features. Histopathology serves as the primary diagnostic method. IHC (immunohistochemistry) can help tell the difference between some types of type-1 and type-2 endometrial carcinomas that have similar morphological features. Several markers help in the diagnosis, like p53, PTEN, p16, and ARID 1A.[10] p53 protein was first discovered as a 53-k Dalton protein from SV40-transformed cells.[11] It had been thought that p53 was an oncoprotein; however, p53 was recognised as a tumor suppressor protein.[12] p53 plays an important role in the regulating of cell proliferation, DNA repair, apoptosis, genomic stability, senescence, and metabolic homeostasis.[13] Several signals, including DNA damage, low oxygen, oncogene expression, ribonucleotide depletion, and osmotic stress, can make the p53 protein work. Its main job is to control transcription. When DNA is damaged, p53 induces the expression of p21. The chemical P21 stops cyclin-

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dependent kinase (CDK) complexes from working, which stops the cell cycle in the G1 phase. G1 arrest can allow DNA repair before replication at S1.[13,14] E-cadherin is a molecule that needs calcium to work. Its molecules are necessary for making and keeping adherent junctions between epithelial cells. Loss of its expression in type-2 endometrial carcinomas is linked to the cancer's ability to spread and its poor prognosis.[15,16] This study looks at the expression of p53 and E-cadherin in all cases of endometrial carcinoma that have been diagnosed. The expression of these proteins is linked to histopathology to help tell the difference between the two types.

Aims and Objectives

To perform the expression of p53 and E-cadherin in all diagnosed cases of endometrial carcinoma and to correlate them histopathologically.

MATERIALS AND METHODS

The study was conducted in the Department of Pathology, Government medical college and general hospital, Mahbubabad and VSN labs, during the period of 16 months, i.e., from August 2023 to December 2024, on endometrial curettage and hysterectomy specimens that were received in the Department of pathology.

Inclusion criteria

Endometrial curettage and hysterectomy specimens of all diagnosed cases of endometrial carcinoma. Only samples with adequate tissue material and definitehistopathological diagnosis were included. Representative areas in the biopsies were only included.

Exclusion criteria

All cases of inflammatory lesions, stromal lesions, and hemorrhagic and necrotic samples were excluded.

Specimen handling

All curettage and hysterectomy specimens were fixed in 10%neutral buffered formalin. After adequate fixation, examination of the specimen for gross details was done. Then representative tissue bits were taken and subjected for routine processing and paraffin embedding. Three to Four microns' thick sections were taken from the paraffin embedded blocks. These sections were routinely stained with haematoxylin and eosin (H&E) and were examined. Histopathological features were noted and the tumors were typed according to the WHO classification system. The paraffin blocks of the samples which had met the inclusion criteria were collected. The details of each case like biopsy number, Age, Histopathological diagnosis, etc were noted. A total of 53 cases were collected and subjected to immunohistochemistry. Endometrioid type carcinoma 46 cases and non- endometrioidtype 7 cases were analyzed.

Immunohistochemical (IHC) assessment

All cases were studied for histomorphology and IHC by experienced pathologists independently. Brown stain in the cytoplasm is considered positive. In the endothelium of the capillaries present in the examined sections (positive internal controls), consistent staining of cytoplasm was noted. Tumor cells with positive cytoplasmic staining were considered positive. Cytoplasmic staining of neoplastic cells showing moderate-to-high intensity was considered positive. Weak or equivocal staining was excluded. p53 and E-cadherin expression was evaluated using a semi quantitative scoring method and scored as 0 (no staining), 1 (singular positive cells, ≤1%), 2 (>1–25%), 3 (26-50%), and 4 (>50%), which was comparable to that proposed earlier by Manocha and Jain.[17] For counting the immunopositive cells, 10 high-power (40×) fields were selected and systematically randomized throughout the section. The correlation of p53 and E-cadherin expression and histological grade was calculated.

Statistical Analysis

Descriptive statistics were analyzed with SPSS version 17.0 software. Continuous variables are presented as mean (min-max). Categorical variables are expressed as frequencies and percentages. The Pearson Chi-square test or the Chi-square test of association was used to determine if there is a relationship between two categorical variables. Probability (P) values <0.05 were considered statistically significant.

RESULTS

A total of 53 endometrial biopsy or hysterectomy specimens from patients with endometrial adenocarcinoma were examined. Minimum age of the patients was 40 years and maximum age of the patient was 82 years. Mean age was (59.26 ±9.25).

Expression of p53 was assessed in all the diagnosed cases using a cut-off level for stratification of patients into high-risk and low-risk groups. Immunoreactivity for p53 was scored by counting the number of positively stained tumor cell nuclei and expressed as percentage of the total number of tumor cell nuclei counted (p53 index). Strong immunoreactivity (p53 index >or =50%) is seen in 13 cases and about40 cases showed (p53 index >or =5% and <50%). Expression of E-cadherin showed weak intensity of staining in about 6 cases out of total 53 cases. Endometrioid (Type-I) of 46 (86%) cases. Non Endometrioid (Type-II) of 07(14%)cases. Table-1 shows age distribution of type I and type II endometrial carcinoma.

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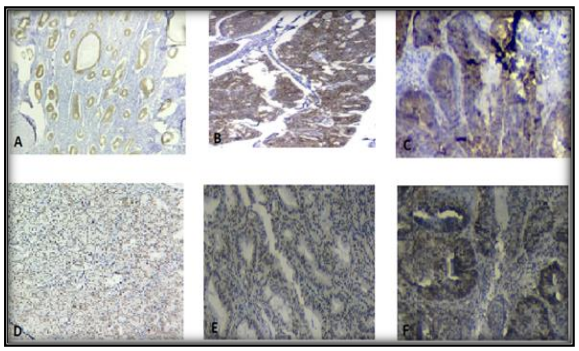

Figure 1: Endometrial carcinoma. A= Normal endometrium –IHC E-Cadherin (10x); B= Storn +ve, IHC E- Cadherin (40X); C= B= Moderate +ve, IHC E-Cadherin (40X); D=Normal Endometrium- IHC P53 (10X); E=IHC -p53 normal expression (40X); F=IHC -p53 –over expression (40X)

The association of expression of the two markers E-Cadherin and p53 known clinicopathological predictors of the prognosis of endometrial carcinoma are investigated and summarizedin [Table 2].

[Table 2] showed the number of E- Cadherin, and p53 type-I and type-II patients in each age group, histological group. Expression of the two markers was not significantly related to the age groups. However, the expression of E-cadherinis significantly higher in endometrioid type as compared to either non-endometrioid (papillary serous and clear cell) carcinomas or carcinosarcoma (P=0.003). On the other hand, endometrioid carcinoma was not significantly related to expression of either p53 (P=0.00037).

Table 1: Age distribution of type I and type II endometrial carcinoma.

Age	Type I	Type II	Total
40-49	17 (32%)	1 (2%)	18 (34%)
50-59	24 (45.2%)	3 (5.6%)	27 (51%)
>60	5 (9.4%)	3 (5%)	8 (15%)
Total	46	7	53

Table 2: Intensity &extent of E-cadherin and p53 immunopositivity

	Type I [N= 46 (86.7%)]	Type II [N= 7 (13.3%)]	P-value
Intensity of p53 immunopositivity			
Score 0-4	29 (54.7%)	1 (1.9%)	0.003
Score 5-8	10 (18.9%)	1 (1.9%)	
Score 9-12	7 (13.2%)	5 (9.4%)	
Intensity of E-cadherin immunopositivity			
Score 0-4	2 (3.7%)	4(7.7%)	0.00037
Score 5-8	5 (9.4%)	2 (3.9%)	
Score 9-12	39 (73.5%)	1 (1.8%)	
Extent of E-cadherin immunoreactivity			
Strong +ve	39 (73.5%)	1 (1.8%)	0.002
Moderate +ve	5 (9.4%)	2 (3.9%)	
Weak+ve	2 (3.7%)	4(7.7%)	

DISCUSSION

Endometrial carcinoma is the most common invasive neoplasm of the female genital tract; the most probable hypothesis is based on prolonged estrogen stimulation of endometrium of genetically prone women, characterized by histopathological features designated as endometrial hyperplasia.[18,19] It is accepted that there is a continuum of changes that subsequently evolve to endometrial carcinoma. The associated risk factors are hyperestrogenism, obesity, HRT, family H/o, Type-2 diabetes, endometrial hyperplasia in the past.

Type 1 cancers are usually not very aggressive and they don't metastasize quickly. Type 1 endometrial cancers are thought to be caused by too much estrogen. They sometimes develop from atypical hyperplasia, an abnormal overgrowth of cells in the endometrium.

Many studies have investigated the molecular basis of endometrial carcinoma, involving carcinogenesis, invasion and metastasis. Many new biomarkers that have diagnostic and prognostic value had been discovered. Therefore, the present study investigated the expression of E- Cadherin, and p53 in endometrial carcinomas to get information about the pathogenesis and to find a prognostic biomarker for endometrial carcinoma.

Expression of E-cadherin is not only critical for the regulation of intercellular cohesiveness, but also for the regulation of the apoptosis of tumor cells. In many malignancies, decreased E-cadherin expression is associated with defective cell– cell adhesiveness, resulting in invasion and metastasis (Buda et al., 2011.[20]

P53; a tumor suppressor gene is normally expressed in Type-1, having a mixture of weakly +ve, strongly +ve stained tumor cell nuclei; whereas it is abnormally expressed in Type-2 carcinomas having either over expression or complete absence.[21,22] The tumors having an over expression had a worst outcome and is included in the present study.

Expression of E-cadherin subsequently showed decreased patterns of staining like moderate +ve or weak +ve; in type-2 carcinomas inturn indicating its invasiveness and adverse prognosis.

p53 was scored by counting the number of positively stained tumor nuclei and expressed as the percentage

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of the total tumor cell nuclei counted (p53 index). Patients with strongly p53 immunoreactive tumors (p53 index >or =50%) had a significantly worse outcome than patients with weak immunoreactivity (p53 index>or=5% and <50%) or p53- negative (p53 index <5% tumors) inType-1 endometrial carcinomas.

Basically, E- cadherin has a major role in establishing cell polarity and in maintaining normal tissue architecture. When the expression of E- cadherin is lost, the degree of tumor differentiation is decreased and the possibility of distant metastasis increases, suggesting the role of Ecadherin is inhibiting tumor invasion or metastasis.[23] However, in the present study there was no significant association between E-cadherin expression and the grade of endometrial carcinoma (P=0.08). This unexpected result can be explained by most of the high grade cases in this study detected by high nuclear grade more than the architecture. Also this result could be referred to the presence of expressed but dysfunctional E- cadherin in high grade carcinoma.

Significant association of E-cadherin expression with both myometrial invasion (P=0.01) and FIGO staging (P=0.01) was found. This result confirms the role of Ecadherin in invasion and metastasis. Also Pećina-Šlaus et al. noticed that there was significant association between Ecadherin expression and the depth of invasion and tumor stage.[23]

In the present study over expression of p53 was assessed in all the diagnosed cases using a cut-off level for stratification of patients into high-risk and low-risk groups. Immunoreactivity for p53 was scored by counting the number of positively stained tumor cell nuclei and expressed as percentage of the total number of tumor cell nuclei counted (p53 index). Strong immunoreactivity (p53 index >or =50%) is seen in 13 cases and about 40 cases showed (p53 index >or =5% and <50%). Expression of E-cadherin showed weak intensity of staining in about 6 cases out of total 53 cases. Endometrioid (Type-I) of 46 (86%) cases. Non Endometrioid (Type-II) of 07(14%) cases.

E- Cadherin, and p53 type-I and type-II patients in each age group, histological group. Expression of the two markers was not significantly related to the age groups. However, the expression of E-cadherin is significantly higher in endometrioid type as compared to either non-endometrioid (papillary serous and clear cell) carcinomas or carcinosarcoma (P=0.003). On the other hand, endometrioid carcinoma was not significantly related to expression of either p53 (P=0.00037. This result was in agreement with Ioffe OB et al,[24] which reported that inverse correlation between E- cadherin and mutant p53 expression in advanced endometrial cancer.

This positive correlation was attributed to the fact that mutant p53 expression, a known regulator of proliferation, but also of apoptosis, was associated with a significantly worse survival only in the subgroup of endometrioid carcinomas. And the proliferation doesn't affect the prognosis of endometrial cancer. Paradoxically Ecadherin expression was also associated with a significantly better patient survival.[25,26]

CONCLUSION

E-Cadherin expression is good predictor of the prognosisof endometrial cancer than proliferation markerp53 due to the significant correlation withthe known predictors of prognosis. Decreased intensity of E-Cadherin staining is seen with Type-2 endometrial carcinoma. The present study supported the significance of immunostaining patterns of both p53 and E-Cadherin in differentiating endometrioid andnon-endometrioid types of endometrial carcinomas, favouring accurate diagnosis and poor prognosis of type-2 endometrial carcinoma. A case without positive internal control is considered non interpretable.

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