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KISS1, P53, and PTEN immunoexpressions and prediction of malignancy in endometrial intraepithelial neoplasia lesion within endometrial polyp

Eser Çolak[1]*, Özgür Hilal Erinanç[2], Semra Eroğlu[1], Tahir Eryılmaz[3], Emel Ebru Özçimen[1], Ali Ayhan[3]

Abstract

Objective: Aim of this study to evaluate the usefulness of phosphase and tensin homologous deleted on chromosome 10 (PTEN), p53, and kisspeptin (KISS1) immunoexpressions in predicting malignancy in endometrial intraepithelial neoplasia within the endometrial polyps.

Material and method: This cross-sectional study was based on chart data from a convenience sample of patients who underwent probe curetage at the Gynecology and Obstetrics Clinic of Başkent University Ankara and Konya Practice and Research Hospitals, Turkey. A total of 169 patients were allocated into 5 groups, comprising the EIN-p group: 62 patients with an endometrial intraepithelial neoplasia lesion within an endometrial polyp, EC group: 17 patients with an endometrial carcinoma, EP-h group: 30 patients with hyperplasia on the background of the polyp but no atypia, EP group: 30 patients with endometrial polyps, and NE group: 30 patients with a normal (proliferative) endometrium. P53, PTEN, and KISS1 expressions between the groups were evaluated.

Results: In the EIN-p and EC groups, P53 and KISS1 expressions were moderate or strong. In the NE, EP and EP-h groups, KISS1 was weakly stained and P53 expression was negative. The number of patients with strong p53 and KISS1 expressions in the EC group was higher and this difference was statistically significant ($P < 0.001$). With PTEN immunostaining, the EC and EIN-P groups were weakly stained, whereas the NE, EP, and EP-h groups had moderate or strong staining. Strong staining rates were higher in patients in the NE and EP groups than in the EP-h group ($P < 0.001$).

Conclusion: In addition to the literature about P53 and PTEN, according to the data obtained herein, it was speculated that KISS1 may play an important role in the malignant transformation of endometrial polyps and it might be used as a predicting marker in this patient group.

Keywords: P53; PTEN; KISS1; Endometrium; EIN; Polyp

Introduction

Endometrial polyps are focal overgrowths of the endometrial mucosa that progress towards the cavity and are generally benign (1). Although they often show spontaneous regression, they rarely show premalignant or malignant changes (2). The rate of malignancy potential of endometrial polyps ranges from 0.3%–4.8% (3).

Endometrial hyperplasia, particularly with atypia, is a significant clinical concern because it can be a precursor to endometrial cancer. Atypical hyperplasia (EIN), as a precancerous lesion, requires a different approach in treatment than other types of hyperplasia and adenocarcinomas.

EIN contains many of the genetic changes seen in endometrioid endometrial carcinomas. The most recent World Health Organization classification of ECs (2014) was based mostly on morphologic features (4). The most common genetic alterations encountered in endometrioid (type 1) ECs are mutations in phosphase and tensin homologous deleted on chromosome 10 (PTEN), Kirsten rat sarcoma virus homolog, catenin beta-1 gene, and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha, and microsatellite instability. In contrast, type 2 ECs, which are mostly serous carcinomas, show consistent TP53 mutations and human epidermal growth factor receptor-2/neu gene amplification (5,6).

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1 Baskent University School of Medicine, Dept of Gynecology and Obstetrics, Konya Medical and Research Center, TR
2 Baskent University School of Medicine, Dept of Pathology, Konya Medical and Research Center, TR
3 Baskent University School of Medicine, Dept of Gynecology and Obstetrics Ankara, TR
*** Corresponding Author:** Eser Çolak **E-mail:** dresercolak@hotmail.com

However, p53 mutation can be seen in 12%–30% of endometrioid endometrial cancers.

To date, many factors, including clinical and biological, have been studied to predict premalignant or malignant changes of endometrial polyps (7,8). In recent years, immunhistochemical studies conducted to predict the risks of malignancy of endometrial polyps have attracted great attention. Studies on the immune expression of tumor supressor genes, such as p53 and PTEN, have been more common (7,9). P53 was one of the first tumor suppressor genes to be described. However, in recent years, it has been understood that it is a promoter oncogen (10). PTEN, which modulates cell proliferation, cell apoptosis, and migration, was isolated as a bit tumor suppressor gene in 1997 (11). In addition to these 2 biological factors, kisspeptin (KISS1) protein expression has also been added in recent years for endometrial malignancies (12,13). However, it is still a matter of debate as to how the KISS1 protein plays a role in the regulation of different organ malignancies (14).

Therefore, in this study, it was aimed to evaluate the usability of PTEN, P53, and KISS1 immunoexpressions in predicting malignancy in endometrial intraepithelial neoplasia within the endometrial polyps, and shed light on this for future studies on this subject.

Material and method

This cross-sectional study was based on chart data from a convenience sample of patients who underwent probe curetage at the Gynecology and Obstetrics Clinic of Başkent University Ankara and Konya Practice and Research Hospitals, Turkey, between January 2010 and December 2019. The study protocol was approved after obtaining the necessary permissions from Başkent University Ethics Committee (register number KA19/257).

In the study period, the pathology reports were reviewed and 62 patients of endometrial intraepithelial neoplasia lesion within endometrial polyp (EIN-p group), 17 patients with EC arising from endometrial polyps (EC group), 30 patients with hyperplasia on the background of the polyp but no atypia (EP-h group), 30 patients with endometrial polyps (EP group), and 30 patients with normal (proliferative) endometrium (NE group) were included the study. Patients in the EIN-p group included those with hysterectomy in the hospital after probe curettage. Thus, the results of the hysterectomy pathologies of patients in the EIN-p group were compared in terms of immunostaining according to malignancy, myometrial invasion, and depth of invasion. Sections were incubated at 56 °C for 24 h and deparaffinized in xylene, followed by rehydration by passing through descending concentrations of alcohol (100%–70%). The sections were then placed in 0.5% hydrogen peroxide in methanol for 5 min to block endogenous peroxidase activity. Antigen retrieval was performed by heating the sections in trisodium citrate buffer (10 mM of sodium citrate, pH 6.0) for 10 min in a microwave. The slides were rinsed 3 times in deionized distilled water and 0.3% hydrogen peroxidase was applied to the sections for 30 min to block endogenous peroxidase activity. The slides were then washed again in phosphate-buffered saline (PBS) for 2–3 mins. To reduce non-specific background staining, Ultra V Block (Thermo Scientific, Cheshire, UK) was applied to the sections for 5 min. The primary antibodies used were PTEN and mouse monoclonal antibody (PTEN (a2B1): sc-7974), Santa Cruz, CA, USA, at a dilution of 1:100 overnight), p53 and mouse monoclonal antibody (p53(DO-1): sc-126), at a dilution of 1:100 for 2 h), and KISS-1 and mouse monoclonal antibody (KISS-I (24-Q): sc-101246 at a dilution of 1:100 for 2 h). After incubation, the primary antibody slides were washed with PBS for 5 min. Biotinylated goat anti-polyvalent (Lab Vision Corp., Fremont, CA) was applied and washed in PBS. Next, streptavidin peroxidase (Lab Vision Corp.) was applied and the slides were incubated for 15 min at room temperature. The immunoreaction was visualized using 3,3'-diaminobenzidine-tetrahydrochloride-dihydrate (Thermoscientific Dako, Glostrup, Denmark) as a chromogen. The slides were counterstained using Mayer's hematoxylin solution and mounted. The specificity of the staining was confirmed using a positive control.

All of the slides were analyzed by 2 pathologist observers. PTEN expression was observed both in stromal cells and endometrial glandular cells in the cytoplasm; however, stromal cells had a stronger immunoreactivity for PTEN than the glandular cells. Stromal staining was present in all of the study groups (EC, EIN-p, EP-h, EP, and NE). However, glandular expression was heterogenous. For rating of the PTEN staining, that performed by Karuna Garg et al. was used (15). PTEN expression was graded as 2 in normal endometria. Weakly staning of PTEN expression was mostly seen in the EC and EIN-p groups (Figure 1). KISS1 staining was graded by taking into account the staining intensity and percentage of staining. KISS proteins were mainly located in the cytoplasm of glandular epithelia. The staining intensity was evaluated by applying the following scale: 0 for negative, 1+ for low, 2+ for moderate, and 3+ for strong intensity. The scoring criteria of the percentage of stained cells were: 0 for <10%, 1 for 10%–25%, 2 for 10%–50%, 3 for 51%–80%, and 4 for >80%. The final score was calculated as the product of the percentage and staining intensity, resulting in weak (0–2 points), moderate (3–6 points), and strong (7-points) KISS-1 expression (16) (Figure 1). The expression of p53 was determined by counting 500 cells over randomly selected high-power fields. Nuclear brown staining indicated positive expression when the percentage of cells stained was >10%, and negative when the percentage of cells stained was <10%. In this study, the positive p53-immunohistochemical staining was scored as moderate and strong nuclear immunoreactivity when in less than 50% and more than 50% of the tumor cells, respectively (Figure 1).

IBM SPSS Statistics 25.0 for Windows (IBM Corp., Armonk, NY, USA) was used to analyze the variables. Variables were given as the median (IQR), percentage, and frequency values. Categorical data were analyzed using the Fisher exact and the chi-square tests. In cases where the expected frequencies were less than 20%, the evaluation was made using the Monte Carlo simulation method to include these frequencies in the analysis. $P < 0.05$ and $P < 0.01$ were accepted as statistically significant.

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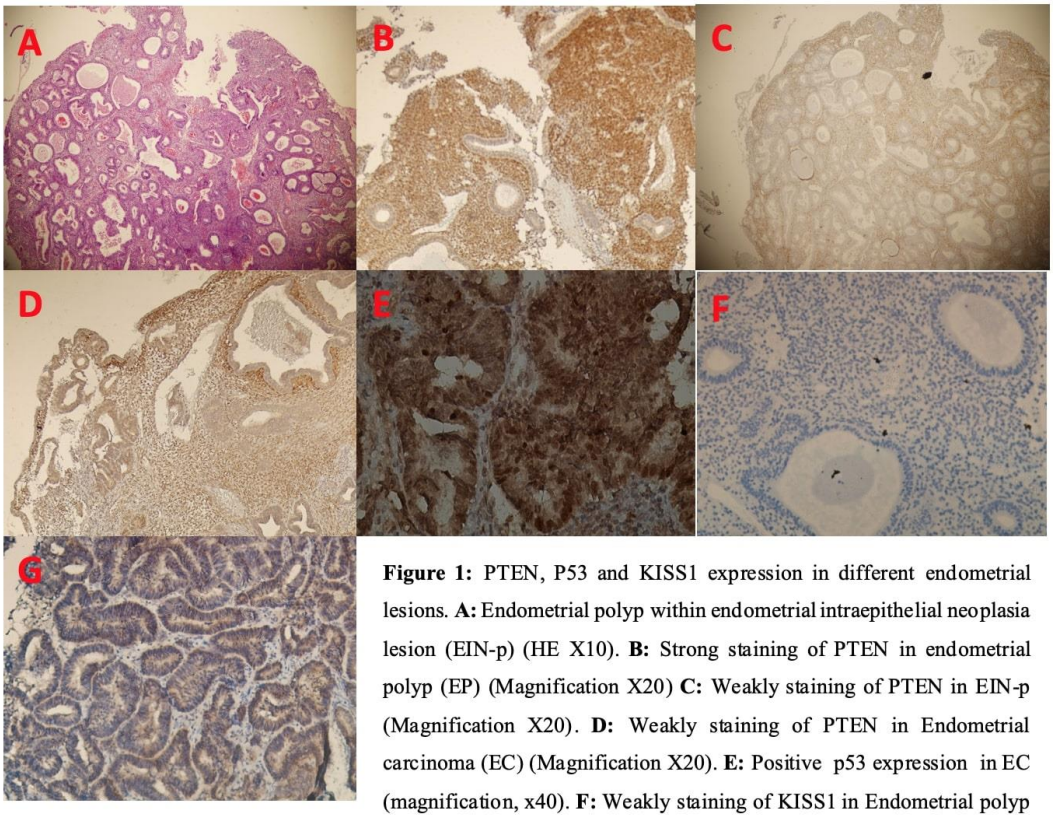

Figure 1: PTEN, P53 and KISS1 expression in different endometrial lesions. **A:** Endometrial polyp within endometrial intraepithelial neoplasia lesion (EIN-p) (HE X10). **B:** Strong staining of PTEN in endometrial polyp (EP) (Magnification X20) **C:** Weakly staining of PTEN in EIN-p (Magnification X20). **D:** Weakly staining of PTEN in Endometrial carcinoma (EC) (Magnification X20). **E:** Positive p53 expression in EC (magnification, x40). **F:** Weakly staining of KISS1 in Endometrial polyp (EP) (Magnification X40). **G:** Increased staining of KISS1 compare to normal endometrium.

Results

Among the patients included in the study, the mean age of the 90 patients in the benign endometrial lesions groups (NE, EP, and EH-p) was 46 years, while the mean age of the 62 patients in the EIN-p group was 52 years, and mean age of the 17 patients in the EC group was 54 years.

The comparison of the study groups according to immunostaining of p53, KISS1, and PTEN is presented in Table 1. In the benign groups, NE, EP, and EP-h, all of the samples showed negative staining with p53 and weak staining with KISS1, while in the EC and EIN-p groups, all of the samples showed moderate or strong staining with p53 and KISS1. By contrast, when staining with PTEN, no strong staining was observed in the EC or EIN-p groups, whereas all of the samples in the benign groups showed moderate or strong staining.

The negative, moderate, and strong staining rates for p53 in the EC group were 17.60%, 11.80%, and 70.60%, respectively, whereas in the EIN-p group, the rates were 24.20%, 37.10%, and 38.70%, respectively.

The weak, moderate, and strong staining rates for KISS1 immunosuppression were 29.40%, 11.80%, and 58.80%, respectively, in the EC group, whereas the rates were 1.60%, 43.50%, and 54.80%, respectively, in the EIN-p group. All of the samples in the NE, EP, and EP-h groups were negative for p53 staining, and they were weakly stained with KISS1.

Similarly, p53 and KISS1 showed stronger staining in the EC and EIN-p groups when compared with the other benign groups, and the EC group showed stronger staining than the EIN-p group. This difference was statistically significant ($P < 0.001$) (Table 2, Figures 2 and 3).

In terms of PTEN staining, no strong staining was observed in the EC or EIN-p groups, whereas 70.60% of the EC group showed weak staining, and 79.00% of the EIN-p group showed moderate staining. PTEN staining in the EC group was statistically significantly weaker when compared with the EIN-p group ($P < 0.001$). Weak staining with PTEN was never observed in the benign lesion groups, while 83.30% of the NE group and 80.00% of EP group showed strong staining, and 80.00% of EP-h group showed moderate staining, and this difference was statistically significant (Table 2, Figure 4).

When the EIN-p group was evaluated within itself, 8 of the 62 patients with hysterectomy were evaluated as having EC based on the pathology results. Of these malignant patients, 3 had myometrial invasion, 1 of which had a depth of >1/2 of the myometrium (Table 3). Of the 8 preparations of patients with malignancy, 7 were stained moderately or strongly with KISS1 and p53, and the preparation of 1 patient was negative for p53 and weakly stained with KISS1. However, this difference was not statistically significant ($P = 0.648$ for p53, $P = 0.023$ for KISS1).

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Table 1: Comparison of endometrial lesion groups according to immunostaining of p53, KISS1, and PTEN.

		EIN-p	EC	EP-h	EP	NE	Total	P-value
p53	**Negative**	15a (13.90%)	3a (2.80%)	30b (27.80%)	30b (27.80%)	30b (27.80%)	108 (100.00%)	0.001 Ω
	Moderate	23a (92.00%)	2b (8.00%)	0b (0.00%)	0b (0.00%)	0b (0.00%)	25 (100.00%)	
	Strong	24a (66.70%)	12b (33.30%)	0c (0.00%)	0c (0.00%)	0c (0.00%)	36 (100.00%)	
kiss	**Weak**	1a (1.00%)	5b (5.20%)	30c (31.30%)	30c (31.30%)	30c (31.30%)	96 (100.00%)	0.001 Ω
	Moderate	27a (93.10%)	2b (6.90%)	0b (0.00%)	0b (0.00%)	0b (0.00%)	29 (100.00%)	
	Strong	34a (77.30%)	10a (22.70%)	0b (0.00%)	0b (0.00%)	0b (0.00%)	44 (100.00%)	
pten	**Weak**	13a (52.00%)	12b (48.00%)	0c (0.00%)	0c (0.00%)	0c (0.00%)	25 (100.00%)	0.001 Ω
	Moderate	49a (53.80%)	5b (5.50%)	26a (28.60%)	6b (6.60%)	5b (5.50%)	91 (100.00%)	
	Strong	0a (0.00%)	0a. b (0.00%)	4b (7.50%)	24c (45.30%)	25c (47.20%)	53 (100.00%)	
Total		62 (36.70%)	17 (10.10%)	30 (17.80%)	30 (17.80%)	30 (17.80%)	169 (100.00%)	

Ω Monte Carlo Chi square method (exact). There is no statistically significant difference between the same letters (by Row). **EIN-p:** Endometrial intraepithelial neoplasia lesion within the endometrial polyp. **EC:** Endometroid carcinom. **EP-h:** Endometrial polyp with hyperplasia without atypia. **EP:** Endometrial polyp. **NE:** Normal (proliferative) endometrium

Table 2: Comparison of the degree of immunostaining of p53, KISS1, and PTEN in the endometrial lesions.

		p53			KISS1			PTEN			Total
		Negative	Moderate	Strong	Weak	Moderate	Strong	Weak	Moderate	Strong	
EIN -p	n (%)	15a (24.20%)	23b (37.10%)	24c (38.70%)	1a (1.60%)	27b (43.50%)	34b (54.80%)	13a (21.00%)	49a (79.00%)	0b (0.00%)	62 (100.00%)
EC	n (%)	3a (17.60%)	2a (11.80%)	12b (70.60%)	5a (29.40%)	2a. b (11.80%)	10b (58.80%)	12a (70.60%)	5b (29.40%)	0b (0.00%)	17 (100.00%)
EP-h	n (%)	30a (100.00%)	0b (0.00%)	0b (0.00%)	30a (100.00%)	0b (0.00%)	0b (0.00%)	0a (0.00%)	26b (86.70%)	4a (13.30%)	30 (100.00%)
EP	n (%)	30a (100.00%)	0b (0.00%)	0b (0.00%)	30a (100.00%)	0b (0.00%)	0b (0.00%)	0a (0.00%)	6a (20.00%)	24b (80.00%)	30 (100.00%)
NE	n (%)	30a (100.00%)	0b (0.00%)	0b (0.00%)	30a (100.00%)	0b (0.00%)	0b (0.00%)	0a (0.00%)	5a (16.70%)	25b (83.30%)	30 (100.00%)
p			0.001 Ω			0.001 Ω			0.001 Ω		

Table 3: Distribution of cases in the EIN-p group

		Total
Carsinoma (negative/positive)	n (%)	54 (87.10%) 5 (62.50%) 2 (66.70%)
Myometrial invasion (negative/positive)	n (%)	8 (12.90%) 3 (37.50%) 1 (33.30%)
Invasion depth (<1/2–>1/2)	n (%)	62 (100.00%) 8 (100.00%) 3 (100.00%)

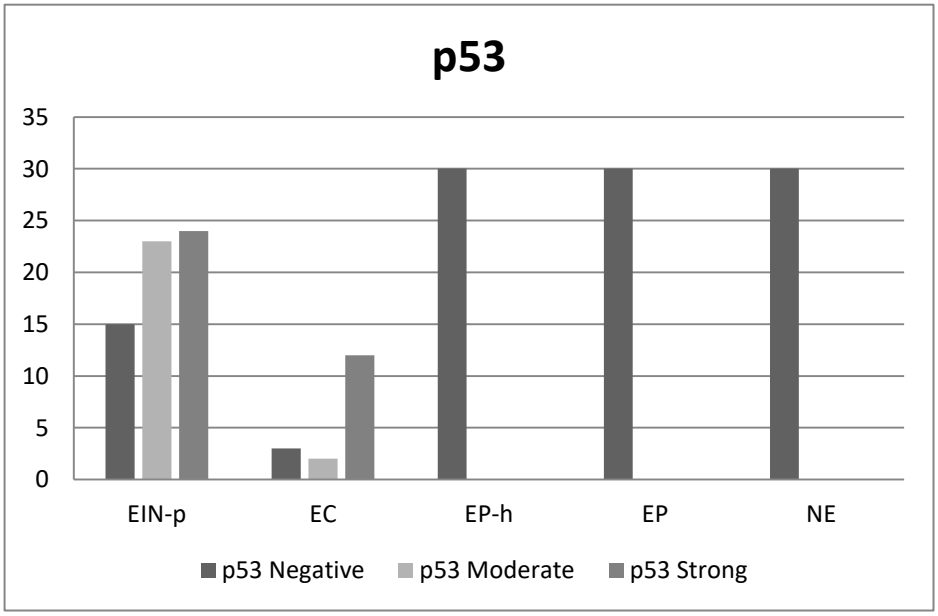

Figure2: immunstaining of p53 in different endometrial lesions.

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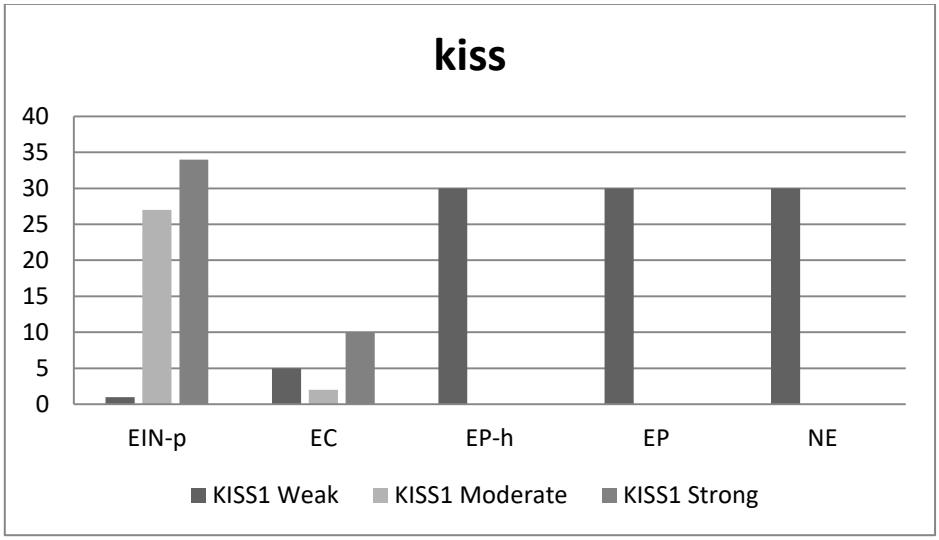

Figure 3: Immunstaining of KISS1 in different endometrial lesions.

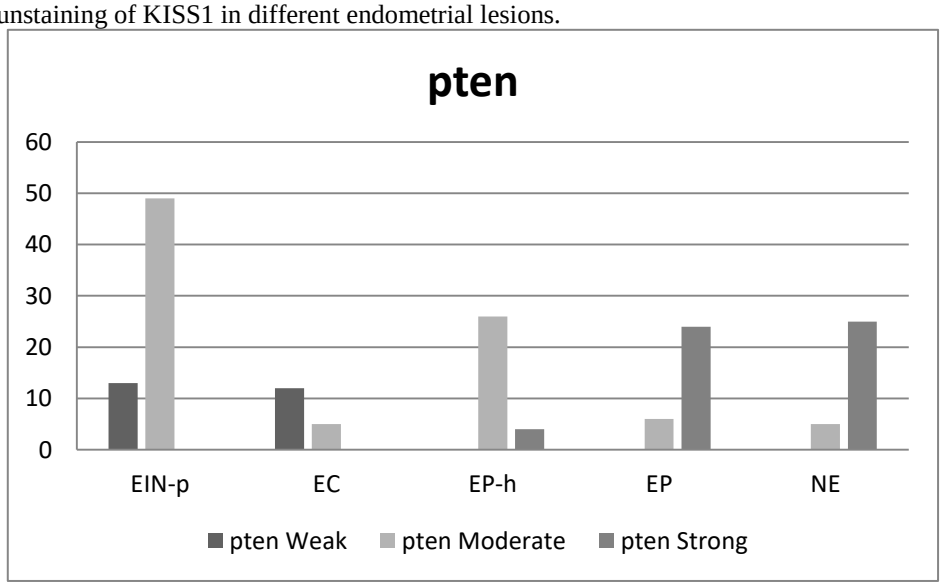

Figure 4: Immunstaining of PTEN in different endometrial lesions.

Discussion

In the current study, we aimed to evaluate the KISS1 in the malignant transformation of EIN-p using immunohistochemistry and compare the KISS1 expression to other tumor suppressor genes, P53 and PTEN, which have been the most studied. It was found that there was decreased PTEN expression in the premalignant and malignant endometrial lesions, while KISS1 expression was high. Expressions of p53 were wild-type. To the best of our knowledge, although there are many studies on p53 and PTEN, there are no studies on the evaluation of KISS1 in both premalignant and malignant endometrial lesions.

In 2016, it was suggested that PTEN immunohistochemistry could be used to distinguish premalignant and malignant lesions, especially among endometrial lesions, in a multidisciplinary panel with the participation of the European Society for Medical Oncology, the European Society for Radiotherapy and Oncology, and the European Society for Gynecological Oncology (17).

Although there is a consensus on the role of PTEN immunoexpression to differentiate endometrial benign tissues from malignant tissues, there is controversy on its role of in premalignant-malignant lesion discrimination.

Yang et al. (18) emphasized that PTEN immunexpression decreased significantly in ECs when compared with normal endometrial tissue. Adomaitiene et al. showed that there was a significant loss of PTEN expression in ECs, whereas malignant polyps (including polyps from patients in whom a polyp was found with coexisting endometrioid cancer or who had a focus of cancer inside) were reported as having high PTEN expression (19). In the current study, decreased PTEN expression in the EC and EIN-p groups was found when compared with the other lesion groups (EP-h, EP, and NE). In addition, weak staning was increased in the EC group when compared to the EIN-p group, which was premalignant. Among the benign groups, 80% of the patients in the EP-h group showed moderate staining with PTEN, and 80% of patients in the NE and EP groups showed strong staining with PTEN. Abrao et al. (7)

reported that PTEN expression decreased in polyps with EIN when compared with polyps without atypia, which was similar to the current results.

Studies have shown that the loss of PTEN and wild-type p53 (focal weak nuclear positivity) expression supported endometrioid carcinomas, while the retained expression of PTEN and aberrant expression of p53 (strong diffuse nuclear staining or completely absent staining), favored serous carcinomas (20,21). In the current study, it was found that p53 was negative in the NE, EP and EP-h groups. On the other hand, when the EC group was compared with the EIN-p group with p53 positivity, it was found that staining in the EC group was significantly stronger than that in the EIN-p group. However, Maia et al. showed that p53 was detected more frequently during the proliferative phase in endometrial polyps, similar to in normal endometria. Heterogeneous and weak expression of p53 in noncancerous endometria has been reported previously in cases of endometrial hyperplasia and metaplasia (22,23), and researchers believed that the presence of p53 expression may have been a consequence of elevations of wild-type p53 to correct DNA damage, and not the accumulation of the stable mutant form (24). Most of the mutation in TP53 increases the stabiliy of the protein, leading to an accumulation that is detectable by immunohistochemical staining. Hence, it was reported that the abnormal diffuse accumulation of p53 has been related to tumor cells and TP53 mutations most commonly seen in high-grade serous carcinomas. In the present study, 70% of the carcinoma patients showed nuclear staining of p53, but not with a diffuse pattern. In another study in which p53 mRNA real-time polymerase chain reaction and p53 protein immunohistochemistry were examined, the control, adenomyosis, polyp, and carcinoma groups were compared and increased p53 expression was reported as highest in the carcinoma group and lowest in the control group (25).

KISS1 expression rates have been reported very differently in different organ and tissue malignancies. Increased KISS1 expression has been reported in pancreatic and ovarian cancers, especially in the early stage, whereas it has been reported to be decreased in colorectal cancers (26,27). There are few studies on KISS1 expression in endometrial lesions. In a study comparing EC, EIN, and normal endometria, KISS1 mRNA expression was reported as 37.5%, 80%, and 83.3%, respectively (12). Similarly, Kang et al. showed that the prognosis of patients with ECs that were negative for KISS1 expression was significantly poorer than those that were positive for KISS1. They believed that a decreased expression of KISS1 was a poor prognostic factor and was relevant to both the invasive and metastatic capacity of endometrial cancers.

In the current study, weak staining with KISS1 was found in the NE, EP, and EP-h groups. The number of patients with strong or moderate staining was higher in the EC and EIN-p groups, whereas the number of patients with strong staining was higher in the EC group. However, little is known about how KISS1 expression is regulated in cancer cells. It is a matter of debate as to whether KISS1 expression is high from the very first moment or whether it increases in the form of a tumor suppressor gene to reduce invasion and improve prognosis and in premalignant tissues (14). In either case, strong KISS1 expression in the EIN-p and malignant tissues was found to aid in early diagnosis in this study. There is a need for further studies on larger numbers of patients with EIN-p who have had an invasive malignancy result after hysterectomy. In addition, studies on malignancies in different stages can provide information about the early or late expressions of KISS1.

This study had some limitations that including the low number of patients. The malignancy rate was 12% in the EIN-p group. Of the 62 patients diagnosed after probe curettage, 8 were diagnosed as having carcinomas after hysterectomy. PTEN, KISS1, and p53 expressions of the patients in this group were compared. There was no difference in terms of the PTEN expression between the 8 patients who were diagnosed as having EC and the 54 other patients. Although the p53 and KISS1 expressions were stronger in the patients with EC, the difference was not statistically significant. It was thought that this was due to the low number of patients, because some of the patients who were diagnosed as having EIN-p after probe curettage may have undergone treatments other than hysterectomy or patients may have gone for the follow-ups at other clinics for treatment. Despite this limitation, the strength of this study is that it is one of the rare studies on EIN-p among endometrial lesions, and it is the first study on KISS1 expression.

In conclusion, according to the data herein, it was speculated that KISS1 may play an important role in the malignant transformations of endometrial polyps and it might be used as a predicting marker in this patient group.

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Conflict of interest: No actual or potential conflicts of interest exist in relation to this article.

Ethical approval: This study was approved by the local ethics committee of Başkent University (register number KA19/257). All of the participants gave written informed consent prior to participation.

Ethical issues: All authors declare originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the authors responsibilities. The study was conducted under defined rules by the local ethics commission guidelines and audits.

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