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Association of CCND1 and HR-HPV16/18 in endometrial tumors

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Abstract:

Background: A number of reports have demonstrated the presence of HPV in endometrial adenocarcinomas(ECs) . alterations in Cyclin D1(CCND1) gene expression has been reported in ECs and the integration of human papilloma virus (HPV)could alter the level of gene expression of CCND1.

Methodology: This study has used in situ hybridization to localized HR-HPV16/18 in tissue specimens from 70 hysterectomized patients diagnosed with malignant endometrial tumors (30 cases), non-malignant endometrial tumors (25 cases),and 15 cases as control tissues groups. Also the study has enrolled detection the gene expression of CCND1 using Immunohistochemistry.

Results: In the cancer sites malignant endometrial tumors group, HR-HPV16/18 was detected in 10 cases(33.3%) ,and in 5 cases (20%) non-malignant endometrial tumors ,and 4 cases (26.7%)of control tissues group. Most HPV16/18 infections have Punctate DNA pattern .The results of moleculare detection of CCND1 revealed 13(43.3%) in malignant endometrial tumor 8(32%) non-malignant endometrial tumor and 6(40%) in control groups. The significant correlation between CCND1 expression and HR-HPV16/18 infection was reported only in malignant endometrial tumors groups.

Conclusions: HR-HPV16/18 may be associated with initiation of endometrial carcinogenesis events as well as play a role in the progression of such malignant tumors.CCND1 could have sharing in early events of tumorgenesis in endometrial carcinoma and a significant correlations of CCND1 expressions with HPV infection was observed among malignant endometrial tumor.

keyword: *CCND1, HR-HPV16/18, endometrial tumors*

Introduction:

Human Papilloma Virus(HPV) origin and mode of in-utero transmission remain unknown. Theoretically the virus could be acquired hematogenously, by semen at fertilization or as asending infection in the genital tract[1] . Some authors identified HPV in the uterine cavity(varying from 3% to 64%) whereas others denied to report any presence of HPV[2]. Several factors could be related to these different rates of HPV prevalence: choice of detection method and different non-apprasied risk factors (low socioeconomic level, number of sexual partners, interaction with other sexually transmitted infections, and smoking habits[2] .

Authors showed that HPV spread on the endometrium (originated from the lower genital tract) residing in its simple or pseudostratified columnar epithelium and having no aetiogical or pathogenical role in the development of endometrial adenocarcinoma since HPV is tissue specific (vulva, vagina, cervix stratified squamons epithelium) and that endometrium glandular session of endocervix may not be a suitable host for HPV replication and maturation as a result absence of epithelial changes [3].

Function of Cyclin D1(CCND1) thought to play pivoted roles in G1-S phase transition. It's a sensor to integrate extracellular Signals with the Cell cycle machinery, through links to cyclin- dependent kinase 4/6 to trigger cell cycle progression[4] .

Several studies investigated CCND1 expression in proliferative endometrium, endometrial hyperplasia and endometrioid adenocarcinoma,and found that CCND1 expression in endometrial carcinoma is higher than proliferative endometrium and simple hyperplasia. These findings support that cyclin D1 may play a role in endometrial carcinogenesis However, CCND1 expression was not correlated with age, depth

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of myometrial invasion, grade, lymph node metastasis and stage[5] ,[6] .

It has been shown that E6 and E7 of HR-HPV types disrupt cell cycle check points after integration of HR-HPV DNA into the host cell genome results in elevated expression levels of E6 and E7 with their interactions with cell cycle machinery. Expression of these viral oncoprotein induce immortalization of cells by inhibit (PRb) through binding with E7, and inhibit of (P53) function through binding with E6. These events leads to alter the cell cycle control, chromosomal instability, and altering in the expression level of Cyclin D1 gene [7],[8].

Cyclin D1 form a complex with cyclin dependent Kinase 4 or 6. This complex and HPV E7 possess similar binding regions for PRb to carry phosphorylation of PRb and release of E2f-1 transcriptional factor, which can induce the expression of genes (e.g. cyclin D1) that required for cells to entre the S-phase of the cell cycle and induction of tumor[8].So the aim of the present Study:Investigation of probability of infections by high-risk HPVgenotype 16 and 18 in patients hysterectomized for cancers in their endometrium using in situ hybridization technique.Also Evaluation of the expression of Cycline D1 oncogene among study groups using immunohistochemistry technique.

Materials and Methods:

1- Subjects(Patients and tissue samples):

seventy (70) formalin-fixed, paraffin embedded uterine tissues blocks were collected from patients who had undergo hysterectomy .The age range of the patients was (39-75) years.They were collected from records of pathological archives of Teaching Laboratories of Medical City and Al-Yarmok Hospitals / Baghdad , These samples were related to the period from 2012 to 2014. The study tissues group comprised thirty malignant endometrial tumor cases represented by 30 (66 samples),25 non-malignant endometrial tumors represented by (62 samples),and 15 control tissues group represented by (30 samples).

2- Laboratory methods

Thick-tissue sections (4 mm) were prepared and stuck onto positively charged slides. An in situ hybridization (ISH) detection system (Zytovision/Germany) was used to target DNA sequences in tissue specimens using a biotinylated long DNA probe for HPV genotypes 16, 18 in tissue specimens. The procedure of the (CISH) assay adopted by this study was carried out in accordance with the manufacturer company leaflet (zytovision/Germany) in the Research Laboratories at Communicable Disease Research Unit/ Baghdad Medical College . Positive reactions were performed by replacing the probe with a biotinylated house keeping gene probe. For the negative control, all reagents were added except the diluted probe. Proper use of this ISH detection system gives an intense blue signal at specific sites of the hybridization probe in positive test tissues, The enzymatic reaction of NBT/BCIP leads to the formation of strong blue violet signals that can be visualized by light microscopy at (10-20x) dry lens. CISH signals were determined for at least 10 high power fields. Nuclear staining was considered as a positive result for HPV-DNA . Positive CISH signal patterns were classified as follows:

1- Diffuse (D), when nuclei were completely stained .

2- Punctuated (P), when distinct dot-like intra nuclear signals were noted .

3- Mixed, diffuse and punctuated (D/P), when both patterns are noted[9] .

Immunohistochemistry: This method was used to demonstrate the gene expression of Cyclin d1 in those uterine tumors tissue and was done according to the manufactoring company (Abcam/UK,Code ab80436). This kit used for detection of : Anti-cyclin D1 antibody (ab6152) . Cyclin D-1 staining was evaluated in the glandular epithelium component among study groups. Two parameters were taken: the intensity of nuclear staining and percentage of positive cells. The intensity of nuclear staining was graded as: no staining (0),weak (1+), moderate (2+) strong (3+). The percentage was estimated by counting at least 50 nuclei and then establishing the ratio of immuoreactive nuclei to total number of nuclei multiplied by 100, percentage were rounded to the nearest 10% when less than 10% of cells were positive, a score of (0) was used,< 25% cell positively was scored as 1,25%-49% cell positively was scored as 2,50%-79% cell positively was scored as 3 ,and more than 80% was scored as 4.Finally multiply the two system : <or = 3for negative; >3 for positive [10].

Statistical analysis: Chi square tests were applied for statistical analysis of all results obtained in this research.

Results:

1- Molecular detection of HR-HPV16/18 infections among tissues from uterine tumors among hysterectomized patients:

The DNA of HR-HPV16/18 was detected in tissue blocks from different endometrial diseases a signal from ISH reactions that gave blue discoloration at the sites of complementary sequences(Figure 1).

The mean age of positive cases for HR-HPV16/18 infections in the endometrial lesions was found (52.8+3.9) years with range of (39 to 68) years.

The results of HR-HPV16/18 CISH-signals in different endometrial lesions are:(10/30) cases in malignant endometrial tumors,(5/25 cases in non- malignant endometrial tumors group,and (4/15) cases in the control tissues group. No significant correlations (P>0.05) of HR-HPV16/18 infections in the endometrial lesions among hysterectomized patients were detected (Table 1).

The DNA patterns of HR-HPV were noted as punctate pattern of intracellular signals in all positive tissues of the hysterectomized patients but the mixed DNA pattern was noted only in positive malignant endometrial tumor tissues (Table 2)(Figure1).

Table (1): Distribution of HR-HPV16/18 CISH-signaling results in endometrial tissues.

Endometrium CISH Signaling results No		Malignant endometrial tumors		Nonmalignt endometrial tumors		Control endmetrial tissues	
		%	No	%	No	%	
HR-HPV16/18 ISH-signal results	Positive	10	33.3	5	20.0	4	26.7
	Negative	20	66.7	20	80.0	11	73.3
	P compared to NT	0.649		0.215		-	
	P compared toCon	0.269		-		-	

No significant differences between proportions using Pearson Chi-square test at 0.05.
P: P-value ,NT:Non-malignant endometrial tumors ,Con:Control uterine tissues

Table(2): Distribution of HR-HPV16/18 CISH-signaling patterns in endometrial tissues.

Endometrium CISH Signaling patterns No		Malignant endometrial tumors		Non malignant endometrial tumors		Control endometrial tissues	
		%	No	%	No	%	
HR-HPV16/18 ISH-signal patterns	Punctate	7	70.0	5	100	4	100
	Diffuse	-	-	-	-	-	-
	Mixed	3	30.0	-	-	-	-

No significant differences between proportions using Pearson Chi-square test at 0.05
P: P-value ,NT:Non-malignant endometrial tumors ,Con:Control endometrial tissues

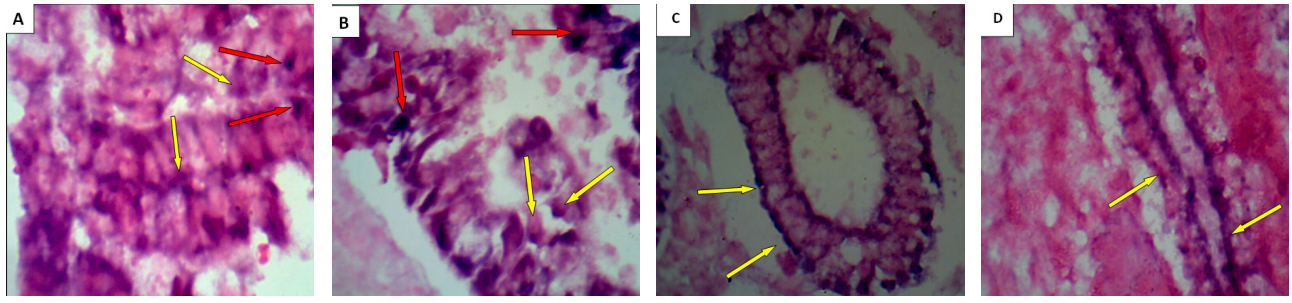


Figure (1): Microphotographs of the HR-HPV 16/18 DNA CISH-signals :A&B- Endometrial adenocarcinoma, two tissue where both blue signal patterns are noticed (punctuated yellow arrow , diffused red arrow,x1000) at complementarity sequence sites. C-Non-malignant endometrial tumor (x400) D- Normal endometrial tissue(x400).Blue signals are detected at complementarity sequence sites. punctuated pattern (dot- like intranuclear) signals are noted (yellow arrow).

2-Association between HR-HPV16/18 DNA patterns with each staging FIGO system, and grading of endometrial carcinoma:

The DNA patterns of HR-HPV16/18 according to FIGO system staging and grading of EC are shown in(Table 3):

I- Punctated form revealed mostly in: (10%) 3 cases of T1/IB, (10%) 3 cases of T2/IIB,and (20%) 6 cases of well differentiated EC.

II- Both (Diffused&Punctated) form revealed mostly in : (10%) 3cases of T1/IB and (6.7%) 2 cases in well differentiated EC.

III- No alone Diffused pattern of HR-HPV16/18 was seen among EC cases.

Table (3): Association between HR-HPV16/18 CISH signal patterns with the FIGO system staging and grading of EC.

	CISH signal patterns	FIGO system staging			Total	Grade		Total
		T1b/IB	T2b/IIB	T3a/IIIA		Well differenciation	moderate differenciation	
	Negative	(56.7%)17	(10%)3	0%	(66.7%)20	(63.3%)19	(3.3%)1	(66.7%)20
	Positive	(20%)6	(10%)3	(3.3%)1	(33.3%)10	(26.7%)8	(6.7%)2	(33.3%)10
Signals patterns	Diffuse alone	0%	0%	0%	0%	0%	0%	0%
	Punctate alone	(50%)3	(100%)3	(100%)1	(70%)7	(75%)6	(50%)1	(70%)7
	Both Diffuse &Punctate	(50%)3	0%	0%	(30%)3	(25%)2	(50%)1	(30%)3

3- Immunohistochemical detection of CCND1 in endometrial tumors:

Cyclin D1 protein [CCND1] staining was captured specifically in endometrial glandular epithelial cell nuclei where the results were :13 (43.3%) cases among malignant endometrial tumors, 8 (32.0%) cases among non-malignant endometrial tumors,and 6 (40.0%) cases among control tissues group. No significant difference (P>0.05) was found among the study groups (Table 4)

Table(4): Results of CCND1 IHC-expression in the endometrial tissues among hysterectomised patients.

Endometrial IHC signal results No		Malignant endometrial tumors		Non-malignant endometrial tumors		Control endometrial tissues	
		%	No	%	No	%	
IHC for CCND1	Positive	13	43.3	8	32.0	6	40.0
	Negative	17	56.7	17	68.0	9	60.0
	P compared to NT	0.831		0.075		-	
	P compared to Con	0.389		-		-	

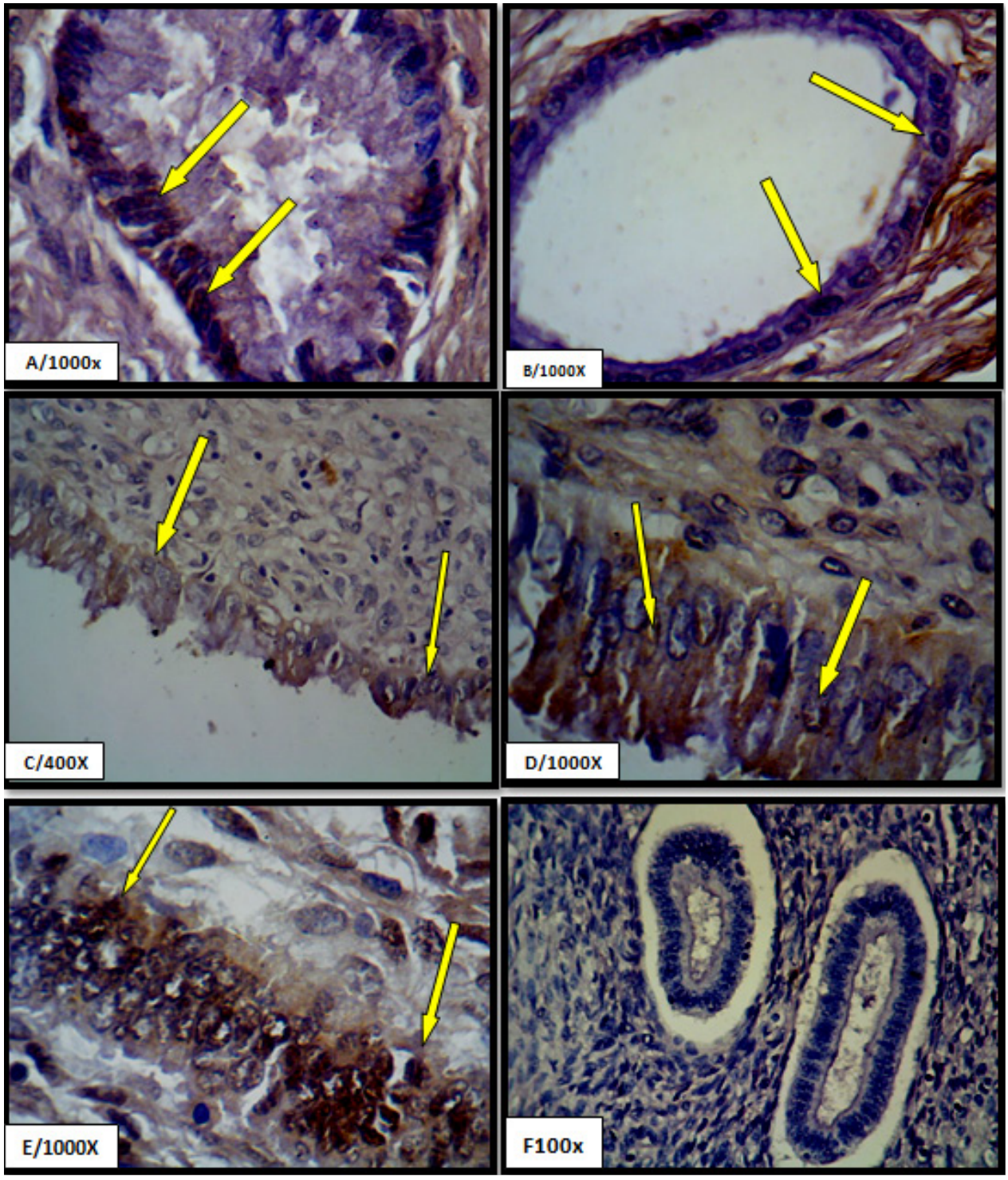
No significant differences between proportions using Pearson Chi-square test at 0.05 level.P:p-value ,NT:Non-malignant endometrial tumors,Con:Control tissues.

The high percentage (16.6%) of each score of 4 among malignant endometrial tumors with the predominated high intensity constituted (30%), whereas (16%) of score 4 was found among non-malignant tumors with predominated high intensity was constituted (20%).No significant differences were detected among the study groups (Table5) (Figure 2).

Table (5): Frequency distribution of IHC-results for CCND1 according to signal score & intensity in the endometrial lesions .

Pathological types	Negative signaling %	Positive signaling %	*Signal Scoring				**Signal intensity			P value x Control tissues	P value x non-malignant tumors
			Score 1	Score 2	Score 3	Score 4	L	M	H		
Malignant endometrial tumors (30)	17 56.66%	13 43.3%	0	3 10%	5 16.6%	5 16.6%	1 3.33%	3 10%	9 30%	0.589	0.389
Non malignant endometrial tumors (25)	17 68%	8 32%	0	3 12%	1 4%	4 16.6%	1 4%	2 8%	5 20%	0.824	
Control uterine tissues (15)	11 73.3%	6 40%	0	3 20%	2 13.3%	1 6.67%	0	3 20%	3 20%		

Nosignificant differences between proportions using Pearson Chi-square test at 0.05 level
*Score 1(<25%),Score2(25-50%),Score3(50-79%),Score4(=>80%)
**L = Low intensity, M = Moderate intensity,H = High Intensity



Figure(2): Microphotographs of IHC staining for CCND1 in cell nuclei (yellow arrow) of glandular tissue in (A,B,C) endometrial carcinoma show score 2 with high intensity,(D,E)-non-secretory endometrial gland associated with adenomyosis and lieomyoma show score2 with high intensity (F)non secretory endometrial gland show negative signal.

4- The CCND1 protein expression according to FIGO staging system and grading of endometrial carcinoma:

Ten cases (48.0%) revealed T1b/IB and three cases (33%) revealed T2b/IIB while 12 cases (44%) revealed well-differentiation grade and one case(33.3%) revealed moderately differentiated grade (Figure 3,4) .

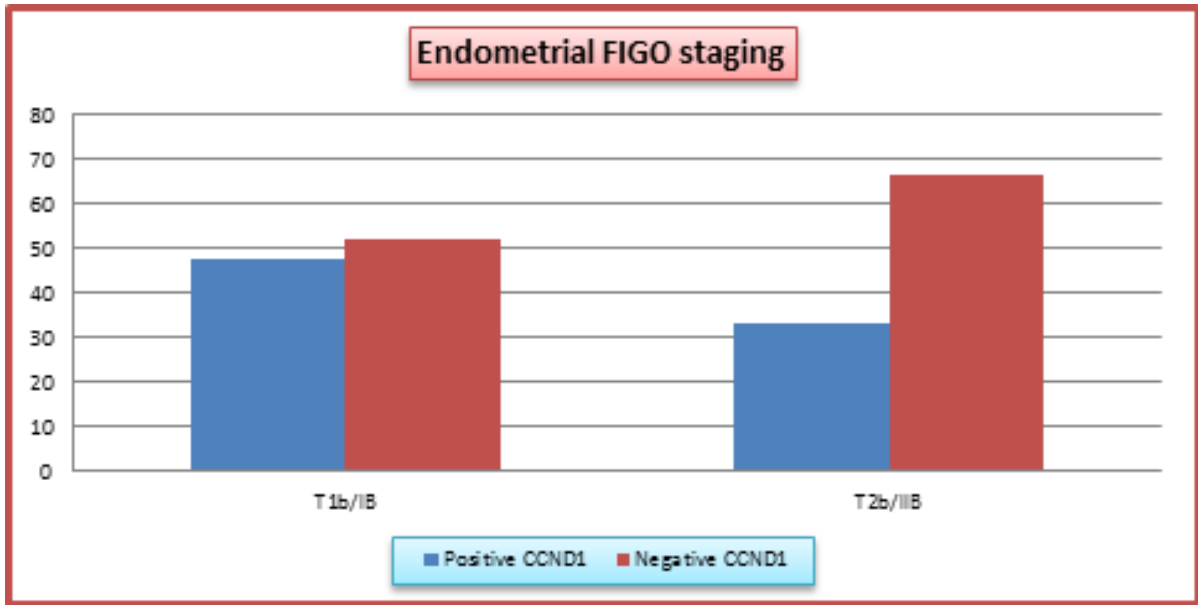
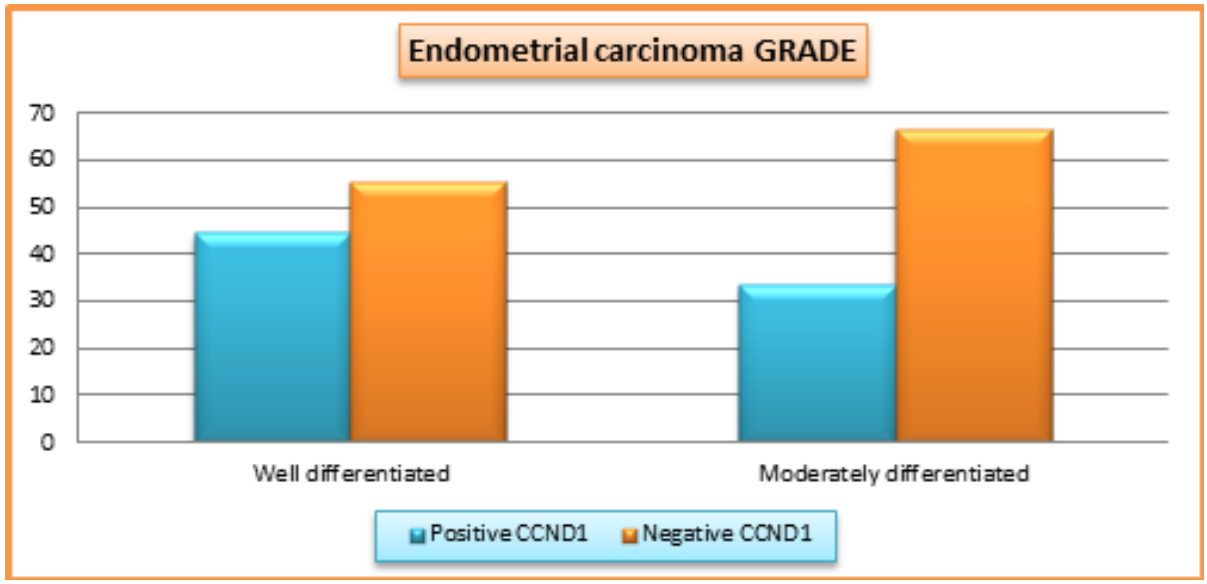


Figure (3): Distribution of CCND1 IHC-results according to FIGO staging.



Figure(4): Distribution of CCND1 IHC-results according to grading of malignancies.

5- Association between CCND1 protein expression and HR-HPV16/18 in the endometrial lesions:

The percentage of positive results for both CCND1 and HR-HPV16/18 in malignant endometrial tumors was (23.33%) 7 cases while in non-malignant endometrial tumor group the percentage of positive results for both CCND1 and HR-HPV16/18 was (10%) 2 cases.In control tissues group, positive results for both CCND1 and HR-HPV16/18 was (13.33%) 2 cases.

A significant association between CCND1 expression and HR-HPV16/18 was revealed in endometrial lesions among malignant endometrial tumors group but no association revealed between CCND1 expression and HR-HPV16/18 in non-malignant endometrial tumor and control tissues group (Table 6).

Table (6): Association between CCND1, HR-HPV16/18,and HMTV in the endometrial lesions among the study groups.

Pathological types	CCND1-IHC results	HR-HPV16/18		P value	HMTV		P value
		ISH-negative results	ISH-positive resilts		ISH-negative results	ISH-positive resilts	
Malignant endometrial tumors (30)	Negative	14 46.6%	3 10%	*0.037	15 50%	2 6.66%	0.410
	Positive	6 20%	7 23.3%		10 33.3%	3 10%	
Non-malignant endometrial tumors (25)	Negative	14 56%	3 12%	0.668	16 64%	1 4%	0.569
	Positive	6 24%	2 8%		7 28%	1 4%	
Control endo-metrial tissues (15)	Negative	7 46.66%	2 13.3%	0.634	8 53.3%	1 6.66%	0.756
	Positive	4 26.66%	2 13.3%		5 33.3%	1 6.66%	

*Significant difference between proportions using Pearson Chi-square test at 0.05 level.

Discussion:

Molecular Detection of HR-HPV16/18 in endometrial tumorous tissues:

The Current study has demonstrated that molecular detection of HR-HPV16/18 DNA was higher in the malignant endometrial tumors in comparison with other groupsnon malignant tumors and control groups (Table 1).

Several authors have detected HR-HPV in their studied endometrial tissue sites but the results are highly controversial where the results in these studies have ranged between zero% [11](3 to 40%)[2] . Our results ranked the middle among these studies.

In the hysterectomized patients group, the ages were more than fifty (>50) . herein three effects of hormonal risk factor should presents, where the steroid hormones influence the carcinogenesis process induced by HR-HPV infections [2]. The HPV genome present in an episomal form in benign and premalignant lesions and when these hormones binding to specific binding sites in the long control region (LCR) of the viral genome [GRE: glucocorticoid responsive element], resulting increase the transcription of E6 & E7 genes of HR- HPV-16/18 and the frequency of integration of viral genome increase with progression to high-grade lesions and invasive carcinoma [12]. The continuous stimulatory effect of the hormones on expression of HPV genes present in the upper genital tract (endometrium) could explain the increase risk of carcinogenesis through long term exposure to these hormones whether endogenously or exogenously [12].While in hysterectomized patients younger than fifty (<50) in which the effects of hormonal risk factor would not be present , EC oncogenes explained by alternations of tumor suppressor gene (e.g :P53), overexpression of HER-2neu, inactivation of P16, interaction with sexually transmitted infection (e.g:HPV), smoking habits and may be genetic make up of the patients [2],[13].All the positive HR-HPV16/18 cases of malignan uterine tumors were in the same pathological features(adenocarcinoma) and mostly with grade 1 and stage T1/IB (Table 3) , Also the clinicalopathological types in those positive-HR HPV16/18 non-malignant endometrial tumors were those that could be progressing to adenocarcinoma (hyperplasia), make a suggestion that this virus may be associated with initiation of oncogenesis events in the endometrium of the studied case.On the other hand, the DNA patterns of HR-HPV16/18 were mostly in the endometrium of the integrated form with no episomal pattern was noted(Table 3 Figure 1) which could give a clue indication that HR-HPV16/18 may be play role in progression of the carcinogenesis since the integration events increase over expression of E6 & E7 which leading to carcinogenesis and our suggestion is in agreement with[14][15] .

Molecular detection of CCND1 in endometrial tumors

In the present study, (43.37%) malignant endometrial tumors revealed the expression of CCND1 in yet no significant differences among study groups were noticed (Table 4 and 5) (Figure 2). These results are in agreement with[16] and [17] who have observed the expression of CCND1 in 46.1% and 52% endometrial carcinoma . Also,several studies[17],[5],[6] had showed that patients with EC were positive for CCND1 in (28.6%-68%) of their examined tissues where our results

are ranks the median on this range.

Moreno-Buero etal(2003) first reported CCND1 gene mutation and amplification in EC and have mention that mutant CCND1 remains in the nucleus throughout the cell cycle due to its reduced binding to nuclear-exporting CRM1 suggested gene mutation may be an explanation for CCND1 over expression in EC[18]. Also,the current study revealed that expression of CCND1 was 47.6% and 33.3% in early stage (T1/IB and T2/IIB) and 40% in well differentiated grade higher than in the moderately differentiated grade (Figure 3 and 4) .Thses results was in agreement with Wistuba etal,1998 who reported that CCND1 higher in well differentiated than moderately which could suggest that CCND1 may be involved in an early event of carcinogenesis[19] .

However the CCND1 expression in the present study is 32% of non-malignant endometrial tumors and 40% in control tissues group (Table 3,4)(Figure 2) are mainly noticed to involved the secretory, late secretory and proliferative endometrial glands. These results could suggest that the CCND1 expression might be induced by estrogen regulated genes.

Since CCND1 is the only molecules whose expression is controlled by extracellular signals so it can be stimulated by various mitogens. Estrogen can induced activation of CCND1 genes mediated by AP-1 sequence of the CCND1 promoter(binding site) and up regulation of CCND1 is mediated through binding of C-Jun or C-fos to AP-1 site of this promoter [4]. Estrogen receptor complex (E2-ER) binds to the function estrogen receptor binding elements(ERE) (located at the promoter of C-Jun gene) and the C-Jun binds to the AP-1 sequence of the CCND1 gene or that the E2-ER act directly (at AP-1 element by serving as coactivator for C-Jun) then induce expression of CCND1 which play role in the growth of normal endometrial glandular cells[20] .

Association between CCND1 expression and HR-HPV 16/18 infection in endometrial lesions as shown in (Table 6):-

Regarding the expression of CCND1 in relation to HR-HPV 16/18 infections, the current study has revealed a possible relationship between the CCND1 expression with HR-HPV 16/18 infection in the endometrial tissues of the malignant cases only . Disruptions of the p16-CDK4/Cyclin D1 pathway (i.e. the pRb pathway) and the p14ARF-MDM2-p53 pathway (i.e. the p53 pathway) are important mechanisms in the development such malignant tumors .One mechanism is the high expression of p16 in HPV- positive tumors that might resulted from the HPV E7 modulation of pRb disruption which could be in form of a loss or mutation of p16. This event induces the upregulation of Cyclin D1/Cdk 4 and CyclinD1/Cdk6 complexes and pRb phosphorylation resulting in the subsequent release of E2F and transcription of genes of cell proliferation [21].The inactivation of pRb by the HPV oncoprotein E7 involves proteolytic degradation which resultsin the increase in the p16INK expression and down regulation of Cyclin D1[22] .

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رابطة CCND1 و HR-HPV16 /18 في أورام بطانة الرحم

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2 كلية الطب/ الجامعة المستنصرية

الخلاصه:

أظهرت عدد من التقارير وجود فيروس الورم الحليمي البشري في الأورام الغدية لبطانة الرحم.كما واظهرت الابحاث تغييرا في في الية التعبير الجيني ل Cyclin D1 في حالات سرطان الرحم المصابة بالفايروس الحليمي البشري. استخدمت هذه الدراسة تقنية التهجين الموضعي لHPV في عينات الأنسجة الماخوذة من 70 مريضة اجريت لها عملية استئصال الرحم منها: (30 حالة) شخصت ضمن الأورام الخبيثة للرحم و(25حالة) ضمن أورام الرحم غير الخبيثة و(15 حالة) كمجموعة انسجة السيطرة. وكانت نسبة الكشف عن HPV16/18 في مجموعة اورام الرحم الخبيثة 10 حالات (33.3٪)، و5حالات (20 %)من أورام الرحم غير الخبيثة، وايضا 4حالات(26.7٪) من مجموعة أنسجة السيطرة.معظم الاصابات ب HPV16/18كانت ذات النمط المنقط من ال DNA. اما التعبير الجيني ل Cyclin D1،فقد تم الكشف عن 13حالة(43.3%) من مجموعة أورام الرحم الخبيثة و(32٪) في ثمان حالات في المصابات بأورام الرحم غير الخبيثة .اما في أنسجة مجاميع السيطرة، تم الكشف عن ست حالات فقط (40٪).كما واظهرت هذه الدراسة الجزيئية وجود علاقة بين الاصابة ب HPV16/18 وبين التعبير الجيني لل Cyclin D1 ضمن مجاميع اورام الرحم الخبيثة.اظهرت الدراسة ان الاصابة ب HPV16/18 قد تلعب دورا بتطور السرطان في بطانة الرحم وقد يكون لها دورا في تقدم المرض كما واظهرت الدراسة وجود علاقة معنوية بين الاصابة ب HPV16/18 وبين التعبير الجيني لل Cyclin D1ضمن مجاميع الاورام الخبيثة لسرطان الرحم .