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Immunohistochemical expression of PTEN (phosphatase and tension homolog) in endometrial carcinoma

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Abstract

Background and objective: Different molecular alterations have been described in the pathogenesis of endometrial carcinoma, among themis mutation of the PTEN (phosphatase and tension homolog), a tumor suppressor gene. This study aimed to detect PTEN immunoexpression in endometrial carcinoma and to asses the association between PTEN immunoexpression with the clinicopathological parameters.

Methods: This cross-sectional retrospective study was carried out between January 2016-December 2021 in Erbil city. A total of 112 formalin fixed, paraffin embedded, archival tissue blocks of total abdominal hysterectomy samples were collected in Erbilcity. The clinicopathological characteristics of the tumors were revised, and the specimens were analyzed immunohistochemically using monoclonal PTEN antibody clone 6H2.1 (Dako.

Results: Seventy- seven cases (68.8%) were labeled as negative for PTEN immunoexpression. While 35 cases (31.2%) were labeled as positive for PTEN immunoexpression. PTEN immunoexpression was significantly associated with the tumor histological types (P = 0.001), while no significant association was found between PTEN immunoexpression and other clinicopathological parameters.

Conclusion: Loss of PTEN immunoexpression frequently seen in endometrioid type of endometrial carcinoma than other types of endometrial carcinoma and is significantly associated with the histological types of endometrial carcinoma.

Keywords: Endometrial carcinoma; PTEN; Immunohistochemistry.

Introduction

Endometrial carcinoma is one of the most prevalent invasive malignant tumors of the female genital tract, as well as the sixth greatest cause of cancer-related mortality among gynecological malignancies in the United States, Japan, and other developing nations.[1,2] It accounts for 7% of all invasive malignancies in women, with an increasing frequency.[2] Furthermore, endometrial carcinoma is the fourth most frequent cancer in women after breast, colon, and lung cancer and contributes significantly to gynecological mortality.[3]

Although there are well-established surgical, radio, and chemotherapeutic treatments, the biomarkers must be identified and characterized in order to improve our understanding of the pathophysiology and molecular pathways and to develop specific novel molecular targeted therapies with the goal of achieving higher accuracy in tumor progression and metastatic processes, as well as accurately evaluating prognosis, particularly for reoccurring and unfavorable disease.[3]

The progress gained in deciphering the human genome in recent decades has uncovered new variables, notably at the molecular and cellular level, that contribute to the etiology of endometrial cancer. Several DNA mutations affecting proteins involved in cell signal transduction and

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communication systems have been explored. The most common gene mutation is connected to the PTEN gene (phosphatase and tensin homolog) which is found on chromosome 10.[4-6]

PTEN is a tumor suppressor gene. It was discovered in 1997 on chromosome 10 (10q23) that suppresses cell proliferation and differentiation and is implicated in the insulin signaling system.[7] PTEN deficiency is caused by mutations or deletions that inactivate the two PTEN alleles, promoter hypermethylation, loss of heterozygosity without mutation, abnormal production of regulatory microRNA, and protein degradation.[8] In cancers, the most of PTEN gene mutations are found in the phosphatase domain, which affects phosphatase activity. Reduced expression of the PTEN gene has been seen in glioblastoma, melanoma, prostate cancer, breast cancer, lung cancer, ovary cancer, and endometrial cancer, among other cancers. PTEN expression is also lower in endometrial hyperplasia and endometrial cancer than in proliferative endometrium, according to earlier research.[9,14] Because there is a lack of research on the immunohistochemical expression of the PTEN gene in endometrial carcinoma in our country, and no data are available about evaluation of PTEN gene expression in endometrial carcinoma thus, this study aimed to provide an insight on the immunohistochemical expression of PTEN gene in endometrial carcinoma and its association with various clinicopathological parameters like age of the patient, histological type of tumor, grade of the tumor, depth of myometrial invasion, lymphovascular invasion, fallopian tube and or/ovarian invasion and pathological stage of the tumor.

Methods

Permission for this study was obtained from the Ethics Committee of the College of Medicine/ Hawler Medical University, Erbil, Iraq. The specimens used in this study were 112 formalin-fixed, paraffin-embedded, archival tissue blocks of cases underwent surgery (total abdominal hysterectomy) for removal of the endometrial carcinoma were recruited during the period of January 2016 to December 2021. The samples were selected from histopathology laboratory of Maternity Teaching Hospital and some histopathological private laboratories in Erbil city. The histopathologic parameters such as histologic type and grade, depth of myometrial invasion, lymphovascular space invasion, fallopian tube and/or ovarian invasion were also retrieved and analyzed statistically.

For histological examination, the slides stained with hematoxylin and eosin had been retrieved and examined under light microscope for re-evaluation of tumor histological type and grading of endometrial carcinoma according to International Federation of Gynecology and Obstetrics (FIGO) grading system and the most represented part were selected which contain 50% of the tumor cells for the immunohistochemical staining avoiding necrotic and hemorrhagic area. The pathological staging of the tumor was performed according to (FIGO).

Immunohistochemical staining

The Dako cytomationEnVision FLEX+ Dual link system-HRP(DAB+) staining protocol was used for immunostaining for detection of PTEN immunoexpression and applied to the selected paraffin embedded tissue blocks which was sectioned at a thickness of 3 µm, dried for 1 hour at 65°C, deparaffinized, rehydrated, and subjected to target retrieval in the pretreatment module, PTLINK (Dako, Glostrup, Denmark) at 95°C for 20 minutes in target retrieval solution, pH 9 (Dako). Endogenous peroxidase was blocked using peroxidase-blocking reagent (Dako) followed by incubation with primary PTEN antibody clone 6H2.1 (Dako) at a dilution 1:100, which recognizes human and mouse PTEN protein. Incubation time for primary antibody was 40 minutes. Secondary EnVision FLEX/HRP (20 minutes)

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was used to amplify signal. Detection was done using 3,3′-diaminobenzidine tetra hydrochloride as chromogen (Dako). Slides were counterstained with hematoxylin, dehydrated, and mounted. Appropriate negative controls were also tested. For all negative cases, the presence of positive staining stromal cells and vascular endothelial cell confirmed that the immunohistochemistry reaction was working.

PTEN scoring system

Positive expression of PTEN gave cytoplasmic and/or nuclear brown staining and loss of PTEN immunoexpression gives negative staining PTEN null gland. The semi quantitative immunoreaction scoring system were evaluated based on the percentage of positive cells stained in the field.[11-15] A total of 100 cells were counted in 10 random fields (with x400 objectives) and the percentage of positive cells was calculated, staining of cells was scored as negative (loss of PTEN immunoexpression) if < 10%, 1+ if 10%-50% and 2+ if >50% of cells were stained. For statistical issue PTEN immunoexpression was defined as negative (loss of PTEN immunoexpression) or positive (score 1+and 2+).

Statistical analysis

The collected data were analyzed using computerized software statistical package for the social sciences program (SPSS version 24). By using the Pearson Chi-square test and Fisher's exact test, assessment of the association between PTEN immunoexpression and clinicopathological parameters had been calculated. A *P* value of ≤ 0.05 is considered as statistically significant.

Results

In this study, a total of 112 of endometrial carcinoma cases were included, 105 were of endometrioid type of endometrial carcinoma, 4 papillary serous carcinomas, 1 clear cell carcinoma and 2 carcinosarcoma. The patient age was ranged from 31-85 years with mean age± standard deviation of 58.53 years ± 11.56 years, and the median age was 54 years. There were three age group, most of the cases (60.71%) were in the 40-65 years' age group, one third (33.93%) of cases were more than 65 years old, followed by only (5.36%) of cases were less than 40 years old. The clinicopathological characteristics of the studied cases are described in Table 1.

Majority of the cases 77 (68.8%) had less than 10% of the cell stained with PTEN antibody so scored as negative (loss of PTEN immunoexpression), while 10-50% of the stained cell were detected in 26 cases (23.2%) and scored as +1 and only in 9 cases (8.0%) there were more than 50% of cell stained with PTEN antibody scored as +2, PTEN immunoexpression was significantly associated with the histological type of the tumor (*P* = 0.001), as shown in Table 2 and Figure 1.

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Table 1 The frequency and characteristics of the clinicopathological parameters of the studied cases:

Clinicopathological parameters	No.	%
Histological type		
Endometrioid adenocarcinoma	105	93.75
Papillary serous carcinoma	4	3.67
Clear cell carcinoma	1	0.89
Carcinosarcoma	2	1.79
Age of the patients		
Less than 40 years	6	5.36
40-65 years	68	60.71
More than 65 years	38	33.93
Tumor grade		
GradeI	29	25.9
Grade II	6	61.6
GradeIII	14	12.5
Tumor staging		
Stage I	90	80.3
Stage II	3	2.7
Stage III	17	15.2
Stage IV	2	1.8
Myometrial invasion		
<50%	52	46.4
> 50 %	60	53.6
Lymph node invasion		
Negative	97	86.6
Positive	15	13.4
Vascular invasion		
Negative	103	92
Positive	9	8
Ovarian invasion		
Negative	99	88.4
Positive	13	11.6
Tube invasion		
Negative	108	96.4
Positive	4	3.6
Total	112	100.0

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Table 2 Association of PTEN immunoexpression with the clinicopathological characteristics.

Clinicopathological parameters	Total No.	PTEN negative frequency (%)	PTEN positive frequency (%)	*P* value
Histological type				
Endometrioid	105	77 (73.3)	28 (26.7)	0.001*
Papillary	4	0 (0)	4 (100)	
Clear cell	1	0 (0)	1 (100)	
Carcinosarcoma	2	0 (0)	2 (100)	
Age of the patient				
<40 years	6	4 (66.7)	2(33.3)	0.999*
40-65 years	68	47 (69.1)	21(30.9)	
> 65 years	38	26 (68.4)	12(31.6)	
Tumor grade				
Grade I	29	23(79.3)	6(20.7)	0.052*
Grade II	69	48 (69.6)	21(30.4)	
Grade III	14	6 (42.9)	8(57.1)	
Tumor stage				
I	90	66(73.3)	24(26.7)	0.114*
II	3	1(33.3)	2(66.7)	
III	17	9(52.9)	8(47.1)	
IV	2	1(50)	1(50)	
Myometrial invasion				
<50%	52	36(69.2)	16 (30.8)	0.919*
>50%	60	41(68.3)	19(31.7)	
Lymph node invasion				
Negative	97	68(70.1)	29(29.9)	0.550**
Positive	15	9(60)	6(40)	
Vascular invasion				
Negative	103	72(69.9)	31(30.1)	0.457**
Positive	9	5(55.6)	4(44.4)	
Ovarian invasion				
Negative	99	70(70.7)	29(29.3)	0.222**
Positive	13	7(53.8)	6(46.2)	
Tube invasion				
Negative	108	76(70.4)	32(29.6)	0.090**
Positive	4	1(25)	3(75)	

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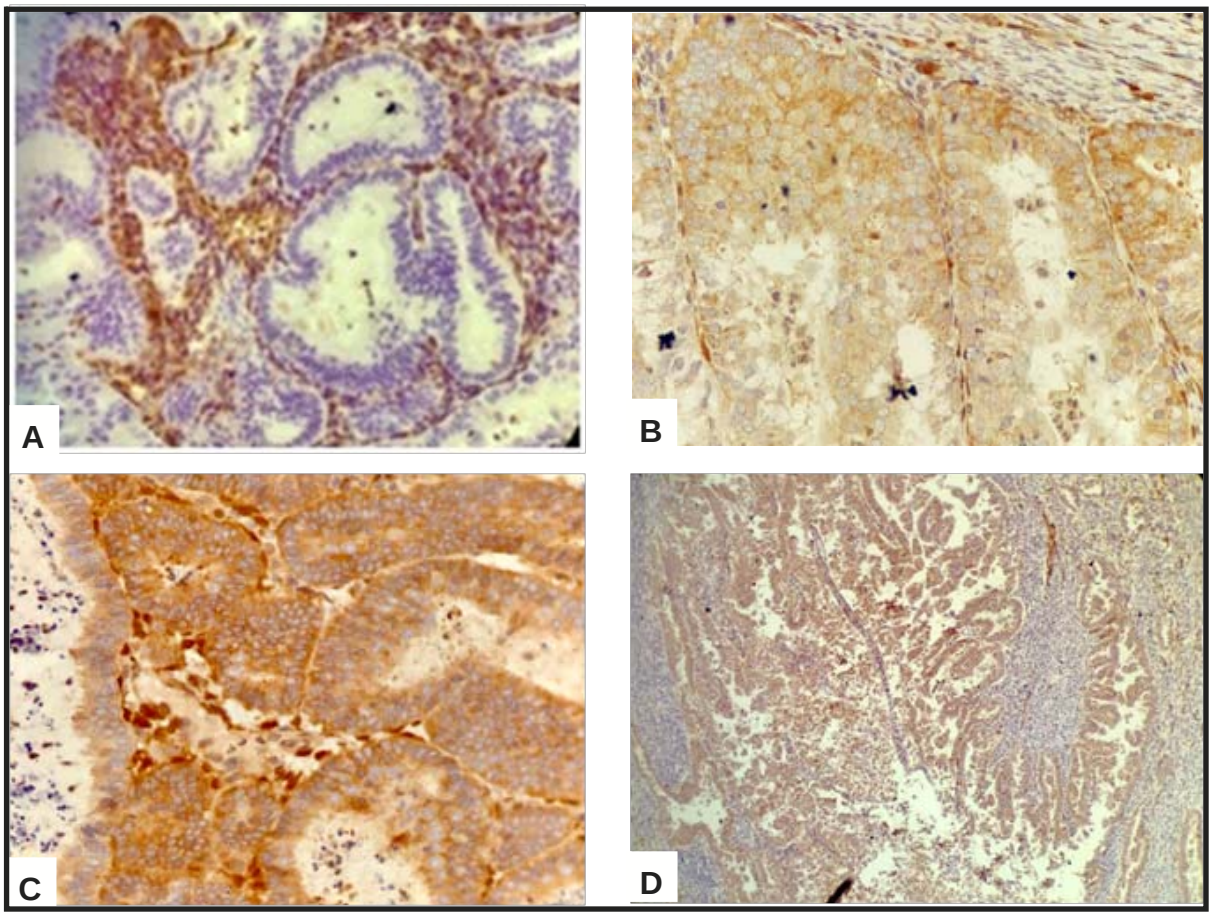

Figure 1 Shows three scores of PTEN immunoexpression: A- PTEN score negative loss of expression< 10%(PTEN IHC staining x 400). B- PTEN score 1+ 10-50% (PTEN IHC staining x 400). C- PTEN score 2+ >50% (PTEN IHC staining x400). D – papillary cell carcinoma score +2>50% (PTEN IHC staining x 200).

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Discussion

The genomic profile of gynecological malignances provides a new field of investigation in order to achieve earlier diagnosis and optimal therapeutic benefit from targeted agents. Previous studies have shown that PTEN signaling pathway might play an important role in the pathogenesis of endometrial carcinoma, as PTEN mutates in 30 -70% of endometrial cancer cases especially of endometrioid endometrial carcinoma type, a rate that is among the highest of any type of cancer analyzed, additionally the mutation was also seen in about 20% of cases of endometrial hyperplasia, precursor of endometrial carcinoma.[7,12] Therefore, accurate identification of this aberration is an important component of patient triage and selection in order to achieve optimal therapeutic benefit from target agent.[16,17] according to the 2017 European society of gynecological oncology (ESGO) guidelines base on the 2018 European society of medical oncology ESGO-Europe society for radiotherapy of oncology conference, the immunohistochemical expression of PTEN is recommended to be used in endometrial carcinoma.[8] The present study has shown that PTEN immunoexpression loss (negative cases) were observed in more than half of the cases and PTEN immunoexpression (positive cases) were found in less than half, a figure lying within the range of previously reported immunohistochemical studies of PTEN in endometrial carcinoma, as shown in the Table 3.

On the other hand, some studies have get different results than our study, this variability in the results of PTEN immunohistochemical expression may be due to a number of factors which could affect the percentage of PTEN immunoexpression in the tumor cells for example: Type of the primary antibody used and its sensitivity, fixation, processing and pretreatment method, type of detection system used, Incubation time of the primary antibody, HRP polymer and chromogen used and Variability in the scoring system.

Table 3 PTEN immunoexpression results of previous researches in comparison to this study

Study	Number of cases	Scoring system	PTEN negative	PTEN positive
Stavropoulos et al [4]	99	Percentage of cell and intensity	23%	77%
Sithara et al[14]	49	Percentage of stained cell	61%	39%
Thukral et a[11]	7	Percentage of stained cell	71.43%	28.57%
Chen et a[5]	40	Percentage of stained cell and intensity	67.6%	32.4%
Shanmugapriya et al[12]	7	Percentage of stained cell	70%	30%
Karnezis et a1[7]	413	Percentage of cell and intensity	46.2%	53.8%
Daniilidou et al [19]	61	Percentage of stained cell	39.3%	60.7%
Akiyama-Abe et al [15]	221	Percentage of stained cell	25%	75%
Garg et al[19]	118	Heterogeneous/negative/positive	70%	30%
Djordjevic et al [21]	154	Heterogeneous/negative/positive	64%	36%
Mackay et al [22]	128	Percentage of stained cell and intensity	55%	45%
Gao et al [23]	73	Computer asses image analysis	74%	26%
Sarmadi et al [13]	29	Percentage of stained cell	52%	48%
Current study	112	Percentage of stained cell	68.8%	31.2%

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In the present study, age at the diagnosis of endometrial carcinoma was not associated with PTEN immunoexpression *P*-(0.999) although loss of PTEN immunoexpression (negative expression) in all age groups were higher than that of the positive expression especially age group (40-65) years near half of the patient were with negative expression but it was statistically not significant, same results were obtained by all of the previous studies that no significant association were found between patients age and PTEN immunoexpression.[4,5,15,19,22]

A significant statistical association was found between PTEN immunoexpression and histological types of endometrial carcinoma (*P* = 0.001), PTEN immunoexpression was either absent or decreased in uterine endometrioid endometrial carcinoma more frequently than it was in uterine serous, clear, carcinosarcoma, these findings support the hypothesis that PTEN is a major gene involved in the genesis of endometrioid endometrial adenocarcinoma and may be a new target for prevention and therapy of cancer, on the other hand, all the cases of papillary, clear, carcinosarcoma were positive, but because of the low number the statistical analysis are inconclusive in contrast to uterine endometrioid carcinoma this difference between these two different types of endometrial carcinoma support the dualistic model of endometrial carcinogenesis incorporating a classic estrogen driven pathway an alternative pathway seemingly unrelated to hormone, our result are the same as reported by other researchers.[5,15,19,21,23]

Unlike our study and another two studies one conducted in Canada by Mackay and the other in Greece by Stavropoulos found no significant association between PTEN immunoexpression and histological types.[4,22] The most likely reason for this difference in findings may be due to difference in the antibody used and antibody dilution, they used dilution 1:200 and rabbit monoclonal antibody and the fixation time, different protocols, various visualization reagents, and use of manual or automated systems as well as the variation of scoring systems between these studies and the present study in addition to the low number of other histological type in this research, which will need a larger study to confirm the results.

The number of uterine endometrial carcinoma with loss of PTEN immunoexpressionin grade I and in grade II was higher than grade III, but this difference was not statistically significant, this result was concordant with many other studies,[4,5,15,18,21] while Daniilidou et al[19] and GAO et al[23] in their study found significant association between grade and PTEN immunoexpression.[19,23]

When considering the clinical stage, loss of immunoexpression of the PTEN was more frequently noticed at stage I and III and it was higher than tumors in stages II and IV however this was statistically not significant, many of previous studies done were in agreement with the result of this study,[4,5,15,18,21,22] only a study done by Daniilidou et al[19] in Greece they found a statistically significant association between stage of endometrial carcinoma and PTEN immunoexpression.

A key difference between the present study and the other study which disagree with our result regarding the non-significant association between both stage and grade of endometrial carcinoma in the study done by Daniilodou et al[19] was that all uterine endometrial carcinoma were examined as a whole in relation to clinicopathological parameters in our study, while in their study they separately studied the clinicopathological parameters and loss of PTEN immunoexpression in endometrioid and uterine serous papillary carcinoma, in addition they used different scoring system that depend on the staining reaction in addition the quality of immunostaining differs depending on many factors such as fixation processing, unmasking of the epitopes and sensitivity of the detection system used.

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Regarding myometrial invasion, in the present study the cases with loss of PTEN immunoexpression cases of myometrial invasion with more than 50% was slightly higher than those with loss of PTEN immunoexpression and level of myometrial invasion of less than 50% and the association was not statistically significant, these results were closely comparable with those obtained by many researches.[4,15,18,23]

The current study indicated that the loss of PTEN immunoexpression in patients who had presented with lymph node metastasis were less than those who were not present with lymph node metastasis and no statistically significant association was detected between PTEN immunoexpression and lymph node status, this result agrees with many other studies.[4,15,18,23]

Concerning the association of PTEN immunoexpression with the vascular metastasis in the studied patients, although the loss of PTEN immunoexpression in cases without vascular metastasis was higher than cases presented with vascular metastasis but there was no statistically significant association, this result is comparable with other studies.[4,15,18]

In cases with fallopian tube and or ovarian invasion although we have taken them separately the cases that presented with loss of PTEN immunoexpression were higher in cases without ovary and tube metastasis than those presented with loss of PTEN immunoexpression and had ovarian and tubal invasion by tumor cells and there was no statistically significant association, these results were in agreement with other researcher's study.[4,5]

Our study limitation is the low number of the non-endometrioid endometrial carcinoma types in this research, which will need a larger study to confirm it, it would have been more satisfactory if we could collect data about survival of the patients, determine the malignant potential of PTEN with various type of endometrial carcinoma and correlation with the survival, but it was impossible due to lack of follow up data.

Conclusion

Loss of PTEN expression seen in endometrial carcinoma especially of the endometrioid type support the dualistic model of endometrial carcinogenesis and suggestive of PI3K-AKT pathway dysregulation therefore these patients may potentially respond to inhibitors of this pathway. There was a significant association with tumor histological type, while no significant association was observed with other clinicopathological parameters.

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Competing interests

The authors declare that they have no competing interests.

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