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Endometrial malignancies arising on endometrial polyps and precursor lesions

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Summary

Introduction: Polyps are covered with endometrial epithelium and composed of varying proportions of gland, stroma, and blood vessels. Traditionally, endometrial polyps are accepted as a precursor of cancer. The aim of this study was to evaluate the relationship between malignancies arising on endometrial polyps and precursor lesions of these malignancies. *Materials and Methods:* Data of patients who underwent total abdominal hysterectomy because of a malignancy diagnosed on endometrial polyps were obtained retrospectively from pathology archives. *Results:* When all malignancies on endometrial polyp were considered, 37% of cases were Type I, 55% were Type II, and 7% were carcinosarcoma. Endometrial intraepithelial carcinoma (EIC) was detected as tumor-adjacent areas on the polyp in eight of the patients who were diagnosed with serous carcinoma. *Conclusion:* The authors found a precursor lesion in 20 (74%) of their patients who showed endometrial malignancy developing on endometrial polyps. Even when an overt malignancy is not detected on polyps in the curettage material, precursor lesions should be carefully searched.

Key words: Polyp; Endometrial hyperplasia; Endometrial disease; Adenocarcinoma; Endometrioid.

Introduction

Endometrial polyps are commonly seen benign neoplasms [1]. The prevalence of symptomatic polyps ranges from 13% to 50% [2-5], and this rate is expected to be between 20% to 55% in asymptomatic cases [6, 7]. Endometrial polyps have never been reported in premenarche period [8]. They are most frequently observed in the perimenopausal age group [7, 9]. In clinical practice, they may cause menometrorrhagia not respondent to medical treatment in premenopausal women or abnormal uterine bleeding in postmenopausal women. They are detected during routine gynecological examination or in examination of hysterectomy specimens in asymptomatic cases [1, 8]. Polyps are covered with endometrial epithelium and composed of varying proportions of gland, stroma, and blood vessels [1]. Overexpression of steroid receptor has been noted on glandular epithelium of polyps and is thought to be a sign of hormones in etiology [10]. Increased incidence of endometrial polyp following tamoxifen and hormone replacement therapy also supports this idea [3,1]. Overall prevalence of malignancy on endometrial polyp is between 0.1% and 13% [1, 12, 13]. It has been reported that invasive or non-invasive malignancies developed in 32% of endometrial polyps in patients over 65 years of age [13, 14]. Despite these rates of endometrial cancer, it is still controversial as to whether endometrial polyps can be a precursor of cancer alone. Focal overgrowth of mucosa is determined on endometrium without polyps having similar biological characteristics and behavior [8]. There is limited information in the literature regarding the presence of precursor lesions of malignancies arising on polyps in contrast to precursor lesions of malignancies of non-polypoid endometrium.

The aim of this study was to evaluate the relationship between malignancies arising on endometrial polyps and precursor lesions of such malignancies.

Materials and Methods

Data on the patients who underwent total abdominal hysterectomy between June 2005 to June 2014 because of malignancy diagnosed on endometrial polyps were obtained retrospectively from pathology archives. Hematoxylin-Eosin and immunohistochemically stained preparations were revised under microscope. Patient data including age, symptoms, menopausal status, histological diagnosis of tumors, histology of endometrium adjacent to the polyps with tumor (proliferative, secretory, atrophic, irregular proliferative, simple hyperplasia, complex hyperplasia without atypia, atypical complex hyperplasia, invasive adenocarcinoma, endometrial intraepithelial neoplasia-EIN, endometrial intraepithelial carcinoma-EIC), lymphovascular and myometrial invasion of tumor, and immunohistochemical results was noted. Tumors were grouped as Type I and Type II endometrial carcinoma and carcinosarcoma. Type II endometrial carcinomas were divided histologically into three groups, namely the

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Table 1. — *Clinical characteristics of the patients with endometrial malignancy arising on endometrial polyps.*

	Age (mean)	Menopausal status	
		Peri-menopausal	Post menopausal
Type-I endometrial cancer (10)	56	2	8
Type-II endometrial cancer: serous (10)	73	0	10
Type II endometrial cancer: clear cell (3)	73	0	3
Type II endometrial cancer: serous+clear cell (2)	70	0	2
Carcinosarcoma (2)	55	1	1
Total (n=27)	62	3	24

serous group, clear cell group and serous + clear-cell groups.

Immunohistochemistry

Five-micron-thick sections stood in an oven at 70 degrees Celsius for 45 minutes for deparaffinisation. After deparaffinisation, the sections were treated with 100% and 95% alcohol, respectively, and washed with distilled water. They were heated in a pressure cooker in 10% citrate (pH 6) and then allowed to cool. After the superblock was removed, primary antibodies p53 (mouse, 1:50), ER (rabbit, SP1 1/100) were added dropwise. After the final wash step in TBS, DAB chromogen (diaminobenzene) was applied for ten minutes. The sections were run through tap water and then stained with hematoxylin for reverse staining. Assessment of p53, ER, PR immunopositivity, and nuclear staining were positive.

Results

This study is a descriptive and retrospective study of 281 consecutive patients who were diagnosed with endometrial carcinoma at the present institution between June 2005 and June 2014. Endometrial cancer arising on polyps occurred in 27 patients (9.6%), which accounted for 3.9% of 686 endometrial polyps diagnosed during that period. These findings seem to be similar to those reported in previous studies in which the malignancy rate was indicated to vary between 0.1% and 13%. When all malignancies arising on endometrial polyp were considered, 37% were Type I, 55% were Type II, and 7% were carcinosarcoma. No patient stated to have used tamoxifen. Only one patient had endometrioid adenocarcinoma simultaneously on both polyp and non-polypoid endometrium. Tumors were limited to polyp in all other patients (Table 1).

Three of the 27 cases were perimenopausal and the remaining 24 were in the postmenopausal period. Ten patients with a mean age of 56 years had Type I endometrial cancer, 15 patients with a mean age of 72 years had Type II endometrial cancer, and two patients were diagnosed with carcinosarcoma, and their mean age was 56 years. The patients with Type II endometrial cancer were significantly older than those with Type I endometrial cancer and endometrial cancer with carcinosarcoma and all were postmenopausal women (Table 2).

Within the scope of this study, the mean tumor size was found to be 1.2 cm and the average polyp size was 2.1 cm in patients with Type I endometrial cancer. Endometrial sampling of endometrium adjacent to endometrial adenocarcinoma that arises on polyps revealed 'atypical complex hyperplasia' in all cases. Endometrial adenocarcinoma was also detected in endometrium outside of the endometrial polyp in one case. While eight cases were grade I FIGO, one patient was grade II, and another patient was grade III (Table 3).

The mean tumor size was 1.4 cm, and the average polyp size was 2.1 cm in patients with Type II endometrial cancer. The mean age was 66 years in patients diagnosed with serous carcinoma, 73 years in those with clear cell carcinoma, and 70 years in serous + clear cell carcinoma. It was noticed that the group of clear cell carcinoma was the oldest group.

Atrophy was observed in endometrium adjacent to tumor arising on the polyp and in the endometrium outside the polyp of Type II carcinoma (15/15). Endometrial intraepithelial carcinoma (EIC) (Figure 1) was detected in tumor-

Table 2. — *Histopathologic characteristics of Type I endometrial carcinoma arising on endometrial polyps.*

Cases	Age	Tumor size (cm)	Polyp size (cm)	Tumor grade (FIGO)	Myometrial invasion	Lympho-vascular invasion	Non-tumoral polypoid endometrium	Immunohistochemistry
1	49	2	2	I	½ inner	-	Complex hyperplasia, atypia	p53 % 5(+), ER % 90(+), PR % 90(+)
2	53	4	6	II	½ inner	-	Complex hyperplasia, atypia	p53 % 10(+), ER % 75(+), PR % 70(+)
3	63	0.4	1	I	-	-	Complex hyperplasia, atypia	p53 (-), ER % 100(+), PR % 90(+)
4	46	1.6	2	I	½ inner	-	Complex hyperplasia, atypia	pP53 (-), ER % 80(+), PR % 60(+)
5	59	0.3	1.5	I	-	-	Complex hyperplasia, atypia	p53 (-), ER % 90(+), PR % 75(+)
6	47	0.5	1	I	-	-	Complex hyperplasia, atypia	p53 (-), ER % 100(+), PR % 90(+)
7	42	1.2	2	I	-	-	Complex hyperplasia, atypia	p53 (-), ER % 90(+), PR % 75(+)
8	75	0.5	2	I	-	-	Complex hyperplasia, atypia	p53 % 10(+), ER % 75 (+), PR % 70(+)
9	77	1	2	II	½ inner	+	Complex hyperplasia, atypia	p53 (-), ER % 100(+), PR % 90(+)
10	50	1	1.5	I	-	-	Complex hyperplasia, atypia	p53 (-), ER % 90(+), PR % 75(+)

Table 3. — *Histological characteristics of Type II endometrial carcinoma arising on endometrial polyps.*

Cases	Age	Tumor size (cm)	Polyp size (cm)	Myometrial invasion	Lympho-vascular invasion	Non-tumoral polypoid endometrium	Immunohistochemistry
Serous							
1	62	1	2	-	-	EIC+atrophy	p53 (+), ER(-), PR(-)
2	65	1	1	-	-	EIC+atrophy	P53 (+), ER % 10(+), PR % 10(+)
3	60	1	3	-	-	EIC+atrophy	p53 (+), ER(+), PR(-)
4	75	0.5	5	-	-	EIC+atrophy	p53 (+), ER(-), PR(-)
5	67	0.5	1	-	-	Atrophy	p53 (+), ER(-), PR(-)
6	72	3	3	½ inner	-	EIC+atrophy	P53 (+), ER(-), PR(-)
7	69	0.6	3	-	-	EIC+atrophy	p53 (+), ER(-), PR(-)
8	64	0.5	1	-	-	Atrophy	p53 (+), ER % 10(+), PR % 10(+)
9	62	2	2	-	-	EIC+atrophy	p53 (+), ER(-), PR(-)
10	65	1.6	1.6	-	-	EIC+atrophy	P53 (+), ER(-), PR(-)
Clear cell							
1	67	0.3	3	-	+	Clear cell EIC +atrophy	p53 (-), ER(-), PR(-)
2	83	1	1	-	-	Atrophy	P53 (+), ER % 10 (+), PR % 10(+)
3	71	5	5	-	+	Atrophy	P53 (+), ER(-), PR(-)
Serous+ Clear cell							
1	67	0.8	0.8	½ inner	-	SEH+atrophy	p53 (+), ER(-), PR(-)
2	74	3	3	-	-	DPH+atrophy	P53 (+), ER (-), PR(-)

Table 4. — *Histological characteristics of uterine carcinosarcoma arising on endometrial polyps.*

Cases	Age	Tumor size (cm)	Polyp size (cm)	Myometrial invasion	Lympho-vascular invasion	Non-tumoral polypoid endometrium	Tumor components
1	58	7	7	+ ½ inner	+	Atrophic	Endometrioid adenocarcinoma (grade III) + leiomyosarcoma
2	52	5	6	-	-	EIC+atrophic	Serous carcinoma + rhabdomyosarcoma

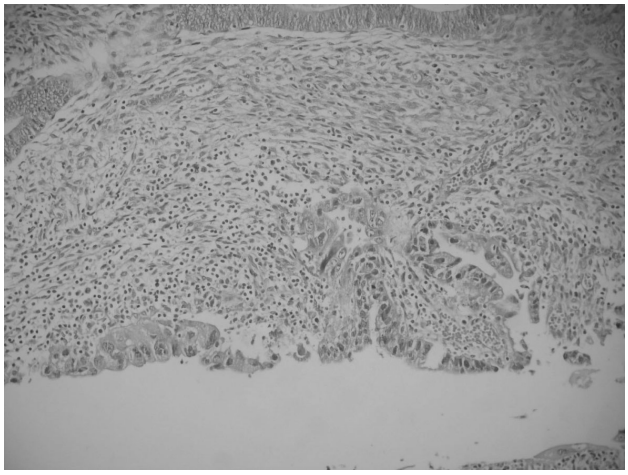

Figure 1. — Endometrial intraepithelial carcinoma.

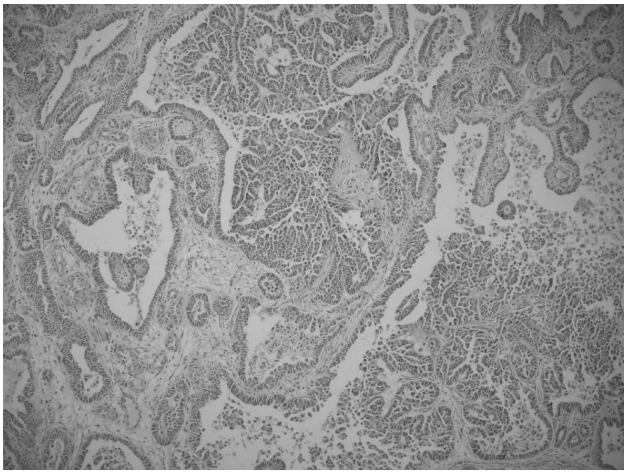

Figure 2. — Serous carcinoma on the polyp.

adjacent areas of the polyps of eight patients who were diagnosed with serous carcinoma (Figure 2).

Tumor cells of all patients were stained immunohistochemically, and eight patients with EIC field showed strong p53 positivity with a ratio of more than 80% (Figure 3, Table 4).

Two patients were detected to have carcinosarcoma on the polyps. The average tumor size was six cm and the

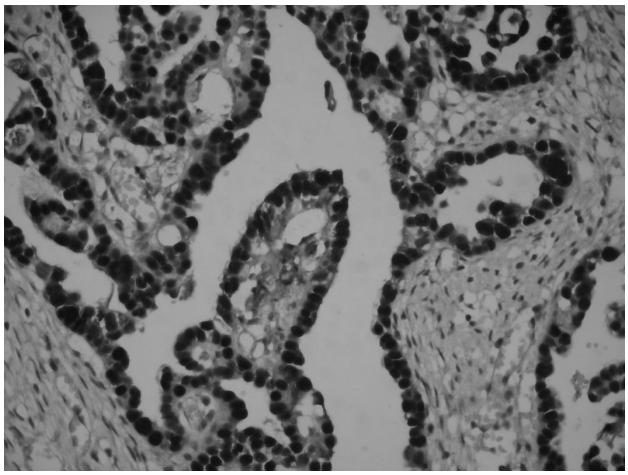

Figure 3. — Serous carcinoma p53 positivity.

polyp size was 6.5 cm in these patients. Atrophy was observed in non-tumoral polypoid endometrium in both patients. EIC was detected as carcinosarcoma with serous carcinoma component.

Discussion

In the present study the authors analysed endometrial malignancies arising on endometrial polyps to demonstrate the precursor lesions on the polyps and to reveal the similarities and differences between histologic types. Additionally, they aimed to determine the relationship between histologic types and clinical parameters.

Postmenopausal women with endometrial polyps have higher rate of malignant potential compared to those in premenopausal carrier [15-17]. In the present study, only three of patients (11%) were in perimenopausal period and the other patients were postmenopausal (89%). There was a correlation between patient's age and histopathologic results. The women with Type II endometrial cancer were significantly older than those with Type I endometrial cancer or carcinosarcoma, and all were postmenopausal women.

When tumors were divided into groups, ten of the patients (37%) had Type I endometrial carcinoma, 15 (55%) had Type II endometrial carcinoma, and two (7%) had carcinosarcoma. Martin-Ondarza *et al.* evaluated 27 patients in a clinical study; 81.5% had endometrioid adenocarcinoma and 19.5% had serous carcinoma. These findings of Martin-Ondarza *et al.* showed a difference compared with the present results [15]. While Type II carcinoma of uterus was 10-15 % of all endometrial tumors, it was seen in 55% of the present cases. The present authors believe that the increased incidence of serous carcinoma was due to fact that 89% of the patients were postmenopausal and at an advanced age.

Uterine serous carcinomas constitute only 5-10% of endometrial carcinomas [11]. In the present study, this ratio was 37% (n = 10) and found to be significantly higher than the overall rate ($p < 0.05$). Serous carcinomas are nearly always associated with atrophic endometrium and atrophic polyps [18, 19]. When non-neoplastic endometrium is diagnosed as secretory, proliferative or hyperplastic, the diagnosis of serous carcinoma is recommended to be reviewed. All of the present cases in non-polypoid endometrial area had atrophic endometrium and that result was consistent with existing literature. Most serous carcinomas contain non-invasive components instead of non-neoplastic atrophic endometrium [20-22]. This element is called serous intraepithelial carcinoma (EIC) and detected in 90% of patients with serous carcinomas [1, 23, 24]. Nuclear pseudostrafication, loss of nuclear polarity, high nucleus / cytoplasm ratio, and prominent nuclear pleomorphism are features of EIC cells. Although EIC does not have stromal or myometrial invasion, it carries a high risk for metastasis [24]. EIC was detected on non-tumoral field of polyps in eight patients (80%), while atrophic endometrium was detected in two patients. Hui *et al.* analyzed 40 patients with minimal uterine serous carcinoma and reported that carcinoma developed on endometrial polyps in 35 patients and 28 had 'intraepithelial serous carcinoma' adjacent to tumor [19]. Similar to the results of the study by Hui *et al.*, the EIC rate adjacent to tumors on the polyps in the present serous carcinoma cases was 80% (8 of 10 patients) [19]. No relationship was found between tumor size and polyp size in the present cases. It has been reported by the earlier studies in the literature that despite the absence of histologically detected myometrial invasion, serous carcinoma may be associated with lymphovascular involvement [20,21]. In the present study, only one case (10%) had one-half inner myometrial invasion but lymphovascular involvement was not observed. Even though the literature contains all endometrial serous carcinomas, there is no information solely regarding lymphovascular involvement of serous carcinoma arising on endometrial polyps. Immunohistochemical methods were quite useful in the differential diagnosis of serous carcinoma and EIC [11]; 90% of the cases were diagnosed to have strong p53 positivity [25-28]. Ki-67 was positive in 75% of cases [28]. Estrogen receptor (ER) was weak and focally positive [30, 31]. All serous carcinoma cases (n=10) arising on endometrial polyp showed p53 positivity, whereas only two cases showed ER positivity. The present findings related to serous carcinoma arising on endometrial polyps and precursor lesions in the neighborhood were consistent with the findings in the literature. Clear cell carcinomas constitute 1-6 % of all endometrial carcinomas [32, 33]. In the present cases, however, this rate was 11%. Despite being not statistically significant, this rate was higher when compared to the literature. Nevertheless, the whole information in the literature relates to endometrial clear cell carcinoma and lacks information about clear cell carcinomas arising on the polyp. Although serous carcinoma and clear cell carcinomas are tumors that are easily distinguishable

from each other morphologically, they have overlapping clinicopathologic features. One-third of serous carcinomas have clear cell components. Some researchers determined that mixed carcinomas with serous and clear cell carcinoma components had p53 mutations in both components [8]. The present study revealed three clear cell carcinomas arising on polyp with an average size of 2.2 cm. The mean age of the patients was 73 years. Clear cell carcinomas may also be associated with atrophic endometrium and endometrial polyps as serous carcinomas [33]. In previous studies, researchers have found putative precursor lesions (PPL) in clear cell carcinoma and defined PPL as a histological criteria for clear cell carcinoma [34]. Eosinophilic nucleolus surrounded with clear cytoplasm and nuclei with coarse chromatin showing intense pleomorphism were defined as precursor lesions. Fadare *et al.* found PPL in 90% of clear cell carcinomas and 6.2% of these tumors were p53 positive [34]. One of the present patients had clear cell EIC on the polyp. Atrophic endometrium was observed on the polyp in other two tumors. p53 positivity was detected in two of three clear cell carcinoma cases arising on endometrial polyps and ER positivity was present only in one case. Myometrial and lymphovascular involvement were reported to be 80% and 25% in clear cell carcinomas, respectively [33-35]. Myometrial invasion was not observed in the present cases but lymphovascular invasion was observed in two (66%). Information solely about clear cell carcinoma arising on polyps is not available in the literature.

Serous carcinomas can be found together with endometrioid, clear cell, and even neuroendocrine carcinoma. It is most frequently seen with endometrioid carcinoma [23, 36]. Two of the present patients developed mixed tumors composed of serous and clear cell carcinoma that formed on polyps. The average size of the tumors was 1.9 cm and the mean age of patients was 70 years. P53 immunohistochemical staining was positive in two of the present cases.

The average age of the patients that had carcinosarcoma arising on polyps was 56 years and it was significantly lower as compared to the cases of Type II endometrial carcinoma. The mean tumor size was six cm and larger than other tumors. One patient was detected to have one-half inner myometrial invasion. EIC was detected adjacent to carcinosarcoma with serous component.

The present authors found precursor lesions in 20 (74%) of the patients. Precursor lesions were detected on malignancies developed on endometrial polyps as a precursor lesion of endometrial malignancies. They believe that these lesions have a role in development of tumors.

The possibility of the presence of a malignancy should be kept in mind especially when a diagnostic curettage materials are examined. Even when an overt malignancy is not detected on polyps in the curettage material, it must be carefully searched for precursor lesions.

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