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Analysis of Bcl-2, PTEN, p53, and Ki-67 expressions in endometrial cancer arising from endometrial polyp

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Summary

Objective: To compare the expression of the proliferation marker Ki-67, the antiapoptotic protein Bcl-2, and the tumor suppressor genes p53 and PTEN between endometrial cancer arising from endometrial polyp and benign endometrial polyps. *Materials and Methods:* The study was performed retrospectively in 40 patients treated at the present institution between 2006-2011. A total of 20 cases that had endometrial cancer arising from endometrial polyp that met study criteria were included consecutively in the study. For each malign case, one case that had a benign endometrial polyp diagnosed at hysterectomy specimen was included in the study. *Results:* The Ki-67 score was significantly higher in endometrial cancer arising from endometrial polyp group in comparison to the benign polyps ($p < 0.05$). However, the Bcl-2 expression was significantly lower in the endometrial cancer arising from endometrial polyp when compared to the benign polyps ($p < 0.05$). PTEN and p53 expressions were not different between groups ($p > 0.05$). In patients with endometrial cancer, Ki-67, Bcl-2, PTEN, and p53 expressions were not different among histological type, stage, grade, myometrial invasion, polyp size, and lymphovascular space invasion, with an exception of p53. p53 expression was significantly increased in higher grade tumors ($p < 0.05$). *Conclusion:* The results of the present study indicate that there is an inhibition of apoptosis and a decrease in proliferation in benign endometrial polyps. Possibly, at carcinogenesis step of endometrial cancer developed from benign polyp, other additional mutations cause a reverse effect and they increase proliferation and prevent the apoptosis inhibition.

Key words: Endometrial cancer; Polyp; Malignancy; p53; Bcl-2; Ki-67; PTEN.

Introduction

Endometrial polyps are benign lesions characterized by localized hyperplastic overgrowth of stroma and endometrial glands around a vascular stalk. Although there is controversy over malignancy potential of the polyps, the rate of endometrial malignancy arising from the polyps ranges from 0.3% to 4.8% [1]. The exact cause is not known; however, endometrial development and differentiation that could be responsible in the pathogenesis is accomplished by a balance between mitotic activity and apoptosis. Cancer development is related to disturbed regulation of programmed cell death or apoptosis. As one of these apoptosis regulating genes, tumor suppressor p53 is also involved in cell proliferation. P53 inactivation provides the tumor cell with higher capacity for division and proliferation [2]. Bcl-2 is a proto-oncogene protein involved in the regulation of programmed cell death or apoptosis. Bcl-2 suppresses programmed cell death [3]. PTEN is a tumor suppressor gene, and its inactivation or mutation has been detected in many cancers including endometrial cancer [4]. Previous studies have shown that p53 and PTEN signalling pathways play an important role in the pathogenesis of endometrial cancer [5]. Ki-67 is a nuclear antigen which increases in proliferative phase of menstrual cycle and it represents an excellent immunohistochemical marker indicating cell proliferation and mitotic activity [6].

Previous studies have attempted to elucidate the pathogenesis of endometrial cancer using Bcl-2, PTEN, Ki-67, and p53 as a marker, however, there are few studies on endometrial cancers arising from endometrial polyps. The aim of the present study was to examine PTEN, p53, Bcl-2, and Ki-67 expression patterns in endometrial cancers arising from endometrial polyps and evaluate the relationship of these markers with clinical prognostic factors.

Materials and Methods

The present study was conducted as a retrospective research at Başkent University Department of Obstetrics and Gynecology, Division of Gynecologic Oncology. Bcl-2, PTEN, Ki-67, and p53 expressions in endometrial cancers arising from endometrial polyps in postmenopausal women were compared with the expression pattern in women with benign endometrial polyps, and the relationship of these markers with clinical prognostic factors was evaluated in cancer patients. An approval was obtained from Başkent University Faculty of Medicine Clinical Ethics Committee (Project No: KA10/71).

The study patients were postmenopausal women who were admitted to the Division of Gynecologic Oncology at Başkent University Department of Obstetrics and Gynecology between 2006 and 2011. Postmenopausal women were chosen in order to rule

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out estrogen effect. Patients receiving hormone therapy, tamoxifen therapy, and those with a history of breast cancer were excluded from the study. All cases with benign endometrial polyps were selected based on hysterectomy specimens in order to ensure sufficient evaluation of the tissue samples. The cases with insufficient tissue block and patients with endometrial cancer arising from endometrial polyps with insufficient staging were excluded.

A total of 323 patients with endometrial cancer were identified between 2006 and 2011. Endometrial cancer developed from endometrial polyps in 26 (8%) of these patients. Of these cases, 20 consecutive patients meeting inclusion criteria were included in the study. The study group comprised patients who underwent total abdominal hysterectomy, salpingo-oophorectomy, omentectomy, and lymph node dissection after the diagnosis of endometrial cancer had been established using endometrial biopsy and in whom final pathologic examination revealed endometrial cancer arising from endometrial polyp, with non-polyp endometrial area atrophy. A patient with benign endometrial polyp was selected for each patient with endometrial cancer. Benign endometrial polyps were reported in 160 cases who underwent hysterectomy in the postmenopausal period between 2006 and 2011. Twenty cases were randomly selected among 160 patients using computerized randomization and included in the study. This group of patients comprised those who underwent hysterectomy due to benign conditions and in whom final pathological examination revealed endometrial polyp. These patients non-polyp endometrial area was atrophic too.

Medical charts of 40 patients included in the study and their pathology reports were reviewed. Age, menopausal status, systemic diseases, height, weight, body mass index, and size of the polyps were recorded. Pathology reports and slides of all patients were re-evaluated in order to standardize pathological data by a senior pathologist.

All patients with endometrial cancer were followed at the present clinic regularly. Cytologic examination result of the abdominal irrigation fluid was available in all patients. The follow-up visits were initiated two months postoperatively and performed every six months in the first two years, yearly after two years, and every ten to 12 months after five years. Control visits consisted of bimanual vaginal examination and vaginal-abdominal ultrasonographic examination. Vaginal smear was also obtained on average twice a year. Chest X-ray and abdominal and pelvic computed tomography scans were obtained on average once a year.

Four-micron thick serial tissue sections were obtained from formalin-fixed and paraffin-embedded tissue blocks of hysterectomy material containing benign endometrial polyp and endometrial carcinoma arising from the polyps and one section was stained with H&E to confirm histopathologic diagnosis. Successive tissue sections were processed for immunohistochemical analysis. After deparaffinization, sections were subjected to 10 mM trisodium citrate buffer solution (pH 6.0) for ten minutes at 110°C for the recovery of antigens. Endogenous peroxidase activity was blocked with incubation of the sections in 1% hydrogen peroxide in PBS solution for five minutes. After blocking non-specific binding with preincubation in 1.5% normal horse serum for 30 minutes, the sections were incubated with primary antibodies of bcl 2 alpha (Mouse monoclonal), PTEN (clone 17.A, mouse monoclonal), p53 (clone DO-7, mouse monoclonal), and Ki-67 (clone SP6, rabbit monoclonal) were applied at room temperature for 45 minutes. The sections were then kept at room temperature after dripping biotinated horse anti-mouse or anti-rabbit serum secondary antibodies. DAB (3,3'-diaminobenzidine) chromogen was added after incubating the sections with avidin-biotin complex for 30 minutes and the sections were then irrigated with tap water and contrast staining was performed with hematoxylin for ten seconds. Known positive control blocks were used for the antibodies used as positive control. Immunohistochemical staining was performed without primary antibody treatment in one section as the negative control.

Immunohistochemical findings were semiquantitatively evaluated by a single pathologist. Nuclear staining for Ki-67 and p53, and cytoplasmic staining for Bcl-2 were considered to be a positive reaction. Accordingly, sections without staining were considered to be negative. Immunohistochemical staining was classified as follows: +, < 25% of cell stained, ++, 25-50% of cells stained; +++, 50-75% of cells stained, and ++++, 75-100% of cells stained [7].

The tissues with inactivation/loss of PTEN function show no staining with PTEN marker, and tissues without loss of PTEN function show positive staining. Negative staining is an indicator of the loss of PTEN function. Nuclear and cytoplasmic staining for PTEN was considered to be positive reaction. Staining of < 10% of cells was considered to be negative, and staining of ≥ 10% of cells was considered to be positive [8].

The research data were analyzed using SPSS version 17.0 software package. Fisher's exact test and Student's *t* -test were used in comparisons between the groups. *P* values less than 0.05 was considered significant.

Results

Clinical features of the study patients are presented in Table 1. Both groups comprised obese, postmenopausal patients aged around 60 years. The diameter of polyps was 2 cm or higher in the majority of patients, particularly in the benign group. There was no difference in terms of age, systemic disease, body mass index, polyp size, and presence of postmenopausal bleeding when patients with benign endometrial polyps were compared with patients with endometrial cancer.

Histopathologic features of endometrial cancers arising from the polyps are presented in Table 2. According to their pathology reports, the majority of these patients were reported to have early-stage endometrioid adenocarcinoma. Only one (5%) patient had lymph node metastasis.

All non-endometrioid cancers were of pure serous papillary histology. Non-tumoral endometrium samples were reported as atrophic endometrium in all cancer patients.

Two (10%) patients received postoperative radiotherapy. Six (30%) patients received postoperative chemotherapy. During the follow-up, 17 (85%) patients showed no recurrence, whereas three (15%) patients showed recurrent disease and these three patients died. The mean disease-free survival of the study patients was 29 (maximum 80 months, minimum 4) patients. Of patients with recurrent disease, one had grade 2, Stage 1 endometrioid carcinoma, and other two patients had Stages 3 and 4 cancer of serous histology. The mean disease-free follow-up period was one year in all three patients despite chemotherapy after surgery.

Distribution of Ki-67, Bcl-2, PTEN, and p53 expression rates is shown in Table 3. Only Ki-67 and Bcl-2 expressions were different between patients with benign endometrial

Table 1. — *Clinical features of the cases. The variables are expressed as number (%) and mean ± standard deviation.*

Characteristics	Benign Histology (n=20)	Malign Histology (n=20)	*p*-value
Age (years)	59.7 ±10.2	60.8 ± 11.4	> 0.05
Body mass Index (kg/m^2)	32.0 ±9.1	30.7 ±5.9	> 0.05
Diabetes mellitus	2 (10)	1 (5)	> 0.05
Hypertension	5 (25)	4 (20)	> 0.05
Diabetes mellitus + hypertension	1 (5)	3 (15)	> 0.05
Polyp size			
< 2 cm	5 (25)	9 (45)	> 0.05
≥ 2 cm	15 (75)	11 (55)	> 0.05
Postmenopausal bleeding			
Positive	14 (70)	16 (80)	> 0.05

Table 2. — *Histopathological features of patients with endometrial cancer arising from the polyps.*

	n	%
Histologic type		
Endometrioid cancer (type 1)	15	75%
Non-endometrioid cancer (type 2)	5	25%
FIGO Stage		
I	16	80%
II	1	5%
III	1	5%
IV	2	10%
Grade		
I	9	45%
II	4	20%
III	7	35%
Myometrial invasion		
Negative	6	30%
< 1/2	13	65%
>1/2	1	5%
Polyp size (nm)		
< 2	9	45%
≥ 2	11	55%
LVSI[1]		
Negative	3	15%
Positive	17	85%
Lymph node involvement		
Negative	19	95%
Positive	1	5%

[1]*LVSI: lymphovascular space invasion.*

polyps and patients with endometrial cancer arising from the polyps. This difference between the groups was found when patients with no staining and weak staining (1+) were considered to be negative, and patients with 2+ or higher staining were considered to be positive. Compared to patients with benign endometrial polyps, Ki-67 expression was higher and Bcl-2 expression was lower in patients with endometrial cancer arising from the polyps. There was no difference between the groups in terms of PTEN and p53 expressions.

With the exception of one patient, Ki-67, Bcl-2, PTEN, and p53 expressions did not vary according to histological type, tumor stage, tumor grade, presence of myometrial invasion, and lymphovascular space invasion in patients with endometrial cancer. The patients with high grade tumor showed increased p53 expression.

Discussion

The present study compared PTEN, p53, Bcl-2, and Ki-67 expression patterns in patients with endometrial cancer arising from endometrial polyps with those of benign endometrial polyps and we found that increased Ki-67 expression and decreased Bcl-2 expression in endometrial cancer arising from endometrial polyps. However the present authors could not demonstrate any significant difference between benign endometrial polyps and endometrial cancer arising from endometrial polyps in terms of p53 and PTEN expression.

Lydia *et al.* reported, in the proliferative phase of menstrual cycle, higher Bcl-2 expression in benign endometrial polyps compared with endometrium [9]. In another study, Ki-67 expression was lower in endometrial polyps compared with proliferative endometrium [7]. Ki-67 is defined as an excellent marker of proliferation and increased Ki-67 expression is normally expected in proliferative endometrium. However, increased Bcl-2 and decreased Ki-67 expression in benign endometrial polyps compared with proliferative endometrium, suggests that endometrial proliferation may not play a role in the pathogenesis of polyps. Bcl-2 suppresses apoptosis [3]. Increased blc-2 expression in endometrial polyps reported in the present study as well as in previous studies suggests that the actual mechanism in the pathogenesis of endometrial polyps was inhibition of apoptosis, prolonged cell survival, and endometrial overgrowth, not proliferation [9].

Complex hyperplasia shows positive staining for Bcl-2, but endometrial carcinoma shows more weakly Bcl-2 staining [10]. Apostolou *et al.* discovered decreased Bcl-2 expression in endometrioid endometrial carcinoma when compared with benign hyperplasia [11]. In light of these findings, it can be argued that Bcl-2 expression decreases as the endometrium gain malignancy potential. Also in the present study, patients with endometrial cancer arising from endometrial polyps compared with benign endometrial

Table 3. — *All patient groups, histological subtype, stage, grade, myometrial invasion, tumor size, and lymphovascular space invasion in relation to Ki-67, Bcl-2, PTEN, and p53 expression rates.*

Variable	n	Ki-67 n (%)	Bcl-2 n (%)	PTEN n (%)	p53 n (%)
All patients					
Benign endometrial polyps	20	7 (35%)	18 (90%)	9 (55%)	13 (65%)
Endometrial cancer arising from endometrial polyps	20	16 (80%)	12 (60%)	4 (20%)	12 (60%)
		$p = 0.005$	$p = 0.032$	$p = 0.088$	$p = 0.5$
Histological subtypes					
Endometrioid	15	12 (80%)	9 (605)	2 (14%)	7 (46%)
Non-endometrioid (pure serous)	5	4 (80%)	3 (60%)	2 (40%)	5 (100%)
		$p = 0.718$	*$p = 0.693$*	*$p = 0.249$*	*$p = 0.051$*
Stage					
1-2 (early stage)	17	13 (76%)	11 (64%)	2 (22%)	9 (52%)
3-4 (advanced stage)	3	3 (100%)	1 (33%)	2 (77%)	3 (100%)
		$p = 0.491$	$p = 0.344$	$p = 0.088$	$p = 0.193$
Grade					
1 (low grade)	9	8 (88%)	5 (55%)	0 (0%)	3 (33%)
2-3 (high grade)	11	8 (72%)	7 (63%)	4 (37%)	9 (81%)
		$p = 0.375$	$p = 0.535$	$p = 0.068$	$p = 0.040$
Myometrial invasion					
Negative	6	4 (%66)	3 (%50)	1 (%17)	2 (%33)
Positive	14	12 (%85)	9 (%64)	3 (%22)	10 (%71)
		$p = 0.343$	$p = 0.455$	$p = 0.657$	$p = 0.137$
Tumor size (cm)					
< 2	9	6 (66%)	7 (77%)	2 (23%)	6 (66%)
≥ 2	11	10 (90%)	5 (45%)	2 (19%)	6 (54%)
		$p = 0.217$	$p = 0.157$	$p = 0.625$	$p = 0.465$
LVSI[1]					
Negative	17	14 (82%)	10 (58%)	3 (18%)	10 (58%)
Positive	3	2 (66%)	2 (66%)	1 (34%)	2 (66%)
		$p = 0.509$	$p = 0.656$	$p = 0.509$	$p = 0.656$

[1]*LVSI: lymphovascular space invasion.*

Table 4. — *Studies in literature which compared Ki-67, Bcl-2, PTEN, and p53 in endometrial cancer arising from endometrial polyp [13-15, 31-40].*

Authors	Year	Endometrial cancer arising from endometrial polyp				
		n	Ki-67	Bcl-2	PTEN	p53
Wheeler *et al.*	2000	7	Strong, diffuse staining	[1]NA	[1]NA	Strong, diffuse staining
Baergen *et al.*	2001	4	[1]NA	[1]NA	[1]NA	Positive
Mccluggage *et al.*	2003	5	Strong, diffuse staining	[1]NA	[1]NA	Strong, diffuse staining
Hui *et al.*	2004	14	20-50%	[1]NA	[1]NA	Strong staining
Zheng *et al.*	2004	14	[1]NA	[1]NA	[1]NA	Strong staining
Trahan *et al.*	2005	10	[1]NA	[1]NA	[1]NA	80% overexpressed
Giordano *et al.*	2007	6	Positive	[1]NA	[1]NA	Positive
Jia *et al.*	2008	7	[1]NA	[1]NA	[1]NA	Strong staining
Yan *et al.*	2010	9	50% overexpressed	[1]NA	[1]NA	3-point score
Antunes *et al.*	2012	NA	Low	low	[1]NA	[1]NA
Yasuda *et al.*	2013	6	[1]NA	[1]NA	[1]NA	80% overexpressed
Pathiraca *et al.*	2013	3	[1]NA	[1]NA	[1]NA	Strong reactive
Ono *et al.*	2014	5	[1]NA	[1]NA	[1]NA	Strong staining
Current study	2016	20	Significantly increased	Significantly decreased	Not significant	Not significant but in serous polyps with strong staining

[1]*NA: not available.*

polyps and the authors discovered increased Ki-67 expression and decreased Bcl-2 expression in endometrial cancer arising from endometrial polyps. It seems that endometrial cancer arising from endometrial polyps have the same carcinogenesis pathway with endometrial cancers unrelated to endometrial polyp. When a polyp gains malignant potential, blc-2 decreasing and increasing apoptosis suggest that various unknown additional mutations in apoptosis pathways might be responsible from the process of carcinogenesis.

The present authors also compared Bcl-2, p53, PTEN,

and Ki-67 expressions between endometrioid and non-endometrioid histological subtypes of endometrial carcinomas arising from endometrial polyps, however they were unable to find any significant difference. When they compared endometrial cancers arising from endometrial polyps with endometrial cancers unrelated to polyps, interestingly they found that p53 expression and loss of PTEN function differed from that reported in the literature for endometrial cancer unrelated to polyps. There are limited literature data (Table 4) with endometrial cancer arising from endometrial polyps. To the present authors' knowledge this is the fist study which evaluated PTEN expression in endometrial cancers arising from endometrial polyps. In this study the loss of PTEN function was 14% in endometrioid endometrial cancers arising from endometrial polyps, which is lower than 50% to 80% reported in the literature for endometrioid endometrial cancers. Also, it was reported to be 10% in non-endometrioid endometrial cancers arising from endometrial polyps; a rate of 40% was found, which is far above that reported in the literature for non-endometrioid endometrial cancer [12]. In addition, p53 expression in patients with endometrial cancer arising from non-endometrioid polyps was similar to that reported for non-endometrioid endometrial cancer unrelated to polyps in the literature (100%), whereas p53 expression in patients was reported to be 10-20% with endometrioid endometrial cancer unrelated to polyps in the literature, the present authors found a p53 expression rate of 46% in endometrioid endometrial cancer arising from endometrioid polyps, much higher than the literature. However, further studies in a larger patient population diagnosed with endometrial cancer arising from endometrial polyps would provide more clear results due to insufficient number of patients in the subgroups of this study.

The studies in the literature have reported increased p53 expression in serous endometrial carcinomas arising from endometrial polyps and aggressive course of these polyps [13, 14]. Giordano *et al.* found a relationship between increased Ki-67 and p53 expressions and advanced disease stage, histological subtype, and presence of deep myometrial invasion in endometrial polyps exhibiting malignant transformation [15]. Zhu *et al.* found a relationship between Ki-67 expression and tumor stage and grade in endometrial cancers unrelated to the polyps [16]. Similar to that reported in the literature, the present authors found p53 expression in 81% of patients with high grade endometrial cancer arising from endometrial polyps and 33% of patients with low grade disease. The difference between the two groups was statistically significant. However, the authors did not observe a relationship between Ki-67 expression and tumor grade and stage in patients with endometrial cancer arising from endometrial polyps.

There is a paucity of studies regarding Bcl-2 and PTEN expression in endometrial cancers arising from polyps. In the search of endometrial cancers unrelated to the polyps, Mitselou *et al.* reported a relationship between increased grade and decreased Bcl-2 expression in endometrial cancers [17]. Daniilidou *et al.* reported a relationship between PTEN expression and endometrial cancer grade and stage, where they did not report a relationship with tumor grade and stage in papillary serous endometrial cancer [18]. Inaba *et al.* reported a relationship between PTEN, the loss of PTEN function, and tumor grade and stage in endometrial cancer [19]. The studies in the literature found a relationship between Bcl-2 and PTEN expressions and tumor grade and stage in endometrial cancers unrelated to polyps, but the present authors observed no significant relationship between Bcl-2 and PTEN expressions and grade and stage of endometrial cancers arising from endometrial polyps.

Farrel *et al.* found that prognosis of endometrial cancer arising from the polyps was similar to that in early stage endometrial cancer unrelated to polyps [20]. Ilker *et al.* reported that lymphovascular invasion was associated with advanced disease stage in papillary serous endometrial cancers arising from endometrial polyps [21]. However, the present authors did not observe any significant relationship between myometrial invasion, tumor size, and presence of lymphovascular invasion and Bcl-2, PTEN, p53, and Ki-67 expressions in patients with endometrial cancer arising from endometrial polyps.

Endometrial polyps malignancy potential is 0.3-4.8%. Menopause could be a risk factor in endometrial neoplasia arising from endometrial polyps [22, 23]. While some studies show that carcinomas arising from endometrial polyps occur solely in postmenopausal women [24], other studies have shown that carcinomas occur only in symptomatic patients [25]. On the other hand, there are also some studies demonstrating that carcinomas arising from endometrial polyps do occur in premenopausal and asymptomatic postmenopausal women [26]. No significant difference was observed in this study regarding postmenopausal bleeding when benign endometrial polyp cases were compared to cases of endometrial carcinoma arising from polyps. Nonetheless, of 20 postmenopausal patients with endometrial cancer arising from endometrial polyps, 80% presented to the clinic with postmenopausal bleeding. It is important not to underestimate those patients (20%) who were asymptomatic, in whom ultrasound detected polyps and the endometrial biopsy report was malignant. The present authors also found that 8% of endometrial cancers arising from endometrial polyps. Even if asymptomatic, endometrial polyps in postmenopausal women pose a risk for malignancy [26]. Although there is no general concensus on the indications of polypectomy, total resection with hysteroscopy is seen as a feasible technique.

Hileeto *et al.* [27] have found a strong correlation between the malignant transformation of endometrial polyps and advanced age. There are other some studies demonstrating the correlation between advanced age and malignant transformation [22-24]. In this study the authors did

not find any significant difference concerning mean age between patients with benign polyps and those with endometrial cancer arising from endometrial polyps, however, the high rate of 8% of malignant transformation from endometrial polyps could be explained by the fact that the patients were in advanced aged and postmenopausal.

A recent study showed that obesity, diabetes mellitus and systemic hypertension are risk factors for the malignant transformation from endometrial polyps [28]. Obesity is a major risk factor for endometrial carcinoma, but the data from literature are inconsistent in providing a relationship between BMI and the histological subtype of endometrial carcinoma or between BMI and survival in patients with endometrial carcinoma [29]. On the other hand some studies have found no statistically significant correlation between them [30]. In the present study the authors also found no concordance in obesity, diabetes mellitus, and systemic hypertension when comparing cases with benign endometrial polyps and endometrial cancer arising from polyps.

As a conclusion, unlike expression pattern in polyps, decreased Bcl-2 and increased Ki-67 expression in endometrial cancer arising from endometrial polyps, and inhibition of apoptosis and prolonged cell survival playing a role in the etiology of polyps, coupled with a reversed mechanism involving prevention of inhibition of apoptosis and increased proliferation in carcinogenesis, in contrast to that in benign polyps suggest presence of additional mutations affecting this cycle. In this study the authors did not find a statistically significant relationship between prognostic factors and Bcl-2, Ki-67, and PTEN expressions due to insufficient number of cases in the subgroups. The present authors suggest that further studies on a larger patient population diagnosed with endometrial cancer arising from endometrial polyps would elucidate this subject.

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References

[1] Litta P., Di Giuseppe J., Moriconi L., Delli Carpini G., Piermartiri M.G., Ciavattini A.: "Predictors of malignancy in endometrial polyps: a multi-institutional cohort study". *Eur. J. Gynaecol. Oncol.*, 2014, *35*, 382.

[2] Urabe R., Hachisuga T., Kurita T., Kagami S., Kawagoe T., Matsuura Y., *et al.*: "Prognostic significance of overexpression of p53 in uterine endometrioid adenocarcinomas with an analysis of nuclear grade". *J. Obstet. Gynaecol. Res.*, 2014, *40*, 812.

[3] Dobrzycka B., Terlikowski S.J., Garbowicz M., Niklinski J., Chyczewski L., Kulikowski M.: "The prognostic significance of the immunohistochemical expression of P53 and BCL-2 in endometrial cancer". *Folia Histochem. Cytobiol.*, 2011, *49*, 631.

[4] Djordjevic B., Hennessy B.T., Li J., Barkoh B.A., Luthra R., Mills G.B., *et al.*: "Clinical assessment of PTEN loss in endometrial carcinoma: immunohistochemistry outperforms gene sequencing".. *Mod. Pathol.*, 2012, *25*, 699.

[5] Garg K., Broaddus R.R., Soslow R.A., Urbauer D.L., Levine D.A., Djordjevic B.: "Pathologic scoring of PTEN immunohistochemistry in endometrial carcinoma is highly reproducible". *Int. J. Gynecol. Pathol.*, 2012, *31*, 48.

[6] Stoian S.C., Simionescu C., Margaritescu C., Stepan A., Nurciu M.: "Endometrial carcinomas: correlation between ER, PR, Ki67 status and histopathological prognostic parameters". *Rom. J. Morphol. Embryol.*, 2011, *52*, 631.

[7] Risberg B., Karlsson K., Abeler V., Lagrelius A., Davidson B., Karlsson M.G.: "Dissociated expression of Bcl-2 and Ki-67 in endometrial lesions: diagnostic and histogenetic implications". *Int. J. Gynecol. Pathol.*, 2002, *21*, 155.

[8] Quddus M.R., Ologun B.A., Sung C.J., Steinhoff M.M., Lawrence W.D.: "Utility of PTEN expression of endometrial "surface epithelial changes" and underlying atypical endometrial hyperplasia". *Int. J. Gynecol. Pathol.*, 2009, *28*, 471.

[9] Taylor L.J., Jackson T.L., Reid J.G., Duffy S.R.: "The differential expression of oestrogen receptors, progesterone receptors, Bcl-2 and Ki67 in endometrial polyps". *BJOG*, 2003, *110*, 794.

[10] Morsi H.M., Leers M.P., Jager W., Bjorklund V., Radespiel-Troger M., el Kabarity H., *et al.*: "The patterns of expression of an apoptosis-related CK18 neoepitope, the bcl-2 proto-oncogene, and the Ki67 proliferation marker in normal, hyperplastic, and malignant endometrium". *Int. J. Gynecol. Pathol.*, 2000, *19*, 118.

[11] Apostolou G., Apostolou N., Biteli M., Kavantzas N., Patsouris E., Athanassiadou P.: "Utility of Ki-67, p53, Bcl-2, and Cox-2 biomarkers for low-grade endometrial cancer and disordered proliferative/benign hyperplastic endometrium by imprint cytology". *Diagn. Cytopathol.*, 2014, *42*, 134.

[12] Liu F.S.: "Molecular carcinogenesis of endometrial cancer". *Taiwan J. Obstet. Gynecol.*, 2007, *46*, 26.

[13] McCluggage W.G., Sumathi V.P., McManus D.T.: "Uterine serous carcinoma and endometrial intraepithelial carcinoma arising in endometrial polyps: report of 5 cases, including 2 associated with tamoxifen therapy". *Hum. Pathol.*, 2003, *34*, 939.

[14] Trahan S., Tetu B., Raymond P.E.: "Serous papillary carcinoma of the endometrium arising from endometrial polyps: a clinical, histological, and immunohistochemical study of 13 cases". *Hum. Pathol.*, 2005, *36*, 1316.

[15] Giordano G., Gnetti L., Merisio C., Melpignano M.: "Postmenopausal status, hypertension and obesity as risk factors for malignant transformation in endometrial polyps". *Maturitas*, 2007, *56*, 190.

[16] Zhu C., Luo J., Shi H., Xie X., Ding Z.: "Expression of tubulin, p53, ki67, receptors for estrogen, and progesterone in endometrial cancer". *Eur. J. Gynaecol. Oncol.*, 2009, *30*, 514.

[17] Mitselou A., Ioachim E., Kitsou E., Vougiouklakis T., Zagorianakou N., Makrydimas G., *et al.*: "Immunohistochemical study of apoptosis-related Bcl-2 protein and its correlation with proliferation indices (Ki67, PCNA), tumor suppressor genes (p53, pRb), the oncogene c-erbB-2, sex steroid hormone receptors and other clinicopathological features, in normal, hyperplastic and neoplastic endometrium". *In Vivo*, 2003, *17*, 469.

[18] Daniilidou K., Frangou-Plemenou M., Grammatikakis J., Grigoriou O., Vitoratos N., Kondi-Pafiti A.: "Prognostic significance and diagnostic value of PTEN and p53 expression in endometrial carcinoma. A retrospective clinicopathological and immunohistochemical study". *J. BUON.*, 2013, *18*, 195.

[19] Inaba F., Kawamata H., Teramoto T., Fukasawa I., Inaba N., Fujimori T.: "PTEN and p53 abnormalities are indicative and predictive factors for endometrial carcinoma". *Oncol. Rep.*, 2005, *13*, 17.

[20] Farrell R., Scurry J., Otton G., Hacker N.F.: "Clinicopathologic review of malignant polyps in stage 1A carcinoma of the endometrium". *Gynecol. Oncol.*, 2005, *98*, 254.

[21] Ilker S., Elmas K., Emre O., Mengu T., Erkaya S., Tayfun G.: "Lympho-vascular space invasion indicates advanced disease for uterine papillary serous tumors arising from polyps". *Asian Pac. J. Cancer, Prev.*, 2015, *16*, 4257.

[22] Mossa B., Torcia F., Avenoso F., Tucci S., Marziani R.: "Occurrence of malignancy in endometrial polyps during postmenopause". *Eur. J. Gynaecol. Oncol*., 2010, *31*, 165.
[23] Idrees R., Din N.U., Fatima S., Kayani N.: "Serous carcinoma arising in endometrial polyps: clinicopathologic study of 4 cases". *Ann. Diagn. Pathol.*, 2013, *17*, 256.
[24] Ben-Arie A., Goldchmit C., Laviv Y., Levy R., Caspi B., Huszar M., *et al.*: "The malignant potential of endometrial polyps". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 2004, *115*, 206.
[25] Wethington S.L., Herzog T.J., Burke W.M., Sun X., Lerner J.P., Lewin S.N., *et al.*: "Risk and predictors of malignancy in women with endometrial polyps". *Ann. Surg. Oncol.*, 2011, *18*, 3819.
[26] Lee S.C., Kaunitz A.M., Sanchez-Ramos L., Rhatigan R.M.: "The oncogenic potential of endometrial polyps: a systematic review and meta-analysis". *Obstet. Gynecol.*, 2010, *116*, 1197.
[27] Hileeto D., Fadare O., Martel M., Zheng W.: "Age dependent association of endometrial polyps with increased risk of cancer involvement". *World J. Surg. Oncol.*, 2005, *3*, 8.
[28] Pergialiotis V,. Prodromidou A., Siotos C., Frountzas M., Perrea D., Vlachos G.D.: "Systemic hypertension and diabetes mellitus as predictors of malignancy among women with endometrial polyps: a meta-analysis of observational studies". *Menopause*, 2016, *23*, 691.
[29] Arem H., Irwin M.L.: "Obesity and endometrial cancer survival: a systematic review". *Int. J. Obes. (Lond.)*, 2013, *37*, 634.
[30] Nappi L., Indraccolo U., Di Spiezio Sardo A., Gentile G., Palombino K., Castaldi M.A., *et al.*: "Are diabetes, hypertension, and obesity independent risk factors for endometrial polyps?" *J. Minim. Invasive Gynecol.*, 2009, *16*, 157.
[31] Wheeler D.T., Bell K.A., Kurman R.J., Sherman M.E.: "Minimal uterine serous carcinoma: diagnosis and clinicopathologic correlation". *Am. J. Surg. Pathol.*, 2000, *24*, 797.
[32] Baergen R.N., Warren C.D., Isacson C., Ellenson L.H.: "Early uterine serous carcinoma: clonal origin of extrauterine disease". *Int. J. Gynecol. Pathol.*, 2001, *20*, 214.
[33] Zheng W., Liang S.X., Yu H., Rutherford T., Chambers S.K., Schwartz P.E.: "Endometrial glandular dysplasia: a newly defined precursor lesion of uterine papillary serous carcinoma. Part I: morphologic features". I*nt. J. Surg. Pathol.*, 2004, *12*, 207.
[34] Hui P., Kelly M., O'Malley D.M., Tavassoli F., Schwartz P.E.: "Minimal uterine serous carcinoma: a clinicopathological study of 40 cases". *Mod. Pathol.*, 2005, *18*, 75.
[35] Jia L., Liu Y., Yi X., Miron A., Crum C.P., Kong B., *et al.*: "Endometrial glandular dysplasia with frequent p53 gene mutation: a genetic evidence supporting its precancer nature for endometrial serous carcinoma". *Clin. Cancer Res.*, 2008, *14*, 2263.
[36] Yan Z., Hui P.: "Minimal uterine serous carcinoma with extrauterine tumor of identical morphology: an immunohistochemical study of 13 cases". *Appl. Immunohistochem. Mol. Morphol.*, 2010, *18*, 75.
[37] Antunes A., Jr., Andrade L.A., Pinto G.A., Leao R., Pinto-Neto A.M., Costa-Paiva L.: "Is the immunohistochemical expression of proliferation (Ki-67) and apoptosis (Bcl-2) markers and cyclooxigenase-2 (COX-2) related to carcinogenesis in postmenopausal endometrial polyps?" *Anal. Quant. Cytopathol. Histpathol.*, 2012, *34*, 264.
[38] Pathiraja P., Dhar S., Haldar K.: "Serous endometrial intraepithelial carcinoma: a case series and literature review". *Cancer Manag. Res.*, 2013, *5*, 117.
[39] Yasuda M., Katoh T., Hori S., Suzuki K., Ohno K., Maruyama M., *et al.*: "Endometrial intraepithelial carcinoma in association with polyp: review of eight cases". *Diagn. Pathol.*, 2013, *8*, 25.
[40] Ono K., Hayashi H., Tateno M., Tanaka R., Suzuki R., Maruyama Y., *et al.*: "Uterine superficial serous carcinomas and extensive serous endometrial intraepithelial carcinomas: clinicopathological analysis of 6 patients". *Int. J. Clin. Exp. Pathol.*, 2014, *7*, 7979.

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