

Association of PTEN and ARID1A Expression in Patients with Atypical Endometrial Hyperplasia and Concurrent Endometrioid Carcinoma: A Retrospective Cohort Study

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ABSTRACT

Objective: Some endometrial biopsies from patients with atypical hyperplasia/endometrial intraepithelial neoplasia (AH/EIN) show concurrent endometrioid carcinoma (EC). Hysterectomy is the standard treatment for AH/EIN; however, hormonal therapy is also acceptable for women who wish to preserve fertility. Few studies have simultaneously evaluated the expressions of PTEN and ARID1A in endometrial biopsies to predict concurrent EC. This study aim evaluated whether the loss of PTEN and ARID1A expressions in endometrial biopsies indicate the presence of concurrent EC.

Material and Methods: Endometrial biopsies from 46 patients with AH/EIN who underwent hysterectomy within 3 months between 2011 and 2021 were reviewed. Loss of or intact PTEN and ARID1A expressions was evaluated using immunohistochemistry. The presence or absence of EC in the hysterectomy specimen indicated the presence or absence of concurrent EC. Logistic regression analysis was used to determine associations.

Results: Concurrent EC was found in 32.6% (15/46) of the patients. Loss of PTEN and ARID1A was observed in 54.3% and 8.7% of the endometrial biopsies, respectively. Endometrial biopsies with loss of PTEN expression had an insignificantly higher prevalence of concurrent EC than those with intact PTEN expression (44% versus [vs.] 19%, p -value=0.107). Loss and intact ARID1A expressions showed no difference in the prevalence of concurrent EC (25% vs. 33.3%, p -value=1). Multivariate analysis showed loss of PTEN tended to be associated with concurrent EC (odd ratio

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[OR]=2.38, 95% CI 0.52–10.96), while loss of ARID1A showed no evidence of association (OR=0.92, 95% CI=0.07–12.97).

Conclusion: One-third of the endometrial biopsies with AH/EIN have concurrent EC. The loss of PTEN expression in AH/EIN may indicate the presence of concurrent cancer. However, further studies with larger sample sizes are needed to confirm the results.

Keywords: ARID1A; atypical endometrial hyperplasia; endometrioid carcinoma; immunohistochemistry; PTEN

INTRODUCTION

Endometrial cancer is the sixth most commonly diagnosed cancer in women worldwide and the second most prevalent female genital organ cancer¹. In recent decades, the incidence of endometrial cancer has increased in several Asian countries, including Thailand². Endometrioid carcinoma (EC) is the major histologic type, accounting for 80% of endometrial cancer cases³. The pathogenesis of EC is associated with prolonged exposure to unopposed estrogen. Under such conditions, the proliferative endometrium progresses to endometrial hyperplasia, then to atypical hyperplasia or endometrial intraepithelial neoplasia (AH/EIN), and finally to EC. Total hysterectomy is recommended for women with AH/EIN, but medical treatment with high-dose progestogens and close monitoring is acceptable for women who want to preserve fertility⁴. However, because of the problem of subjective histologic criteria of endometrial hyperplasia and the imperfect accuracy of endometrial biopsy in the detection of endometrial cancer, up to 40% of endometrial samples diagnosed with AH/EIN have concurrent EC^{5–8}. Therefore, adjunctive testing aimed at specifically detecting AH/EIN and excluding co-existing carcinoma is needed, particularly in women who desire future fertility or in patients unsuitable for surgical treatment.

Whole-genome mutational analysis has demonstrated a high mutation frequency in phosphatase and tensin homolog (PTEN) and AT-rich interaction domain 1A (ARID1A) in precancerous lesions and EC^{9,10}. PTEN and ARID1A are involved in cell proliferation and differentiation^{11,12}. Inactivating mutations and loss of protein

expression of both genes have been observed with increasing frequency from precursor lesions to EC^{9,10,13,14}. Additionally, a previous study reported that inactivation of both PTEN and ARID1A promotes cell growth more than inactivation of PTEN or ARID1A alone¹⁵.

Many studies have found that the loss of ARID1A or PTEN expression, as detected by immunohistochemistry, is associated with the existence of EC or its subsequent progression to EC^{16–19}. However, there has been only one study that simultaneously evaluated the expressions of ARID1A and PTEN in endometrial biopsies to predict concurrent EC¹⁹. Therefore, this study aimed to evaluate whether the loss of ARID1A and PTEN expressions in endometrial tissue samples with AH/EIN is associated with concurrent EC.

MATERIAL AND METHODS

Sample size estimation

The sample size was estimated to test the differences between two independent proportions, i.e., the proportion of outcome (concurrent EC) in an exposed group (loss of protein expression) versus the proportion of outcome in an unexposed group (retained protein expression). Based on previous studies, such values were 93% vs. 38% for PTEN¹⁸ and 94% vs. 14% for ARID1A¹⁶. We used a two-sided significance level of 5% and a power of 80%. We got at least 30 cases to cover both PTEN and ARID1A.

Patients, samples, and clinical data

This retrospective cohort study included patients diagnosed with AH/EIN in endometrial tissue from any

collection procedure (aspiration, curettage, or biopsy) who subsequently underwent hysterectomy within 3 months at a university hospital between January 2011 and December 2021. Similar to most previous studies^{20,21}, we used an interval of surgery no later than 3 months to define concurrent EC. Patients diagnosed with endometrial cancers other than endometrioid carcinoma were excluded. This study used the term “endometrial biopsy” to represent any endometrial tissue collection procedure.

We searched for eligible cases in the surgical pathology database of the Department of Pathology using the search terms “complex hyperplasia with atypia”, “simple hyperplasia with atypia”, “atypical hyperplasia”, or “endometrial intraepithelial neoplasia”. The terms “complex and simple” were used in the prior version of the World Health Organization classification of endometrial hyperplasia, whereas a two-tier system (endometrial hyperplasia without atypia and atypical hyperplasia/endometrioid intraepithelial neoplasia) has been recommended since 2014²².

Clinical data, including age, body mass index (BMI), parity, history of diabetes, and hormonal treatment after AH/EIN diagnosis, were obtained from electronic medical records. Information on smoking status and endometrial thickness was not included as a study variable because of a large amount of missing data.

Histopathological evaluation

All histological slides of endometrial biopsies diagnosed with endometrial hyperplasia and subsequent hysterectomy were reviewed to confirm the diagnosis of AH/EIN based on the World Health Organization classification, fifth edition²³. Briefly, AH/EIN is morphologically defined as endometrial changes with crowned glandular architecture (glands exceeding the stroma) and altered epithelial cytology, distinct from the surrounding endometrium. Cytological changes (various types of metaplasia) may accompany nuclear atypia, with irregularly distributed, enlarged, vesicular nuclei with distinct nucleoli. A third-year pathology resident and senior pathologist independently

reviewed all slides. If there was a disagreement between the two reviewers, the slides were reviewed together and a conclusion was made through discussion.

The diagnosis of the hysterectomy specimens was based on pathological reports and also reviewed. Patients who showed the presence of EC in hysterectomy specimens were defined as having concurrent EC, whereas those with other diagnoses were denoted as having no concurrent EC.

Immunohistochemistry and evaluation

We selected one formalin-fixed, paraffin-embedded tissue block per case which had the largest quantity of the lesion. The tissue block of each case was sectioned at a thickness of 4 µm, transferred to glass slides, heated in a microwave for 10 minutes, followed by a hot air oven (60 °C) for 15 minutes, and placed in an Autostainer (Bond-max; Leica). The sections were deparaffinized with xylene, rehydrated by treatment with a series of graded alcohols, and then processed for antigen retrieval using the ER solution (Tris EDTA, pH 8.9–9.1) and blocking endogenous enzyme using 3% hydrogen peroxide with stabilizers. The sections were incubated with primary antibodies against ARID1A (EPR13501, 1:500; Abcam) or PTEN (6H2.1, 1:100; Dako). Antibody-antigen interaction was detected by a detection reagent (Biotinylated secondary antibody), followed by visualization using 3,3'-diaminobenzidine as a chromogen and counterstaining with hematoxylin.

Nuclear staining for ARID1A and nuclear and/or cytoplasmic staining for PTEN were defined as positive immunoreactivity. Endometrial stromal cells were used as the positive controls. The percentage of positively stained cells, regardless of the intensity, was recorded and classified as intact or lost. The absence of any positively stained epithelial cells (0%) was considered a loss of expression; otherwise, intact staining was assigned.

Statistical analysis

Patient characteristics are presented as percentages, means, or medians, as appropriate. Clinicopathological

characteristics and the protein expression status between patients with and without concurrent EC were compared using the t-test or Wilcoxon rank-sum test for continuous variables (e.g., age, BMI) and the chi-squared test or Fisher exact test for discrete variables (e.g., hormonal treatment). Logistic regression analysis was used to determine the association between variables and concurrent EC. All statistical analyses were performed using R software (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at a p-value<0.05.

Ethical approval

The Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Thailand, approved the study (REC. 64-510-5-1).

RESULTS

Patient characteristics

Sixty-six patients diagnosed with AH/EIN by endometrial biopsy underwent subsequent hysterectomy within 3 months. Upon review, 12 patients had non-AH, five had invasive carcinoma, and two had inadequate tissue for further immunohistochemistry. Additionally, one patient with a histologic diagnosis of serous carcinoma in the hysterectomy specimen was excluded, leaving 46 patients in the final analysis. The endometrial sample collection procedures included endometrial biopsy (n=27), curettage (n=17), and manual vacuum aspiration (n=2). Fifteen hysterectomy specimens showed EC (15/46, 32.6%). The noncancer diagnoses in the remaining 31 patients included AH/EIN (n=1), benign hyperplasia (n=11), and other benign endometrial conditions (n=19).

Table 1 Clinical characteristics of patients and protein expressions in endometrial tissue samples

Variable	All patients	Concurrent carcinoma (n, row%)		p-value
	n (column %)	Presence (n=15)	Absence (n=31)	
Age, median (IQR)	50 (8)	49 (7)	51 (8)	0.169
<50 years	19	8 (53.3)	11 (35.5)	0.249
≥50 years	27	7 (46.7)	20 (64.5)	
BMI, kg/m ² , median (IQR)	29.8 (24.3, 33.0)	29.9 (26.1, 32.6)	28.3 (24.2, 32.7)	0.574
Parity, median (IQR)	1 (0, 2.0)	1 (0, 1.5)	1 (0, 2.0)	0.275
Diabetes				
No	41 (89.1)	15 (36.6)	26 (63.4)	0.157
Yes	5 (10.9)	0	5 (100)	
Hormonal treatment				
No	35 (76.1)	14 (40)	21 (60)	0.073
Yes	11 (23.9)	1 (9)	10 (91)	
Tissue quantity, median (IQR)	1.5 (0.5, 3.0)	2 (1, 3.25)	1 (0.5, 2.75)	0.295
Sampling procedure ^a				
Biopsy	26 (60.5)	6 (23)	20 (77)	0.127
Curettage	16 (37.2)	8 (50)	8 (50)	
MVA	1 (2.3)	0	1 (100)	
PTEN expression				
Intact	21 (45.7)	4 (19)	17 (81)	0.107
Loss	25 (54.3)	11 (44)	14 (56)	
ARID1A expression				
Intact	42 (91.3)	14 (33.3)	28 (66.7)	1
Loss	4 (8.7)	1 (25)	3 (75)	

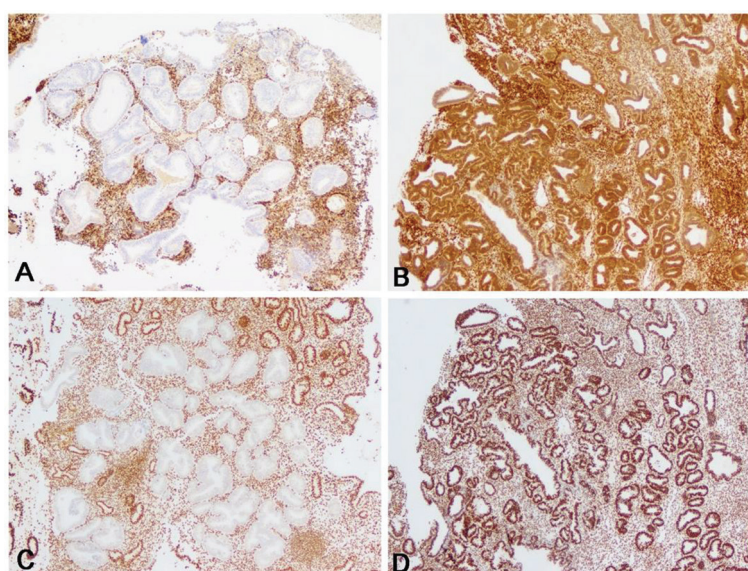
IQR=interquartile range; BMI=body mass index; MVA=manual vacuum aspiration; PTEN=phosphatase and tensin homolog; ARID1A=AT-rich interaction domain 1A; ^a Three missing data

Table 1 shows the clinical characteristics and protein expression levels of all the patients according to the presence or absence of concurrent EC. The median patient age was 50 years (n=46). Eleven patients received progesterone treatment after the diagnosis of AH/EIN. Endometrial biopsy accounted for more than half of the cases (60.5%), followed by curettage (37.2%). There were no significant differences in the prevalence of concurrent EC with respect to age, BMI, parity, or diabetes. Patients who did not receive hormone treatment had a higher frequency of concurrent EC than those who received hormone treatment (40% versus [vs.] 9%), with marginal significance (p-value=0.073). Curettage specimens had a higher proportion of concurrent EC (50%) compared to biopsy samples (23%), however, the difference was not statistically significant (p-value=0.127). The tissue volume of endometrial specimens between the concurrent EC and no concurrent EC was also not significantly different.

ARID1A and PTEN expressions

Immunostaining of representative samples is shown in Figure 1. The result of immunostaining in endometrial biopsy is shown in Table 1. Loss of PTEN expression was observed in 54.3% (25/46) of patients, whereas loss of ARID1A was observed in 8.7% (4/46). Only one patient showed loss of ARID1A and PTEN expressions.

Patients with loss of PTEN expression on endometrial biopsy had a higher prevalence of concurrent EC than those with intact PTEN expression (44% vs. 19%); however, the difference was not statistically significant (p-value=0.107). Endometrial biopsies with loss of ARID1A expression showed a non-significant difference in the prevalence of concurrent EC compared with those with intact ARID1A expression (25% vs. 33.3%, p-value=1).



PTEN=phosphatase and tensin homolog; ARID1A=AT-rich interaction domain 1A

(A) Loss of PTEN expression; (B) Intact PTEN expression; (C) Loss of ARID1A expression; (D) Intact ARID1A expression

Figure 1 Representative slides of immunostaining

Association of variables with concurrent EC

Table 2 presents the results of univariate and multivariate logistic regression analyses for the risk of concurrent EC. Hormonal treatment was inversely associated with the presence of concurrent EC; however, the effect did not exist in the multivariate model. Loss of PTEN expression was associated with an increased risk of concurrent EC in univariate (odds ratio [OR]=3.34, 95% confidence interval [CI]: 0.87–12.82) and multivariate analyses (OR=2.38, 95% CI 0.52–10.96), but it was not statistically significant, likely owing to the small sample size. Loss of ARID1A expression and other factors, including age, BMI, diabetes, and parity, were not significantly associated with concurrent EC in univariate and multivariate analyses.

DISCUSSION

We found that one-third of patients with AH/EIN confirmed by endometrial biopsy had concurrent EC. Our results suggest that the loss of PTEN expression is a common event in AH/EIN, as half of the endometrial biopsies showed loss of PTEN expression. In contrast, loss of ARID1A expression was found in only 8.7% of patients. Consistent with previous studies, a loss of PTEN expression was potentially associated with concurrent EC.

PTEN is a protein encoded by the tumor suppressor gene PTEN. It plays a crucial role in cell growth, proliferation, and differentiation by acting as a negative regulator of the phosphatidylinositol 3-kinase pathway¹¹. PTEN mutations account for the most frequent mutations

Table 2 Association of clinical factors and protein expressions with concurrent EC according to univariate and multivariate logistic regression analyses

Variable	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age (years)				
<50	1	0.253		
≥50	0.48 (0.14–1.68)		0.58 (0.13–2.67)	0.486
Body mass index, kg/m ²	1.03 (0.93–1.14)	0.597	1.04 (0.91–1.18)	0.593
Parity				
Nulliparous	1			
Parity ≥1	0.63 (0.18–2.2)	0.468	0.78 (0.17–3.56)	0.746
Diabetes				
No				
Yes	0 (0–Inf)	0.992	0 (0–Inf)	0.992
Hormone treatment				
No				
Yes	0.15 (0.02–1.31)	0.086	0.22 (0.02–2.16)	0.192
PTEN expression				
Intact				
Loss	3.34 (0.87–12.82)	0.079	2.38 (0.52–10.96)	0.267
ARID1A expression				
Intact				
Loss	0.67 (0.06–7.01)	0.735	0.92 (0.07–12.97)	0.952

CI=confidence interval; OR=odds ratio; EC=endometrioid carcinoma; PTEN=phosphatase and tensin homolog; ARID1A=AT-rich interaction domain 1A

in EC and AH/EIN^{10,24}, and loss of PTEN function has been implicated in the pathogenesis of several different tumors, including EC. The complete absence of PTEN staining by immunohistochemistry has been proven to reliably indicate the loss of functional PTEN mutation²⁵.

We found a loss of PTEN expression in half of the patients with AH/EIN (54.3%), which is consistent with the findings of previous studies (range, 50–64%)^{17,19,26}. Moreover, we found a considerably higher frequency of concurrent EC in AH with loss of PTEN expression than in those with intact PTEN expression, which is also consistent with the findings of three previous studies that have similar aims to the current study^{17,19,27}. However, these studies and the present study did not find a statistically significant association between the loss of PTEN expression and the presence of concurrent EC. In contrast, Robbe et al. found a significantly higher frequency of concurrent EC in AH with loss of PTEN expression than in those with intact PTEN expression (93% vs. 46%)¹⁸. However, their study used a longer interval (9 months) for hysterectomy after endometrial biopsy to define concurrent cancer. Therefore, the results may not be comparable. Additionally, the inconsistent results may be due to the small sample size of the individual studies. The meta-analysis, which included three aforementioned studies by Pavlakis et al., Robbe et al., and Berg et al., showed that loss of PTEN expression was significantly associated with concurrent cancer (OR=2.51, 95% CI: 1.36–4.61) with a pooled sensitivity of 0.68 and a pooled specificity of 0.44²¹. Based on all of this evidence, the evaluation of PTEN expression in endometrial biopsy with AH/EIN is of value to some extent. As various proteins are also aberrantly expressed in AH/EIN, using a multi-marker scheme to increase the predictability of concurrent EC should be considered²⁶.

ARID1A is a member of the SWI/SNF chromatin-remodeling complex and is involved in the regulation of cell proliferation and differentiation²⁸. ARID1A mutations are found in many cancers, particularly ovarian and uterine

cancers^{29,30}, and most of them are frameshift or nonsense mutations resulting in abnormal or truncated proteins¹². We found loss of ARID1A expression in only 8.7% of patients, which is consistent with findings of two previous studies that found loss of ARID1A expression in 0% and 5% of AH/EIN cases, respectively^{14,19}. In contrast, Yen et al.¹⁶ found a 30.8% loss of ARID1A expression. However, the authors defined aberrant ARID1A expression as either a complete loss or heterogeneous loss, whereas complete loss of expression was assigned in our study and in Vierkoetter et al.'s study¹⁹. We did not find a significant association between loss of ARID1A and the presence of concurrent EC, which is inconsistent with the findings of the two aforementioned studies. These discrepancies may be due to the difference in the criteria used to define the loss of expression and the small sample size of our study.

ARID1A and PTEN are involved in cell proliferation. Ayhan et al. demonstrated that the inactivation of ARID1A and PTEN promotes cell growth more than the inactivation of ARID1A or PTEN alone¹⁵. In addition, they found that all 17 AH/EIN specimens with loss of ARID1A expression had concurrent loss of PTEN expression. However, we found that only one of the four patients with loss of ARID1A expression had concomitant loss of PTEN expression. So, this study could not strongly support the role of the dual loss of ARID1A and PTEN expressions in predicting EC. Further studies with larger sample sizes are warranted.

Our study has some limitations. We did not include certain confounding factors that may affect the results. We did not assess the severity of hyperplasia nor the degree of nuclear atypia. Based on the current WHO classification, there are no definite criteria for these features. However, there was one study found that the degree of nuclear atypia in biopsy samples strongly predicted carcinoma in hysterectomy specimens³¹. However, the authors found no significant differences in the mutational load of various genes, including ARID1A and PTEN, with regard to the degree of nuclear atypia. This suggests that the

severity of nuclear atypia may not influence ARID1A and PTEN expression. Hormonal treatment might affect the concurrent EC, but we minimized the effect by multivariate logistic regression analysis. However, we did not include certain factors, such as endometrial thickness or smoking status, as confounding variables that may have affected the association of interest. Additionally, the small sample size may have limited the power of this study to detect differences or associations.

CONCLUSION

In conclusion, our study confirms that approximately one-third of endometrial samples with AH/EIN have co-existing endometrial cancer. The loss of PTEN expression in AH/EIN may indicate the presence of concurrent cancer, whereas the loss of ARID1A expression may not. However, further studies with a larger sample size are needed to confirm the results.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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