Original Article

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Prevalence of Co-existing Endometrial Carcinoma in Patients with Preoperative Diagnosis of Endometrial Hyperplasia

Obstetrics and Gynecology Section

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ABSTRACT

Introduction: Endometrial hyperplasia has been associated with the presence of concomitant endometrial carcinoma. In this study, patients who were diagnosed with endometrial hyperplasia and had hysterectomy, determination of the incidence of endometrial cancer accompanying postoperatively and clinical parameters associated with cancer are aimed.

Materials and Methods: Endometrial biopsies were taken from patients for various reasons and among them 158 patients diagnosed with endometrial hyperplasia from pathologic examination results were retrospectively evaluated. All of the patient's age, parity, weight, transvaginal ultrasound measured by endometrial thickness, concomitant systemic disease (diabetes, hypertension, hypothyroidism), tamoxifen use, hormone use and whether in reproductive age or menopause were all questioned. Patients who applied with endometrial cancer, their cervical stromal involvement, lymph node involvement, cytology positivity and omental metastases were examined. Patients were classified according to their stage and grade. Patients who had intraoperative frozen were re-evaluated.

Results: Fifteen cases with preoperative endometrial hyperplasia diagnosed with endometrial cancer postoperatively, 2 cases had complex hyperplasia without atypia and 13 cases had complex atypical hyperplasia. The rate of preoperative hyperplasia with postoperative endometrial cancer was found to be 10.8% where by 15 cases of patients diagnosed with endometrial cancer postoperatively 11 cases were in postmenopausal period. In patients diagnosed with endometrial cancer according to their histologic types 14 cases had endometrioid adenocarcinoma while one patient with preoperative complex hyperplasia without atypia was diagnosed with serous papillary carcinoma postoperatively. Evaluation of stages in patients diagnosed with cancer, 7 cases of patients had stage IA, 7 cases of patients had stage IB, and 7 cases cases of patients with serous papillary carcinoma were evaluated as stage 3C.

Conclusion: The risk of endometrial cancer in patients diagnosed with endometrial hyperplasia especially endometrial hyperplasia ranges between 15% to 45% and among them 7.9%–51% are found to have myometrial inversion. Therefore, preoperative ultrasound and magnetic resonance imaging should be perfomed in patients diagnosed with complex atypical hyperplasia. Even intraoperative frozen section examination can provide useful information in selected cases.

Keywords: Atypical hyperplasia, Endometrial cancer, Frozen section

INTRODUCTION

Endometrial hyperplasia, is defined as irregular proliferation of endometrial glands and an increase at glands/stroma. By World Health Organization (WHO) in 1994, endometrial hyperplasia is divided into four groups as simple hyperplasia without atypia, complex hyperplasia without atypia, simple atypical hyperplasia and complex atypical hyperplasia and there is particulary strong relationship with atypical endometrial hyperplasia and endometrial cancer. Therefore, due to the high risks of endometrial cancer associated with postmenopausal atypical hyperplasia hysterectomy is recommended [1]. But the 1994 criterias of WHO are quite subjective and especially lead to inconsistency in distinction of atypical endometrial hyperplasia and endometrial cancer. The concept of endometrial intraepithelial neoplasia have been proposed in recent years. Therefore, investigations need to be done more carefully in terms of the risks of endometrial cancer associated with endometrial hyperplasia [2].

Endometrial hyperplasia usually develop as a result of excess estrogen unmet with progesterone. However, histologically simple hyperplasia without atypia is similar to normal proliferative endometrium while complex atypical hyperplasia is similar to well-differentiated endometrioid adenocarcinoma. The rates of cancer accompanying with endometrial hyperplasia vary between 15-54% at many studies [3]. In this study, patients diagnosed with endometrial hyperplasia and had hysterectomy, determination of the incidence of endometrial cancer accompanying postoperatively and clinical parameters associated with cancer are aimed.

MATERIALS AND METHODS

This study was retrospectively performed between January 2006 and September 2012 at our Gynecologic Oncology Department. Medical data were collected from 158 patients diagnosed with endometrial hyperplasia and who have undergone hysterectomy in our clinic and evaluated retrospectively. The study was approved by the ethics Committee of Ankara Numune Education and Research Hospital. Demographic characteristics and pathological results were evaluated retrospectively. We did not collect data on non-surgical management of hyperplasia. In all patients; age, parity, body mass index (BMI), endometrial thickness measured by transvaginal ultrasound (TVUSG), whether accompanied by systemic diseases (diabetes, hypertension, hypothyroidism), tamoxifen use, hormone replacement therapy (HRT) use and whether in postmenopausal period were all questioned during surgery. Patients with a preoperative tissue diagnosis of endometrial cancer and hyperplasia that cannot rule out malignancy were excluded. Patients diagnosed with preoperative endometrial hyperplasia were classified as without atypia (simple and complex) and atypical (simple and complex). Histopathological diagnosis from paraffin sections examination results of all patients after hysterectomy were compared with preoperative endometrial biopsy. Surgical staging was performed in patients diagnosed with postoperative endometrial cancer. In these patients lymph node involvement, cytology positivity, omentum metastasis and CA-125 levels were evaluated before surgical staging.

STATISTICAL ANALYSIS

Datas were analysed using SPSS (Statistical Package for Social Sciences) for Windows 16.0 software package and the appropriateness of the normal distribution of the data was assessed by Kolmogorov-Smirnov test. The independent samples t-test was used to compare the groups. The small size of the p-value of 0.05 was considered statistically significant.

RESULTS

In our study, 158 patients diagnosed with preoperative endometrial hyperplasia after endometrial biopsy, their postoperative paraffin sections results were evaluated. In patients diagnosed with preoperative endometrial hyperplasia after endometrial biopsy, 15 cases of them were diagnosed with endometrial cancer postoperatively and the rate of ednometrial cancer was found to be 10.79%. In these patients 2 cases of them were diagnosed with preoperative complex hyperplasia without atypia while 13 cases of them were diagnosed with preoperative complex atypical hyperplasia [Table/Fig-1].

Demographic characteristics of the patients included in our study are summarized in [Table/Fig-2]. In patients diagnosed with postoperative endometrial cancer, mean ages was significantly higher and mean parity significantly lower than those patients diagnosed with postoperative endometrial hyperplasia ($p<0.05$). Considering the two groups in terms of BMI, there was no statistical significant difference ($p>0.05$). In patients diagnosed with postoperative endometrial hyperplasia, 62.1% of them were in postmenopausal period while 73.3% of patients diagnosed with postoperative endometrial cancer were in postmenopausal period. Patients evaluated in our study, none of them were using tamoxifen or HRT. The mean of endometrial thickness of the patients, who were diagnosed postoperatively as endometrial cancer was bigger than who were diagnosed as endometrial hyperplasia and it is statistically significant [Table/Fig-2].

The patients who were diagnosed with preoperative endometrial hyperplasia by endometrial biopsy and then diagnosed with postoperative endometrial cancer;14 cases of them were diagnosed with endometroid adenocarcinoma while one case of patient diagnosed with preoperative complex atypical endometrium hyperplasia was diagnosed with postoperative papillary carcinoma. In surgical classification of patients diagnosed with postoperative endometrium cancer; 11 (73.4%) cases were evaluated as stage 1A, 3(20%) cases were in stage 1B and 1(6.6%) case was evaluated as stage 3. Histopathological grading of patients diagnosed with endometrium cancer was as follows; 8(53.4%) cases were in grade 1, 6 (40%) cases were in grade 2, 1(6.6%) case was in grade 3 [Table/Fig-3].

In our study, preoperative endometrial biopsy results of patients diagnosed with endometrial hyperplasia and then diagnosed with postoperative endometrium cancer, 15 cases of them only 1 case had lymph node envolvement, cytology positivity and omentum metastasis was observed and postoperative pathological results revealed serous papillary endometrium cancer grade 3. Patients diagnosed with endometrium cancer only one patient was found to have preoperative ca 125 level >35IU/L and diagnosed with postoperative serous papillary carcinoma.

Intraoperative frozen section examination was performed in 6 cases of patients with BMI > 30 and diagnosed with preoperative complex atypical hyperplasia from endometrial biopsy results. Frozen section results in 4 cases of these patients were referred to as malignant while 2 cases of these patients gave out negative results [Table/Fig-4].

DISCUSSION

Endometrial hyperplasia is the most common gynecologic pathology and precursor lesions for the most common gynecologic malignancy known as endometrial cancer. Women who are diagnosed with endometrial hyperplasia particularly in postmenopausal period are at risk of endometrial cancer. Progression risk of endometrial hyperplasia to endometrial carcinoma depends on presence of cytologic atypia and its severity [4]. Hysterectomy specimen of patients diagnosed with endometrial hyperplasia especially complex atypical hyperplasia by preoperative endometrial biopsy the probability of being accompanied with endometrial cancer ranged from 15-54% [2,3,5-9]. In our study, endometrial hyperplasia diagnosed patients by preoperative endometrial biopsy result and diagnosed with endometrial cancer by histopathological examination results was found to be 10.79% which is proportionaly lower than those reported in litertures.

	Postoperative endometrial hyperplasia non-observed	Postoperative simple hyperplasia without atypia	Postoperative complex hyperplasia without atypia	Postoperative simple atypical hyperplasia	Postoperative complex atypical hyperplasia	Postoperative Endometrium cancer
Preoperative simple hyperplasia without atypia (n=109)	17	90	-	1	1	-
Preoperative complex hyperplasia without atypia (n=9)	1	-	6	-	-	2
Preoperative simple atypical hyperplasia (n=8)	-	-	-	8	-	-
Preoperative complex atypical hyperplasia (n=32)	1	-	-	-	18	13
Total (n=158)	19	90	6	9	19	15

[Table/Fig-1]: Comparison of preoperative endometiral biopsy and postoperative histopathological results

	Patients diagnosed with postoperative endometrial hyperplasia (n=124)	Patients diagnosed with postoperative endometrial cancer (n=15)	p
Age	49.58 ± 6.64	58.27 ± 13.42	<0.05
Parity[a]	3.11 ± 1.62	1.93 ± 1.79	<0.05
BMI (kg/m^2)[a]	30.2 ± 2.2	31.7 ± 2.5	>0.05
Patients in postmenapausal period (n;%)	77 (62.1%)	11 (73.3%)	<0.05
Endometrial thickness (mm)[a]	10.3 ± 5.9	16.1 ± 6.75	<0.05
Diabetes (n;%)	42 (33.9%)	5 (33.4%)	>0.05
Hypertension(n;%)	57 (45.9%)	7 (46.6%)	>0.05
Hypothyroidism (n;%)	25 (20.1%)	3 (20%)	>0.05

[Table/Fig-2]: Comparison of demographic characteristics between patients diagnosed with postoperative endometrial hyperplasia and endometrial cancer

	Results of preoperative endometrial biopsy	Results of postoperative histopathology	stage	Grade
1. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1A	1
2. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1A	1
3. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1A	1
4. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1A	1
5. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1A	1
6. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1A	2
7. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1A	2
8. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1A	2
9. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1A	2
10. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1A	2
11. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1B	1
12. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1B	1
13. case	Complex atypical hyperplasia	Endometrioid adenocarcinoma	1B	2
14. case	Complex hyperplasia without atypia	Endometrioid adenocarcinoma	1A	1
15. case	Complex hyperplasia without atypia	Serous papillary carcinoma	3C	3

[Table/Fig-3]: Distribution of preoperative endometrial biopsy and surgical staging results of patients diagnosed with postoperative endometrial cancer

	Frozen results	Histopatological results	Stage	Grade
1. case	Malignity(-)	Endometrioid adenocarcinoma	1A	1
2. case	Malignity(-)	Endometrioid adenocarcinoma	1A	1
3. case	Malign	Endometrioid adenocarcinoma	1B	1
4. case	Malign	Endometrioid adenocarcinoma	1B	1
5. case	Malign	Endometrioid adenocarcinoma	1B	2
6. case	Malign	Serous papillary carcinoma	3C	3

[Table/Fig-4]: Frozen and histopathological results of patients diagnosed with preoperative complex atypia hyperplasia and BMI > 30

Endometrial hyperplasia diagnosed at a young age tend to have a low malignancy potential while it tends to be higher in perimenopausal or postmenopausal period in endometrial hyperplasia diagnosed patients. Endometrial hyperplasia atypical are seen more often over 50 years and postoperatively endometrial cancer diagnosis is seen more often in cases with postmenopausal endometrial hyperplasia with atypical [10]. In our study the mean of the age 15 patients who were postoperatively diagnosed as endometrial cancer was higher and 11 of this patients were at postmenopausal period. In postmenopausal age group especially with complex atypical endometrial hyperplasia endometrial cancer is seen more often and our study supports this.

There is a positive correlation between endometrial hyperplasia with endometrial thickness and risk of endometrial cancer in postmenopausal women. Endometrial hyperplasia is more likely to be accompanied by endometrial cancer as endometrial thickness increases and risk increases especially in patients with prolonged abnormal bleeding, chronic anovulation, nulliparity, diabetes, obesity, hypertension and use of tamoxifen [11]. In our study comparing groups of patients diagnosed with endometrial cancer and those without endometrial cancer in terms of endometrial thickness; patients diagnosed with postoperative endomerial cancer were found to have endometrial thickness of 16.1 ± 6.75 mm which is statistical significantly high.

The risk of endometrial cancer and complex typical endometrial hyperplasia decreases as the number of parity increase. The increase of parity with decrease in sexs binding hormone and free estradiol during postmenopousal period is expected not to stimulate the growth of endometrium [12]. In our study the patients who are associated with postmenopousal endometrial cancer have been found to have an average parity of 1,93 ± 1,79 which is statistical significantly low.

There is a strong relationship between BMI and typical endometrial hyperplasia due to that obesity increases the amount of ostrogen circulating in blood which increases the growth of endometrium [13]. The risk of endometrial cancer shows a significant increase in women diagnosed with metabolic syndrome [14]. In our study the patients diagnosed with preoperative endometrial hyperplasia by endometrial biopsy and then diagnosed with postoperative endometrial cancer; hypertension and diabetes which are components of metabolic syndrome were evaluated. Fifteen patients who were diagnosed with preoperative endometrial hyperplasia by endometrial biopsy and then diagnosed with postoperative endometrial cancer; 5 cases had diabetes, 7 cases had hypertension. The presence of these diseases are considered as one of the factors which increases risk of endometrial cancer.

The use of tamoxifen is well know to increase the risk of endometrial cancer especially in woman who are in postmenopousal period [15]. Also, the use of hormone replacement therapy during postmenopousal period increases the risk of endometrial cancer and endometrial hyperplasia [16]. Patients who were included in our study did not had history of tamoxifen use and HRT.

Patients diagnosed with atypical endometrial hyperplasia associated with endometrial cancer are generally lower graded, well differentiated and early stage tumours. Eddib et al., found out that; the incidence of endometrial cancer in patients undergone hysterectomy after being diagnosed with atypical endometrial hyperplasia was 17% and none of them was observed to have advanced tumour of more than grade 2 or stage 1B [17]. In similar study done by Rakha et al., suggested that patients who undergone hysterectomy due atypical endometrial hyperplasia and diagnosed with endometrial cancer; their tumours are endometrioid in morphology, early staged, low-graded and show good prognosis [18]. Although most of endometrial hyperplasia associated with endometrial cancer have early stage tumours, it may be accompanied by myometrial invasion. Merisio et al., in their study showed that association of endometrial cancer with atypical endometrial hyperplasia occurs in 43% and patients diagnosed with endometrial cancer 10% of their tumour occurs in endometrial mucosa while 90% of them were found to have myometrial invasion. Patients with myometrial invasion 92% of them is less than a half while 8% of them is more that a half [7]. In our study, 11(73.4%) cases of patients diagnosed with postoperative endometrial cancer have myometrial invasion of less than half (stage 1), and 3 of them (20%) more than half (stage 1B) while 93.4% of all patients where in stage 1. In our study, only 1 patient (6.6%) was found to be stage 3 were by histologically was diagnosed as papillary serous carcinoma. Therefore, during preoperative period detailed examination with TVUSG and magnetic resonance imaging (MRI) should be done especially in patients with obese, postmenopausal and cystic atypical hyperplasia.

In endometrial carcinoma the relationship between degree of tumourn and its prognosis is well known for many years and atypical hyperplasia associated with endometrial malignancies are usually low graded and are good prognostic tumours [18]. In our study, patients with postoperative diagnosis of endometrial cancer; 8 cases had grade 1, 6 cases had grade 2 and only one case had grade 3 tumours.

Recurrence of lymphovascular invasion is an independent risk factor for all types of endometrial cancer in terms of death. The overall incidence of lymphovascular invasion in the early stage endometrial cancer is 15%. However, these tumours increases with increase in grade and myometrial invasion. Endometrial carcinoma that develops after atypical endometrial hyperplasia is largely in early stage, low graded and less associated with lymphovascular invasion [19]. In our study,15 patients diagnosed with postoperative endometrial cancer; only 1 patient was evaluated with lymphovascular invasion and reported to be diagnosed with papillary serous endometrial cancer grade 3. In patients with early stages, lymphovascular invasion was found to be negative. In this case, as it is confirmed by many literatures, early stages of carcinoma is less associated with lymphovascular invasion and occurence of this in early stages is a reason as to why endometrial hyperplasia is less associated with endometrial carcinoma.

Frozen section examination can be used for separation of atypical endometrial hyperplasia with a well-differentiated superficial endometrial cancer and deep myometrial invasion with poorly differentiated endometrial cancer. Morotti et al., in their study used frozen examination of endometrial hyperplasia as aid during operation. Comparing frozen section results with postoperative outcomes, sensitivity was poor while it had specificity of above 90%. In other words, intraoperative diagnosis of carcinoma was confirmed by histopathology [10]. On the other hand, false negative frozen section results in a large proportion of patients histopathologically was reported as low-risk endometrial cancer [7]. However 90% of frozen investigation in patients with endometrial cancer and deep myometrial invasion had some degree of specificity. Intraoperative frozen section results in the majority of patients with endometrial cancer were found to have poor differentiation, deep myometrial invasion and poor histologic type [10]. Contrally in a study conducted by Shim et al., showed that in cases whose frozen section were free of myometrial invasion, 45% of them showed myometrial invasion in the histopathologic examination. Therefore, it is difficult to rule out endometrial cancer in patients whose frozen section results were negative especially in cases without myometrial invasion or minimal myometrial invasion [20].

Surgical staging can be planned in patients who shows high risk intraoperatively according to their frozen section results [21]. Morotti et al., in their study done in series of patients, 94% of their patients lymphadenectomy was perfomed. According to the results of frozen section examination, in these patients if frozen section could not be sent then patients could have undergone surgery for the second time or exposed to unnecessary radiotherapy. Four cases (23.5%) of these patients had lymph node metastases and this data was consistent with the Gynecologic Oncology Group study [10]. Considering these results preoperative diagnosis of atypical endometrial hyperplasia should be investigated thoroughly. Underlying risk of endometrial cancer particularly in patients diagnosed with complex atypical hyperplasia is significantly higher. Frozen examination can be adventageous in subgroups based on these results.

Bilgin et al., in their study showed that frozen section misleaded them in diagnosis of only 2 patients [5]. Ienderma et al., in their study had reported sensitivity and specificity of 27% and 100% respectively where by 23 cases of patients with the diagnosis of atypical endometrial hyperplasia were evaluated with preoperative frozen section [22]. Oz et al., reported that evaluation of cancer by intraoperative frozen section was found to have sesitivite of 76% and specificity of 100% [1]. In our study, 6 cases of patients with a high risk factor for endometrial cancer and endometrial biopsy results of preoperative atypical cystic endometrial hyperplasia. Four cases of patients whose frozen section results were positive, 3 of them had myometrial invasion of greater than a half and diagnosed as stage 1B adenocarcinoma where by one patient was diagnosed with stage 3 papillary carcinoma. their intraoperative frozen section were evaluated. The results of these 6 cases of patients, 4 cases of them were specified as malignant and 2 cases of them had false negative results. Two patients whose frozen sectino results were evaluated as false negative were diagnosed with stage 1A adenocarcinoma and this data was relevant with those in literatures.

CONCLUSION

Endometrial hyperplasia especially cystic atypical endometrial hyperplasia is under risk of being associated with endometrial cancer and likely to have myometrial invasion. Therefore in order to identify association of endometrial cancer in patients diagnosed with endometrial hyperplasia, preoperative TVUSG, MRI and risk factors should be determined. In order to identify association of endometrial cancer in preoperative high-risk patients intraoperative frozen section examination can be helpful. Prevention of re-operation and unnecessary radiotherapy in patients diagnosed with preoperative endometrial hyperplasia and patients under high risk factors, intraoperative frozen section should be evaluated.

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