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Concurrent endometrial carcinoma in hysterectomy specimens in patients with histopathological diagnosis of endometrial hyperplasia in curettage specimens

Występowanie raka endometrium w materiale z histerektomii u pacjentek z histopatologicznym rozpoznaniem rozrostu endometrium na podstawie łyżeczkowania macicy

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Abstract

Objectives: *The purpose of this study was to appraise the presence of Endometrial Carcinoma (EC) sequence in patients undergoing hysterectomy for Endometrial Hyperplasia (EH).*

Material and methods: *Eighty-two patients undergoing hysterectomy with the indication of EH based on endometrial curettage between January 2009 and December 2013 were analyzed respectively. All patients with a diagnosis of EH were investigated for age, parity, history of diabetes mellitus and hypertension. The histopathology of the hysterectomy specimens were compared with their curettage specimens.*

Results: *A total number of 82 women; 48 (58.5%) postmenopausal and 34 (41.5%) premenopausal were determined to have EH on histopathological evaluation of endometrial tissues obtained by endometrial curettage performed for evaluation of various bleeding abnormalities. Mean-age of patients was 54.6±8.7. Among 82 patients found to have EH on curettage specimens 39 had EC on hysterectomy specimens (39/82. 47.5%). Consequently we determined well differentiated endometrial adenocarcinoma in 66% (35/53) of the patients with hyperplasia with atypia (17/35. 48.5% Grade 1 and 18/35.51.4% Grade 2) and 13.7% (4/29) hyperplasia without atypia (4/4.100% Grade 1).*

Conclusions: *Postoperative diagnosis of endometrial pathology might be different from that of preoperative especially in cases with complex EH with atypia.*

Our study indicated that most of women diagnosed preoperatively with Atypical endometrial hyperplasia (AEH) may have a cancer at final examination of hysterectomy specimens. It may be useful to operate patients with AEH in specific centers because of invasive endometrial cancer risk in final histopathological evaluation.

Key words: **obesity** / **diagnosis** / **endometrial hyperplasia** / / **coexisting endometrial carcinoma** /

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Streszczenie

Cel pracy: *Celem badania było oszacowanie obecności raka endometrium (EC) u pacjentek po histerektomii z powodu rozrostu endometrium (EH).*

Materiał i metoda: *Analizie retrospektywnej poddano 82 pacjentki, którym w okresie od stycznia 2009 do grudnia 2013 usunięto macicę z powodu rozrostu endometrium zdiagnozowanego podczas wyłyżeczkowania macicy. Wszystkie pacjentki z rozpoznaniem EH analizowano pod kątem wieku, rodności, występowania cukrzycy i nadciśnienia tętniczego. Wyniki histopatologiczne usuniętych macicy porównywano z materiałem uzyskanym podczas łyżeczkowania.*

Wyniki: *82 pacjentki, 48 (58.5%) po menopauzie i 34 (41.5%) przed menopauzą miały rozpoznane EH w histopatologii z łyżeczkowania macicy wykonanego z powodu nieprawidłowych krwawień. Średnia wieku pacjentek wynosiła 54.6±8.7. Spośród 82 pacjentek z EH w łyżeczkowaniu, 39 miało EC w materiale z histerektomii (39/82. 47.5%). Konsekwentnie stwierdziliśmy dobrze zróżnicowanego raka endometrium u 66% (35/53) pacjentek z rozrostem endometrium z atypia (17/35. 48.5% Grade 1 i 18/35.51.4% Grade 2) oraz u 13.7% (4/29) pacjentek z rozrostem bez atypii (4/4.100% Grade 1).*

Wnioski: *Pooperacyjna diagnoza patologii endometrium może różnić się od diagnozy przedoperacyjnej zwłaszcza w przypadku złożonego rozrostu endometrium z atypia.*

Nasze badanie pokazuje, że większość kobiet, u których przed operacją rozpoznano atypowy rozrost endometrium (AEH) może mieć raka endometrium z rozpoznaniu ostatecznym. Powinno się operować pacjentki z AEH w doświadczonych ośrodkach z uwagi na ryzyko rozpoznania inwazyjnego raka endometrium w ostatecznym wyniku histopatologicznym.

Słowa kluczowe: **otyłość** / **diagnoza** / **rozrost endometrium** / **współistnienie raka endometrium** /

Introduction

In developed countries, endometrial cancer (EC) is the most common malignancy of the female genital tract and the fourth most common cancer in women [1]. EC has 2 main histological variations: type 1 and type 2. The most important and well-recognized risk factors for type 1 EC are obesity, hypertension, diabetes mellitus, sustained unopposed hyperestrogenism and adenomatous endometrial hyperplasia (EH) [2]. According to 1994 World Health Organization (WHO) system, EH can be classified based on structural complexity into simple or complex and on nuclear feature as hyperplasia with or without atypia [3]. There is no doubt that atypical hyperplasia carries a greater risk of progressing to cancer compared with hyperplasia without atypia [4]. On the other hand, 17-52% of these cases may be associated with coexistent EC at the time of diagnosis [5]. Surgical management is an acceptable management for both Atypical endometrial hyperplasia (AEH) and EC; however the preoperative counseling, and the planning of the type and the extend of the surgery depends on the diagnosis. In order to guarantee convenient management and patient safety, it is important to have better comprehension about coexisting EC among women with EH as diagnosed by biopsy.

Objectives

The purpose of this study was to compare histopathological findings in endometrial biopsy and hysterectomy specimens, to appraise the presence of EC sequence in patients undergoing hysterectomy for EH and to exhibit influence of the method of biopsy in diagnosis and the cancer histology, grading, staging in concurrent cases.

Material and method

Eighty-two patients undergoing hysterectomy with a diagnosis of EH in Erciyes University between January 2009 and December 2013 were analyzed retrospectively. Preoperative endometrial sampling was made by pipelle biopsy in fifty-seven patients Ita

The classification of EH was made according to WHO classification based upon two features: a) The glandular/stromal architectural pattern of the endometrium, which is described as either simple or complex b) The presence or absence of nuclear atypia. It is classified as 1) Simple hyperplasia without atypia 2) Complex hyperplasia without atypia 3) Simple atypical hyperplasia 4) Complex atypical hyperplasia [6]. All samples were evaluated by one gynea pathologist.

All patients with a diagnosis of EH were investigated for age, parity, weight, Body Mass Index (BMI), history of diabetes mellitus and hypertension (Table I). Preoperative transvaginal pelvic ultrasonographic examinations were performed with Voluson 730 Pro equipped with a 5- to 8-MHz transvaginal transducer (GE, Healthcare, Austria) for endometrial thickness. After a true longitudinal view of the uterus had been obtained, the endometrial thickness was measured as the maximum thickness between the highly reflective interfaces of the endometrial-myometrial junction.

The interval between diagnosis and hysterectomy was less than 6 weeks without any medical treatment. Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) was the standard procedure in our patients.

The criteria for EC based upon architectural evidence of stromal invasion, usually in the form of stromal disappearance,

desmoplasia, necrosis, or combinations of these findings between adjacent glands [3]. EC was classified according to WHO classification for tumor grade (Grade 1; well differentiated Grade 2; moderately differentiated and Grade 3; poorly differentiated) and FIGO 2009 staging system was done in all patients.

In the statistical analysis categorical variables were given as numerical and percentage. Chi-square tests were used to compare the variables between groups. The p value for statistical significance was set at 0.05 ($p<0.05$).

Results

During the study period January 2009–December 2013, a total of 82 women were registered in our tertiary centre with a preoperative diagnosis of EH. The mean age of subjects was 54.6±8.7 in patients with EH. The histopathological findings from endometrial curettage showed 40 (48.7%) patients with complex hyperplasia with atypia, 13 (15.8%) with simple hyperplasia with atypia, 20 (24.3%) patients with simple hyperplasia without atypia and nine (10.9%) with complex hyperplasia without atypia. Among 40 patients that were found to have complex hyperplasia with atypia on curettage specimens, 28 had EC (70%), nine EH (22.5%) and three (7.5%) endometrial polyps were detected on hysterectomy specimens. Of the 13 patients preoperatively diagnosed as simple hyperplasia with atypia, seven had EC (53.8%), three EH (23%), two endometrial polyps (15.3%) and one adenomyosis (7.7%) on hysterectomy specimens.

In the simple hyperplasia without atypia group, seven (35%) patients had complex hyperplasia without atypia, two (10%) patients endometrial polyp, and 11 (55%) patients simple hyperplasia without atypia on final examination of hysterectomy specimens.

Among nine patients with complex hyperplasia without atypia on curettage specimens, the hysterectomy specimens indicated four (44.4%) EC, three (33.3%) EH and two (22.2%) adenomyosis.

Figure 1 and figure 2 depict data analysis as diagrams which divide preoperatively diagnosed hyperplasia in two groups, hyperplasia with or without atypia.

The coexistence rate of EC with EH was 47.5% (39 patients out of 82). Of 39 patients with eventual diagnosis of EC. 30 (76.9%) patients were postmenopausal and nine (23.1%) premenopausal ($p<0.05$). All patients with a diagnosis of EC had endometrioid adenocarcinoma. Myometrial invasion was present in 94.8% (37/39) of cases: superficial invasion in 92.3% (36/39) and deep in 2.5% (1/39). In two patients the cancer was confined to the endometrium. Well differentiated tumor (G1) was found in 53.8% (21/39) of cases and moderately differentiated (G2) in 46.1% (18/39). There was no poorly differentiated (G3) tumor in our group of patients (Table II).

The statistical analysis in the two cancer (Group 2) and no-cancer groups (Group 1) to evaluate age, weight, parity, BMI, hypertension, diabetes mellitus and menopausal status was performed. Mean age, patient weight and BMI were statistically higher in EC group when compared to EH group ($p>0.05$). (Table III). Diagnosis of hyperplasia was made by pipelle biopsy in 57 (69.5%) cases. while the remaining 25 (30.5%) cases were diagnosed with dilatation and curettage (D&C). EC was detected in 27 of 57 patients (47.3%) who underwent pipelle biopsy and in 12 of 25 (48%) women by the D&C method ($p>0.05$).

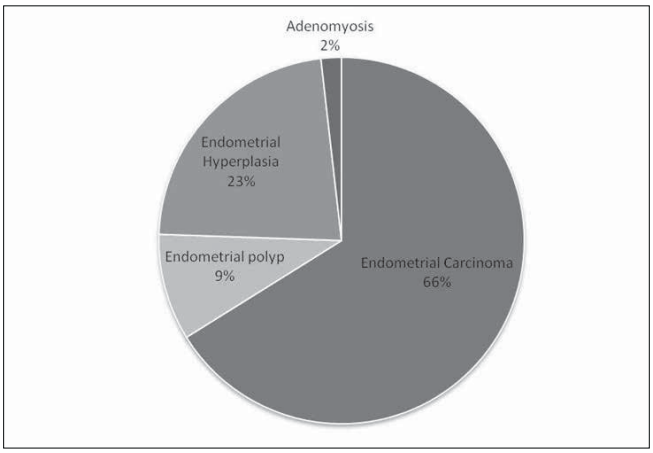

Figure 1. Pathologic results from hysterectomy specimens for those cases preoperatively diagnosed as hyperplasia with atypia (n = 53).

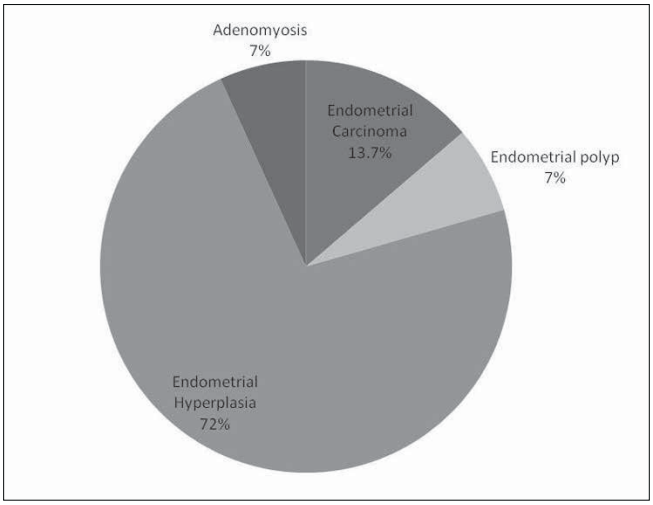

Figure 2. Pathologic results from hysterectomy specimens for those cases preoperatively diagnosed as hyperplasia without atypia (n = 29).

Discussion

In the present study we examined the prevalence of coexistence EC among 82 women with a preoperative diagnosis of EH. From the literature of last years it is evident that the rate of coexisting EC with AEH varies (10-59%) according to different studies (Table IV). In our case series, the coexistence rate of EC and EH was 47.5% (39/82). It was 66.0% (35/53) and 13.7% (4/29) in hyperplasia with and without atypia respectively.

Through a review of the literature it was found that the risk of EC is positively correlated with older age. early menarche & late menopause, obesity, family history of EC (especially among close relatives), radiation exposure, and infertility particularly in the presence of Polycystic Ovarian Syndrome. Long-term use of unopposed estrogens for hormone replacement therapy and EH with atypia also increases the risk of EC [7].

Cytological atypia is the most important feature in patients with EH in coexisting EC [8]. At the same time, patients with complex hyperplasia with atypia have greater risk of coexisting EC when compared to simple hyperplasia with atypia [9]. In our study, coexisting EC rates were elevated in complex hyperplasia

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Table I. Characteristics of patients with preoperative diagnosis of endometrial hyperplasia.

	Mean ± S.D. (range)	
Age	54.6±8.7	
Parity	2.7±4.17	
Weight	79.2±10	
BMI	29.27±4.13	
	n	**%**
Postmenopausal status	15	18.2
Hypertension	48	25
Diabetes Mellitus	58.5	30.4
Diagnosis Method: D&C	9	57
Diagnosis Method: Pipelle Biopsi	19.9	69.5

Table II. Myometrial invasion and grade distribution of patients with endometrial cancer (n= 39).

	Myometrial invasion			TOTAL
	M0	**M1**	**M2**	
Grade 1	2	19	0	21
Grade 2	0	17	1	18
Grade 3	0	0	0	0
Total	2	36	1	39

M, myometrial invasion; M0, no myometrial invasion; M1, superficial invasion <50%; M2, deep myometrial invasion >50%.

Table III. Characteristics of patients with preoperative diagnosis of EH versus patients with final diagnosis of EC.

	Group 1 (n:43)	Group 2 (n:39)	p
Age	52.5±6.94	56.8±9.97	**<0.05**
Parity	2.53±0.82	2.89±1.04	>0.05
Weight	74.1±8.39	84.84±8.76	**<0.05**
Menopausal status	25	30	>0.05
BMI	28.75±4.08	32.42±3.40	**<0.05**
Hypertension	3	6	>0.05
Diabetes Mellitus	3	12	**<0.05**

Group 1: Final examination, no cancer; Group 2: Final examination, endometrial cancer.

Table IV. Literature compilation of coexisting EC in patients with AEH.

	Year of publication	Coexistence percentage of EC in AEH patients (%)	Number of patients
Kurman and Norris	1982	17	89
Janicek and Rosenshein	1994	43	44
Widra et al.	1995	50	24
Bilgin et al.	2004	24	46
Merisio et al.	2005	43	70
Chen et al.	2009	54	26
Hahn et al.	2010	10	126
Antonsen et al.	2011	59	773
Current study	2014	66	53

Abbreviations; EC: Endometrial cancer, AEH: Endometrial hyperplasia with atypia.

with atypia group than simple hyperplasia with atypia group in parallel with literature.

It is well known that the age and menopausal status are the most efficient factors predicting EC. Brownfoot et al. described that the postmenopausal women have high rates of ongoing disease and cancer progression with conservative treatment in their study [10]. The median age of our study population was 56.8±9.9 years that higher than the patients described in previous studies [5, 11, 12, 13]. The 30 of 39 (76. 9%) coexisting cancer patients were in postmenopausal status. It was significantly higher than non-cancer patients ($p < 0.05$). The higher cancer rate that we found in our study compared with other studies might be explained by the elevated age and postmenopausal status of the patients.

EC is strongly associated with overweight and obesity [14]. This association is well described by unopposed estrogens which derive from the conversion of adrenal androgen into estrogens in adipose tissue. Joehlin-Price et al. reported that the BMI showed statistically significant associations with Mismatch repair (MMR) gene expression. tumor grade and stage amongst 1049 consecutive EC. Obesity correlates with lower grade and stage EC [15]. Zhang et al.'s meta-analysis strongly supported that the conditions of excess body weight (EBW), overweight, and obesity are all associated with an increased risk of EC especially type 1. Also. the strength of the association increases with increasing BMI [16]. The most popular hypothesis explaining the association between obesity and cancer is that of hyperinsulinemia and insulin resistance [17]. The molecular mechanism is thought to involve activation of key signaling pathways including PI3K/Akt and Ras/MAPK − although these signaling pathways are shared among insulin. IGF-1 and estrogen pathways. This activation of the PI3K/Akt and Ras/MAPK pathways results in exaggeration of IGF-1 and IGFBP expression which promotes mitogenesis of cancer cells in the endometrium [18] and one study has shown that IGF-1 was significantly abundant in the endometrium in women with EC [19]. In our study we determined twelve women with diabetes mellitus in EC group. Despite that this score was three in EH group. After all, the higher rate coexisting cancer could be explained by obesity. The statistical analysis carried out a significant high BMI rates in EC group than EH group ($p<0.001$) (Table III).

In the present study all of tumors which found at the final histological examination were endometrioid histology. According to FIGO 2009 classification most of the tumors stage was Ia. (38/39 Stage Ia, 1/39 Stage Ib). There were no poorly differentiated (G3) and deeply infiltrated tumors. The median BMI of EC group was significantly higher than the EH group. As the published literature revealed that the obesity and EH correlates with low grade and stage tumors, we found well and moderate differentiated (G1, G2) tumors with superficial myometrial invasion [20]. Given the possibility of deep myometrial invasion and grade 3 endometrial tumors an intraoperative frozen biopsy is necessary to avoid the possibility of suboptimal surgery in EH patients.

In reported series accuracy of endometrial biopsy with pipelle was demonstrated to be superior to D&C in postmenopausal patients. Again, the endometrial biopsy with pipelle was the most sensitive technique with a sensitivity of 81%. The specificity of all devices was higher than 98% [21]. Despite that some studies pointed that the office-based pipelle biopsy carries a higher possibility of missing coexistent EC, such as in cases of focally originating small volume tumors [5]. In this study there were no statistically difference between endometrial biopsy with pipelle and D&C in detecting the EC/EH association.

In some studies magnetic resonance examination has been helpful in differentiation between benign lesions and EC [22]. Transvaginal ultrasonography may be performed to determine myometrial invasion as well. Diagnostic accuracy and sensitivity of ultrasonography on showing any myometrial invasion of is very low [11]. Therefore, hysteroscopy with endometrial biopsy could have a potential advantage in these patients. The sensitivity and specificity of hysteroscopy to predict a diagnosis of infiltrating EC was found 84.6% and 100% in a study [23]. However the diagnostic use of hysteroscopy in patients with high risk of EC is controversial and is not used in many clinics for fear of spreading tumor cells to peritoneal cavity. Despite the fact that the accuracy of pipelle biopsy and D&C in detecting coexisting EC is similar, all two method's false negativity for EC rates were very high in our study.

As stated before, the ECs coexisting with EH that seen in postmenopausal and obese women were usually Type 1 and early stage tumors. Although the current standard treatment of patients with low grade, early stage EC and EH with atypia is hysterectomy and BSO, in the high grade tumors staging surgery is required.

Conclusions

In conclusion, the accuracy of detecting the frequency of coexisting EC in hysterectomy specimens in patients with histopathological diagnosis of atypical hyperplasia patients with pipelle biopsy was similar to D&C. Our study indicated that most of women diagnosed preoperatively with AEH may have a cancer at final examination of hysterectomy specimens. It may be useful to operate patients with AEH in specific centers because of invasive endometrial cancer risk in final histopathological evaluation.

Authors' contribution:

1. Mehmet Dolanbay – concept, assumptions, study design.
2. Mehmet S. Kutuk – concept, assumptions, study design.
3. Semih Uludag – concept, assumptions, study design.
4. Ayça N. Bulut – acquisition of data.
5. Mahmut T. Ozgun – corresponding author.
6. Bulent Ozcelik – article draft.
7. Ibrahim S. Serin – revised article critically.

Authors' statement

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