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Original Research Article

Expression of E-Cadherin, Her2/neu, and P53 in endometrial carcinoma: Relation to different clinicopathological predictors of the prognosis

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Abstract

Background: Endometrial carcinoma is one of the commonest cancers in woman. E Cadherin, Her2/neu, and P53 had an important role in predicting the prognosis of endometrial carcinoma. The objective is to evaluate expression of E-cadherin, HER2/neu and p53 in Endometrial Carcinoma and to find their relationship with clinicopathological characteristics. Material and Methods: 92 specimens were tested for E- cadherin, HER-2/neu and p53 expression using immunohistochemical analysis. The significance of association of expression of the markers with clinicopathological parameters was assessed. Results: Significant association of E- cadherin overexpression with endometrioid type (P=0.001). While this was not the case as regard HER2 or p53. P53 was significantly related to high grade (P=0.02). There was statistically significant association between myometrial invasion and either E- cadherin expression or P53 (P=0.01, 0.03) respectively. There was significant considerable negative correlation between E- cadherin and p53 expression (P=0.000, co: -0.428). Conclusion: E- cadherin expression is good predictor of the prognosis of endometrial cancer than proliferation marker HER2/neu or p53. Endometrial cancer–specific HER2 IHC testing and scoring guidelines need to be developed in the future to reflect the unique biology and pathogenetic features of these tumors.

Keyword: Endometrial carcinoma, endometrioid, E Cadherin, Her2/neu, and P53

INTRODUCTION

Endometrial Carcinoma (EC) is the fourth most common cancer in women. About 90% of this tumor is sporadic and 10% is hereditary (Waqar et al., 2018). The incidence rate of EC in the last decades is markedly increased attributable at least in part to global epidemic of obesity (Sheikh et al., 2014). The increased use of estrogen products in the treatment of post-menopausal symptoms may have resulted in increased emergence of endometrial cancer (Waqar et al., 2018).

Bokhman et al. in 1983 described two types of EC, Type-1 and Type-2 which are different in their etiology, clinical behavior and treatment modalities (Bokhman, 1983). There was emergence of another group that is mixture of these two. Also another group has carcinomas like Carcinosarcoma which are high grade and poorly differentiated (Waqar et al., 2018).

Traditionally, the majority of tumors (approximately 80% to 90%) classified as type I endometrial carcinoma arise in the background of unopposed estrogen stimulation due to obesity or an ovulatory cycles (Buza et al., 2014). Type I tumors are often preceded by endometrial hyperplasia. Commonly it shows low-grade (grade 1 or 2) endometrioid morphology, and generally expresses estrogen and progesterone receptors. Patients with type I tumors are usually younger

(premenopausal or perimenopausal), present at an early stage, and have a favorable clinical outcome. Type II tumors, on the other hand, typically occur in older patients in the background of endometrial atrophy, are not related to hormonal factors, and are characterized by high histologic grade and serous or clear cell morphology (Bokhman, 1983; Buza et al., 2014).

Uterine serous carcinoma (USC) is the most biologically aggressive variant of endometrial carcinoma, with predilection for deep myometrial and Lymphovascular space invasion, as well as peritoneal and distant metastatic spread. Although USC represents only approximately 10% of endometrial carcinomas, it has been shown to account for a 50% of relapses and 40% of endometrial cancer deaths. Peritoneal spread occurs early in the course of disease and may even be present in up to 45% of tumors without myometrial invasion (minimal USC) (Buza et al., 2014).

However, recent evidence indicates that EC are more heterogenous than previously thought. Molecular analyses derived from the Cancer Genome Atlas study subdivide them into four categories: cancers with low mutation rates and low frequency DNA copy number alterations, hypermutated cancers with mismatch repair defects, ultramutated cancers with polymerase epsilon (*POLE*) mutations, and cancers with low mutation rate but high frequency DNA copy number alterations (Suarez et al., 2016; Talhouk et al., 2015). The first 3 molecular categories predominately correspond to endometrioid histology, whereas the fourth group corresponds largely with serous or serous-like carcinomas (Piulats et al., 2016).

HER2 is a known member of the epidermal growth factor receptor family. It is expressed in different malignant tissues and generally indicates poorer prognosis and more aggressive cancers. HER2 status has been previously studied in EC and it was shown that overexpression was associated with a shorter overall survival mainly in advanced disease stage, high-grade tumors, and especially non-endometrioid cancers (Abdel Azim et al., 2017). In type II ECs, HER2 expression was found in up to 40% of cases, whereas in type I cancers it is rarely seen (Grushko et al., 2008).

E-cadherin has been shown to play a central role in the organization and maintenance of epithelial tissue structure. Decreased cell-to-cell contact in epithelial cells has been shown to be largely attributable to down-regulation in the expression of E-cadherin (Holcomb et al., 2002). Decreased E- cadherin expression has also been associated with decreased cell-to-cell adhesion and increased invasive and metastatic potential in endometrial and other carcinomas (Yalta et al., 2009).

The human *TP53* gene encodes a nuclear protein that induces growth arrest and apoptosis in response to both endogenous and exogenous stressors. Functional inactivation of p53 proteins plays a crucial role in malignant transformation, as p53 inactivation provides the tumor cell with a higher capacity for division and proliferation. Immunohistochemistry is a common method for assessing *TP53* mutation status because mutant p53 proteins are not degraded and accumulate in the nucleus. Wild-type *TP53* is also stabilized by several physiological stimuli, resulting in positive staining in the absence of a mutation. P53S was more frequently detected in non-endometrioid tumors than endometrioid tumors (González-Rodilla et al., 2013; Nguyen et al., 2015).

Endometrial carcinoma having high incidence and prevalence and increasing death rates world-over. This fact motivates one to investigate and search for targeted treatment modalities as surgery and chemotherapy have significant morbidity (Waqar et al., 2018).

The rationale of this study is to investigate the expression HER-2/*neu*, E- cadherin, and P53in endometrial carcinoma and analyze their association with the clinicopathological parameters of EC including histological type, grade and stage of the tumor and its significance in prediction of the prognosis of EC.

MATERIAL AND METHODS

Patients and Specimens

92 specimens of endometrial carcinomas were selected from the surgical samples (total abdominal hysterectomy) received at pathology lab. of El Galaa Teaching Hospital between 2006 and 2017. The Ethical Committee of our hospital approved the study protocol. Clinical data including patient age, menopausal state vaginal bleeding, abdominal pain and lower abdominal mass, tumor grade and stage were extracted from the hospital database and patient records. Patients were randomly selected on the basis of tissue availability. This was required for the IHC procedure to determine HER2, p53 and E- cadherin expression. We did not exclude patients on the basis of age.

Hematoxylin and eosin-stained slides (cut from formalin fixed, paraffin wax-embedded specimens) were retrieved from the archive of pathology lab of El Galaa Teaching Hospital. Then they revised by 3 pathologists and reassessed as regard the grade, stage and WHO histopathologic type. Clinical tumor stage was retrospectively determined on the basis of postsurgical pathology reports and assessed according to the 2009 FIGO classification (Werner et al., 2012). Histology was classified according to WHO 2014 criteria (Lax, 2016).

Tissue Microarray Construction

A manual tissue microarray (TMA) was performed using a mechanical pencil tip method of Shebl et al. (2011) and Soliman and Yussif (2016). Cores from the surrounding

normal endometrial tissue were also taken as an internal control.

Immunohistochemistry

IHC examination was performed using a Ventana Benchmark Ultra machine automated staining system. The primary antibody used was HER-2/neu (clone 4B5, rabbit monoclonal primary antibody) (Ventana, Tucson, AZ, USA), E- cadherin (clone EP700Y, rabbit monoclonal primary antibody) (Ventana, Tucson, AZ, USA), and p53 (clone DO-7, rabbit monoclonal primary antibody) (Ventana, Tucson, AZ, USA).

Check for accuracy through positive internal controls for E- cadherin, HER-2/neu, and p53 in normal endometrial tissue. Negative controls were also prepared by PBS instead of primary antibody.

Interpretation of immunohistochemical staining

E- Cadherin Immunostaining

In general, there are four different staining patterns for E-cadherin: depending on the distribution of staining and either membranous or cytoplasmic or both. Yalta. Et al 2009 reported that the four pattern are negative, diffuse linear, (crisp membrane staining is seen in > 75% of tumor cells in the absence of cytoplasmic staining); diffuse granular (membrane and cytoplasmic staining is seen in 26 –100% of the tumor cells); and focal granular (membrane and cytoplasmic staining is seen in 5 – 25% of the tumor cells). In our study, specimens were classified as positive when ≥ 5% of the tumor cells showed staining for E- cadherin and as negative when < 5% of the tumor cells showed staining, irrespective of pattern (Yalta et al., 2009).

Her-2/neu immunostaining

The scoring of HER-2/*neu* was done according to American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) guidelines. For the overexpression of the protein HER-2/*neu*, immunohistochemistry was done on selected representative slides of the tumor. HER-2/*neu* cases were taken positive when there was complete membranous staining of more than 30% of the tumor cells (Score 3+). The cases with no staining (Score 0) or weak incomplete membrane staining in any proportion or weak complete membranous staining in <10% cells (Score 1+) was considered negative. Incomplete and/or weak/moderate staining within >10% of the cells or complete / circumferential intense staining in <10% cells (Score 2+) was considered as borderline /equivocal (Waqar et al., 2018; Xu et al., 2010).

P53 Immunostaining

The intensity of nuclear staining was scored as negative (0) weak (1). moderate (2) or strong (3) The N-LI was scored as less than 10% (0), from 10 to 25% (1), from 26 to 50% (2), or greater than 50% (3). The final score was calculated of the addition of both partial scores (Norimatsu et al., 2013). The p53S was defined as the presence of morphologically benign appearing endometrial epithelial cells, with either a glandular or surface growth pattern, with moderate to strong intensity of p53 (Nguyen et al., 2015).

Statistical Analysis

Data of all cases were arranged, coded, and analyzed using SPSS version 20 (IBM). Descriptive statistics was presented as mean±standard deviation and frequency (number-percent). Chi square test (χ2-value) was used for intergroup comparison of categorical data. The IHC expression of E- cadherin, HER-2/ neu, and p53 were correlated with clinical and pathological parameters that predict the prognosis of endometrial carcinoma, including age, histological type, grade of tumor, FIGO staging, myometrial invasion, lymphovascular and perineural invasion. Spearman's and Pearson's coefficients were used for the correlation analyses between E-cadherin, HER-2/ neu, and p53.

RESULTS

A total of 92 endometrial biopsy or hysterectomy specimens from patients with endometrial adenocarcinoma were examined. Minimum age of the patients was 11 years and maximum age of the patient was 83 years. Mean age was (58.26 ± 10.94). The clinicopathological and immunohisto-chemical characteristics of the study cases were illustrated in table 1.

This study was done on 92 cases of endometrial carcinoma. 80 cases aged 50 years old or more. 12 cases aged less than 50 years old. 67 cases (72.2%) were endometrioid type. Some of them revealed squamoid differentiation or mucinous activity. While 25 cases (20.7%) were of non endometrioid type. 18 cases (19.6%) were papillary serous. 1 case (1.1%) was clear cell type. 6 cases (6.5%) were carcinosarcoma. 50% of the cases were of grade II. The rest of the cases were grade I and grade III (29.3%, 20.7% respectively). 55.4% of the cases invade less than half of the myometrium, the remaining cases were either limited to endo-metrium or invade more than half of the myometrium

Table 1. Clinicopathological characteristics of the study cases

Age	≥50		80	87%
	<50		12	13%
Histological subtypes	Endometrioid		67	72.8%
	Carcinosarcoma		6	6.5%
	Papillary serous		18	19.6%
	Clear cell		1	1.1%
Grade	I		27	29.3%
	II		46	50%
	III		19	20.7%
Myometrial invasion	Limited to endometrium		4	4.3%
	Less than half of myometrium		51	55.4%
	More than half of myometrium		37	40.2%
Lymphovascular/perineural invasion	Absent		80	87%
	present		12	13%
FIGO stage	I (67)	IA	2	2.2%
		IB	50	54.3%
		IC	15	16.3
	II(12)	IIA	5	5.4%
		IIB	7	7.6%
	III(12)	IIIA	10	10.9%
		IIIB	1	1.1%
		IIIC	1	1.1%
	IV(1)	IVB	1	1.1%
E Cadherin	Negative		11	12%
	positive		81	88%
Her2	Negative		89	96.7%
	positive		3	3.3%
P53	Negative		79	85.9%
	positive		13	14.1%

(4.3%, 40.2% respectively). Only 12 cases (13%) showed lymphovascular or perineural invasion. 67 cases (72.8%) were FIGO I (A, B, C) (2.2%.54.3%,16.3% respectively). 12 cases (13%) were FIGO II (A, B) (5.4%,7.6% respectively). 12 cases (13.1%) were FIGO III (A, B, C) (10.9%,1.1%,1.1% respectively). Only one case was FIGO IVB (1.1%). As regard immunohistochemically positivity for E- Cadherin was present in 81 cases (88%). Positivity for HER2/*neu* was found only in 3 cases (3.3%). While Positivity for p53 was found only in 13 cases (14.1%).

The association of expression of the three markers E-Cadherin, HER2/*neu*, and p53 and known clinicopathological predictors of the prognosis of endometrial carcinoma are investigated and summarized in table 2.

Table 2 showed the number of E- Cadherin, Her2/neu and p53 positive and negative patients in each age group, histological group, grade and FIGO stage. Expression of the three 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*=0.001). On the other hand, endometrioid carcinoma was not significantly related to expression of either Her2 or p53 (*P*=0.2 both). Only 3 cases were positive for HER2, two of them were of papillary serous type and one of them was of endometrioid type. Only 13 cases were positive for p53, 7 of them were endometrioid, 5 of them were papillary serous, and one case was carcinosarcoma. As regard the grade only p53 expression was significantly higher in high grades (II,III) (*P*=0.02) while grade was not significantly related to E- cadherin or HER2 expression (0.08, 0.11 respectively). Myometrial invasion showed significant positive association with p53 expression (*P*=0.03) and significant negative association with E-cadherin expression (*P*=0.01). However, there was no significant association between HER2 expression and myometrial invasion. As regard the presence of lymphovascular invasion and or perineural invasion, there was no significant relation with neither E- cadherin, HER2, nor p53 expression (*P*=0.15,0.49, 0.24 respectively)

Correlation between E- cadherin, HER2/*neu*, and p53 expression in endometrial carcinoma was illustrated in

Table 2. Association of positivity for E- cadherin, HER2, and p53 with the clinicopathological parameters of endometrial carcinoma

		E- cadherin			HER-2/*neu*			p53		
		Neg	**Pos**	**p**	**Neg**	**Pos**	**p**	**Neg**	**Pos**	**p**
Age group										
≥ 50		11	69	0.17	78	2	0.28	69	11	0.78
<50		0	12		11	1		10	2	
Histological Types										
Endometrioid		3	64	0.001*	66	1	0.2	60	7	0.2
Papillary serous		5	13		16	2		13	5	
Clear cell		0	1		1	0		1	0	
Carcinosarcoma		3	3		6	0		5	1	
Grade										
I		3	24	0.08	27	0	0.11	26	1	0.02*
II		3	43		45	1		40	6	
III		5	14		17	2		13	6	
Myometrial invasion										
Limited to end		2	2	0.01*	4	0	0.6	2	2	0.03*
Less than1/2		3	48		50	1		47	4	
More than 1/2		6	31		35	2		30	7	
Lymphovascular/ perineural invasion										
Absent		8	72	0.15	77	3	0.49	70	10	0.24
present		3	9		12	0		9	3	
FIGO Stage										
I	A	0	2	0.01*	2	0	0.6	2	0	0.01*
	B	4	46		49	1		47	3	
	C	1	14		13	2		11	4	
II	A	1	2		5	0		4	1	
	B	4	5		7	0		5	2	
III	A	1	9		10	0		9	1	
	B	0	1		1	0		1	0	
	C	1	0		1	0		0	1	
IV	B	1	0		1	0		0	1	

*Association is significant at the 0.01 level (2-tailed), Neg: negative, Pos: positive, P: P value

Table 3. Correlation between E Cadherin , Her2/neu, and P53 expression in endometrial carcinoma

		E-Cadherin	Her2
E-Cadherin	Pearson Correlation	1	-.121-
	Sig. (2-tailed)		.251
	N	92	92
Her2	Pearson Correlation	-.121-	1
	Sig. (2-tailed)	.251	
	N	92	92
p53	Pearson Correlation	-.428-**	.277**
	Sig. (2-tailed)	.000	.008
	N	92	92

**Correlation is significant at the 0.01 level (2-tailed).

(table 3) which revealed only significant considerable negative correlation between E-cadherin and p53 expression (*P*=0.000, co: -0.428).

DISCUSSION

The prognosis of endometrial carcinoma is highly variable and depends on many factors either histological or non-histological. The histological factors include histological type, grade, myometrial invasion and FIGO stage. The non-histological factors include tumor ploidy, hormone receptor status, tumor suppressor genes, oncogenes, proliferation markers and morphometry (Silverberg et al., 2014).

Many studies have investigated the molecular basis of

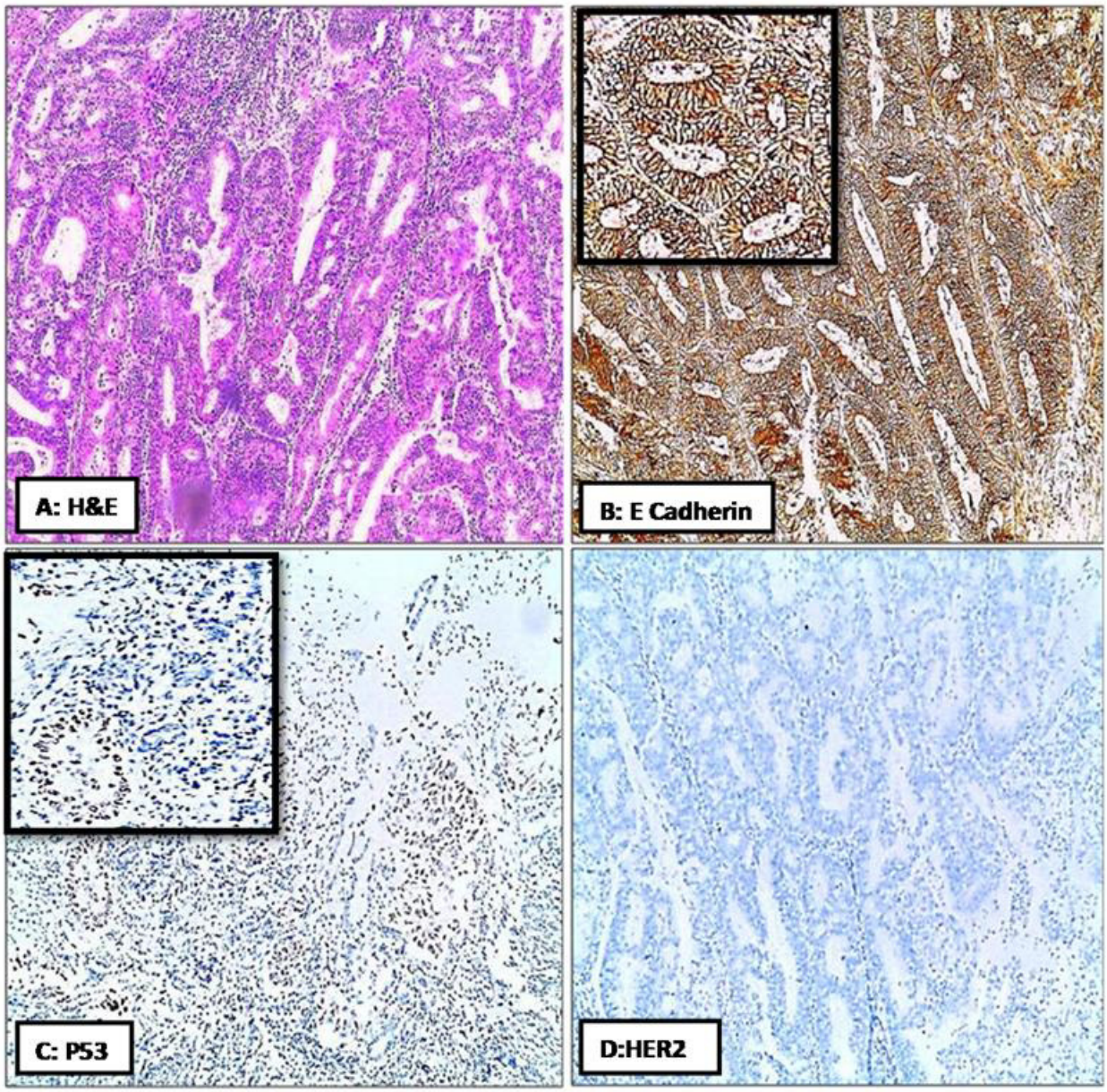

Figure 1. Endometrioid carcinoma. (A) (hematoxylin and eosin x100). (B) E-cadherin diffuse strong membranous pattern (original ×100; inset x 400). (C) P53 Focal and moderate nuclear staining (x 100;inset x400) . (D) HER2/neu negative staining (x 100).

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, HER2/*neu*, 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 (Yalta et al., 2009).

In this study the expression of E- cadherin was diffuse strong linear staining in 81 cases (88%) table 1 figure IB, IIB. This result was considerable as most of the cases were of endometrioid type (67 cases) with limited ability for invasion and metastasis as illustrated in table 2 while negative E- cadherin was present in 3/67 of endometrioid carcinoma and 5/18 of papillary serous carcinoma with high ability for invasion and metastasis. These results explain the significant association between E- cadherin expression and the histological type of

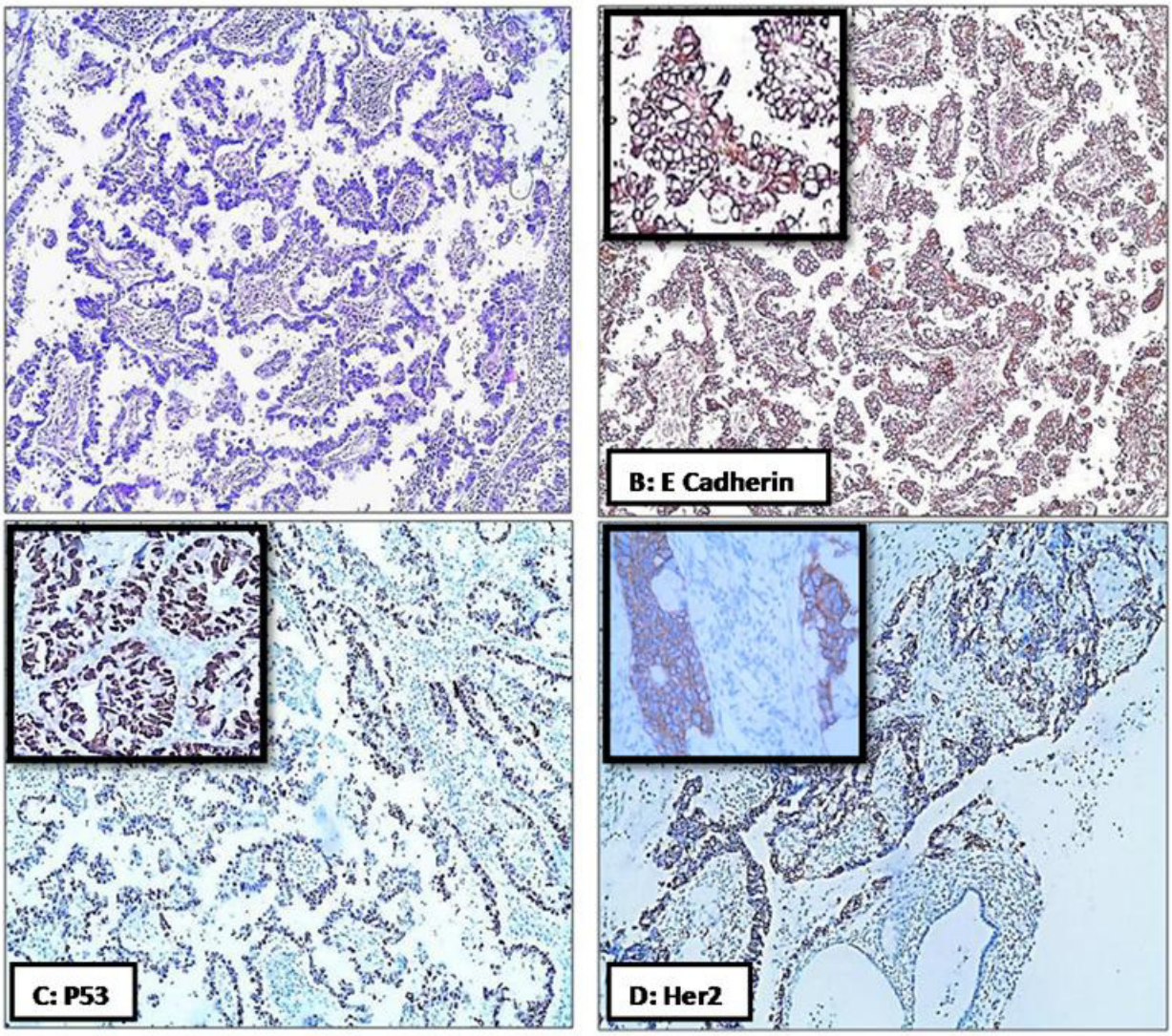

Figure 2. Papillary serous carcinoma (A) (hematoxylin and eosin x100). (B) E-cadherin-diffuse positive membranous staining (original ×100; insetx400) (c) P53 Diffuse strong nuclear staining (x 100; inset x 400). (D) Her2 moderate complete membranous staining (x 100; inset x 400)

endometrial carcinoma as shown in table 2 (P=0.001). Similar results were detected by Yalta et al. (2009).

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 E-cadherin is inhibiting tumor invasion or metastasis (Deng et al., 2014). However, in the present study there was no significant association between E- cadherin expression and the grade of endometrial carcinoma (*P*=0.08) table (2). 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 E-cadherin in invasion and metastasis. Also Florescu et al. noticed that there was significant association between E-cadherin expression and the depth of invasion and tumor stage (Florescu et al., 2016).

Her2/*neu* plays an important role in the pathogenesis of uterine serous carcinoma which explain over-expression and amplification of HER2/*neu* in large proportion of the tumor. Previous studies revealed variation in the expression rate of Her2/*neu* in endometrial carcinoma, which is attributed to variability in the testing methods, interpretation, and scoring criteria used. Unlike in breast cancer, currently there are no established guidelines for Her2 testing in endometrial carcinoma (Waqar et al., 2018; Buza et al., 2014). Some studies have considered Her2/ *neu* positivity and

negativity without considering complete or incomplete staining, while other studies were based only on the staining intensity of Her2/*neu* (Santin et al., 2002).

In this study, both percentage of complete and incomplete staining and the intensity of staining were taken in consideration according to ASCO/CAP guideline. HER2/*neu* positivity was found only in 3 cases (3.3%). One case was of endometrioid type (1.5%) and the other 2 were of papillary serous type (36%) figure IID. As regard the rate of overexpression in endometrioid carcinoma relative to the papillary serous carcinoma are in concordance with previous studies (Waqar et al., 2018). However, it didn't reach the significance level due to the causes listed above. There was no significant association of HER2/*neu* positivity with patient age, histological type, grade, myometrial invasion, or FIGO stage. Wager et al. study showed that histological types and grades of the tumors are positively associated with Her2/*neu* expression, where as no significant association of Her-2/neu was seen with the stage of EC (Waqar et al., 2018), this difference can be attributed to the variation in methodology of testing (i.e., tissue handling/fixation requirements, antibodies used, controls, and artifacts) and interpretation of the staining.

Previous studies reported that, the mutational status of TP53 is the single most important molecular factor, which predicts prognosis in endometrial carcinomas. Tthe presence of a TP53 mutation being associated with an unfavorable outcome (Köbel et al., 2018). Kounelis et al. (2000) reported that, p53 positivity was significantly higher in papillary serous than in endometrioid carcinomas. The high rate of p53 positivity found in UPSA could be compared only with that reported for uterine carcinosarcoma that shares the same aggressive behavior (Kounelis et al., 2000).

In the present study overexpression of p53 was detected in 13 cases (14%). 7 of the positive cases were of endometrioid carcinoma (7/67) (10%) figure IC and 5 of them were papillary carcinoma (5/19) (26%) figure IIC and one case was carcinosarcoma (1/6) (16%). There was insignificant association between p53 expression and the histological type (*P*=0.2) table (2). This difference from the literature could be explained as some low-grade endometrioid adenocarcinomas contain TP53 mutations and exhibit mutation-type immunoreactivity. These condition must be diagnosed as serous carcinoma with intermediate grade nuclear features and the reverse can occurs as a small percentage of morphologically prototypical endometrial serous carcinomas that exhibit a wild-type pattern of p53 immunoreactivity but still harbor a TP53 mutation (e.g. truncating). Also some cases showed complete absence of staining and we can't consider it mutant P53 due to absence of positive internal control in the focus of microarray. This explanation was noticed by Köbel et al. 2018. There was significant association of p53 positivity with tumor grade (*P*=0.02), myometrial invasion (0.03), and tumor stage (0.01) table (2). These results were in agreement with other studies (Köbel et al., 2018; Kounelis et al., 2000).

In this study there was a significant considerable negative correlation between E- cadherin and p53 expression (*P*=0.000, co:-0.428). This result was in agreement with Singh et al. (2011) which reported that inverse correlation between E- cadherin and mutant p53 expression in advanced endometrial cancer (Singh et al., 2011). However Gonzalez-Rodill et al study found a significant positive relationship between the expression of E-Cadherin by endometrial carcinoma and the expression of all the tested molecular markers of cell proliferation (Ki67, c-ERB-B2, p53) (Gonzalez-Rodill et al., 2013). 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 E-cadherin expression was also associated with a significantly better patient survival (Gonzalez-Rodill et al., 2013).

CONCLUSION

E- Cadherin expression is good predictor of the prognosis of endometrial cancer than proliferation marker HER2/*neu* or p53 due to the significant correlation with the known predictors of prognosis. Breast cancer–specific Her2 testing guidelines cannot be simply applied to endometrial cancer. Endometrial cancer–specific Her2 IHC testing and scoring guidelines need to be developed in the future to reflect the unique biology and pathogenetic features of these tumors. During interpretation of p53, we must consider complete absence of p53 as mutational type of p53 as well as overexpression. But this requires the presence of a positive internal control with staining of non-neoplastic cells such as lymphocytes, fibroblasts, or endothelial cells. And this can't be applied well in the microarray study. A case without positive internal control is considered non interpretable.

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