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GYNECOLOGIC ONCOLOGY

The incidence and predictors of gynecologic malignancies among postmenopausal patients with endometrial fluid collection

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Abstract

Objective To investigate the incidence and predictors of gynecologic malignancies among postmenopausal patients with endometrial fluid collection (EFC).

Methods All patients with EFC diagnosed by transvaginal sonography (TVS) were retrospectively reviewed if they had undergone biopsy of the endometrium from January 2008 to January 2016 in a tertiary teaching hospital. Follow-up ended in June 2017. The incidence of gynecologic malignancies was described, and predictive factors were determined by comparing the epidemiological and clinico-pathological characteristics of the patients.

Results During the study period, 273 women with EFC (3.4%) were enrolled. Biopsy pathology and the following hysterectomy revealed 29 (10.6%) cases of gynecological cancer. In the multivariable analysis, patient-reported genital symptoms [odds ratio (OR) 16.2, 95% confidence interval (CI) 1.9–139.3], abnormal serum CA125 (OR 14.5, 95% CI 4.5–46.5), lesions in the uterine cavity (OR 18.8, 95% CI 6.0–59.1) and endometrial thickness (OR 1.1, 95% CI 1.0–1.2) determined by TVS were independent factors associated with malignancy. Only 1.1% (1/90) of the asymptomatic patients had gynecologic cancer. During the follow-up, gynecologic cancer was diagnosed in nine patients, six of whom had vaginal bleeding at the time of initial enrollment. The prognosis of patients with cancer was worse than that of patients with benign results.

Conclusion The risk of gynecologic malignancies in postmenopausal patients with EFC is related to genital symptoms, TVS findings and CA 125 levels. Asymptomatic EFC is associated with an extremely low risk of malignancy.

Keywords Menopause · Endometrial fluid collection · Hysteroscopy · Malignancy · Vaginal bleeding

Introduction

With improved health awareness and the wide use of transvaginal sonography (TVS), there is an increasing number of asymptomatic postmenopausal women with endometrial fluid collection (EFC). The incidence of EFC in TVS ranges from 4 to 14% [1–4]. Goldstein proposed that normal atrophic postmenopausal endometrium with cervical stenosis could result in EFC [5]. In postmenopausal patients, the causes of EFC are as follows: (1) cervical stenosis as a result of senile atrophy, obstetric trauma, instrumentation, foreign bodies, radiation therapy, previous surgery, primary tumor or recurrent tumor (cervical carcinoma, endometrial carcinoma and rectosigmoid carcinoma); (2) hematometra produced by carcinoma, endometrium, polyps or cystic endometrial hyperplasia; (3) pyometra caused by infection or tumor; (4) exogenous estrogen administration; and (5) treatment with tamoxifen [6]. However, there is no consensus regarding the risk of malignancies and management of postmenopausal EFC. The benefits and complications of aggressive and invasive interventions, such as hysteroscopy and dilation and curettage (D and C), are lacking in evidence. Moreover, routine endometrial sampling in all postmenopausal EFC patients leads to more adverse events and increased economic cost. We aimed to investigate the incidence and predictors of gynecologic malignancies among postmenopausal patients with EFC in a retrospective study.

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Materials and methods

Study design

This was a hospital-based retrospective study that included postmenopausal patients who were evaluated for EFC by TVS at the Department of Obstetrics and Gynecology, Peking Union Medical College Hospital (PUMCH), in Beijing, China. The Institutional Review Board of PUMCH approved this study. Written informed consent was obtained from all the participants. Based on the 9% incidence of malignancies in postmenopausal women with vaginal bleeding [7] and 0% incidence [8] in postmenopausal women with asymptomatic EFC in previous reports, with a class I and class II error probability (α and β) of 0.05 and 0.10, respectively, and odds ratio (OR) of 1.5 for the risk of malignancies among symptomatic EFC women, at least 258 cases with definite pathological outcomes were required to determine the significance of cancer incidences.

Data collection

Records of patients undergoing hysteroscopy and D and C from January 2008 to January 2016 were searched and reviewed, and patients were followed up till June 2017. The inclusion criteria were the following: (1) postmenopausal women; (2) detection of EFC by TVS but the absence of adnexal masses; (3) performance of last TVS within 4 weeks before endometrial biopsy; and (4) the presence of pathologic diagnosis of the endometrium. Patients who had undergone a previous hysteroscopy or D and C for EFC were excluded. Epidemiological and clinico-pathological data were retrospectively collected from medical records by Z. Li and checked by L. Li. We paid particular attention to data on the age at treatment, body mass index (BMI), menopausal periods, patient-reported genital symptoms, metabolic syndrome, cancer history (breast cancer and colorectal cancer), medication history [menopausal hormone therapy (MHT), tamoxifen and other hormone regimens] and serum CA125. Patient-reported genital symptoms include low abdominal pain, vaginal bleeding and abnormal discharge (vaginal fluid or purulent leucorrhea). Metabolic syndrome in our study consisted of hypertension, dyslipidemia or impaired glucose tolerance. Serum CA125 was classified as normal (<35 U/ml) and abnormal (≥ 35 U/ml).

Transvaginal sonography

TVS discoveries included EFC, endometrial thickness, lesions in the uterine cavity, and Doppler flow signals of lesions in the uterine cavity. In our study, EFC was defined as an anechoic area of any size within the uterine cavity. The endometrial thickness was determined as the thickest part in the sagittal plane of the uterus, with the diameter of the fluid subtracted from the total thickness. A focal lesion in the uterine cavity was any protrusion above the endometrial 'baseline surface' into the uterine cavity [9].

Follow-up

Survival outcomes and new cases of gynecologic cancer were determined by medical records, follow-up in outpatient clinics and interviews by email and/or telephone by Z. Li.

Statistics

Statistical analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, IL, USA) at the 95% confidence level and a significance level of 0.05. Comparisons between patients with and without malignancies were performed using the χ^2 test or Fisher's exact test. Multiple parameter analyses were performed using binary logistic analysis and calculating the OR and 95% confidence intervals (95% CIs). Overall survival (OS) and cancer-specific OS, along with their influencing factors, were calculated by survival table, Kaplan–Meier, and Cox regression analyses.

Results

Patient characteristics

During the study period, among the 8100 women receiving D and C or hysteroscopy for various reasons, 273 women with EFC were included in the study. The median age and menopausal period were 65 years (range 49–90) and 14 years (range 1–40), respectively. The average BMI was 23.3 ± 3.2 kg/m^2. A total of 19 (7.0%) and 21 (7.7%) patients had a medication history of MHT and tamoxifen, respectively, and 27 (9.9%) and 16 (5.9%) patients had a history of breast cancer and colorectal cancer. Before treatment, the median serum CA125 level was 22.6 IU/ml (range 9.0–232.0), and 36 (14.0%) patients had an elevated serum CA125 value. A total of 127 patients (46.5%) had various manifestations of metabolic syndrome. There were 183 (67.0%) patient-reported genital symptoms, including 169 patients with vaginal bleeding, 22 patients with abnormal vaginal discharge, and 18 patients with abdominal pain. Ninety patients (33.0%) reported no symptoms at all. The median endometrial thickness measured by TVS was 9 mm (range 1–25). Sixty-one patients had endometrial lesions detected by TVS, 22 (36.1%) of whom had positive Doppler flow signals.

Of the 273 patients, 172 (63.0%) underwent hysteroscopy and endometrial biopsy, while 101 (37.0%) underwent only D and C. After the endometrial biopsy, 53 patients agreed to undergo hysterectomy or comprehensive staging for detection of cancer or precancerous lesions or for assessment of repeated or persistent symptoms.

Pathological outcomes and predictors

In total, 29 patients (10.6%) were diagnosed with gynecological cancer. The details are listed in Table 1. Twenty-three patients were diagnosed by primary endometrial biopsy, and six patients with no malignant discoveries in the D and C sampling were finally proven to harbor gynecologic malignancies based on the hysterectomy specimens. Other biopsy pathological outcomes include 51 (18.7%) cases of endometrial polyps, 99 (36.3%) cases of normal endometrial tissues (atrophic endometrium or proliferative endometrium), 1 (0.4%) case of leiomyoma, 19 (7.0%) cases of endometrial hyperplasia, 57 (8.4%) cases of insufficient tissue (mainly of blood clots and mucus), and 23 (8.4%) cases of endometrial intraepithelial neoplasia (EIN).

As shown in Table 2, in univariate analysis, factors related to cancer include age ($P=0.001$), menopausal periods ($P=0.001$), endometrial thickness ($P<0.001$), patient-reported genital symptoms ($P<0.001$), symptom of low abdominal pain ($P=0.030$), symptom of vaginal bleeding ($P=0.001$), abnormal serum CA125 level ($P<0.001$), lesions in the uterine cavity detected by TVS ($P<0.001$), Doppler signals of lesions in the uterine cavity ($P=0.001$), and a history of colorectal cancer ($P=0.018$). Logistic regression analysis indicated that factors related to cancer

Table 1 Details of the 29 gynecological cancer patients

No.	Carcinoma	Stage	Treatment	Survival status	Cancer-related death
1	Ovarian, high-grade serous	IIIC	Comprehensive staging	Death	Yes
2	Fallopian tube, high-grade serous	IC	Comprehensive staging	Death	Yes
3	Endometrial, endometrioid, G1	IA	Hysterectomy and BSO	Death	No
4		IA	Hysterectomy and BSO	Survival	
5		IA	Hysterectomy and BSO	Survival	
6		IA	Hysterectomy and BSO	Survival	
7		IA	Hysterectomy and BSO	Survival	
8		IA	Hysterectomy and BSO	Death	Yes
9		IA	Hysterectomy and BSO	Survival	
10		IA	Lost		
11		IC	External radiotherapy	Death	Yes
12		IA	None	Death	No
13		IA	None	Survival	
14		IA	Hysterectomy and BSO	Death	Yes
15		IA	Hysterectomy and BSO	Survival	
16		IA	Hysterectomy and BSO	Survival	
17	Endometrial, endometrioid, G2	IB	Comprehensive staging	Death	No
18		IA	Hysterectomy and BSO	Survival	
19		IA	Hysterectomy and BSO	Death	Yes
20	Endometrial, endometrioid, G3	IA	Comprehensive staging	Death	No
21		IA	Hysterectomy and BSO		
22		IC	Comprehensive staging	Death	Yes
23		IA	Hysterectomy and BSO	Death	No
24	Endometrial, clear cell	IB	Comprehensive staging	Death	Yes
25	Endometrial, high-grade serous	IIIB	Comprehensive staging	Death	Yes
26		IA	Comprehensive staging	Death	Yes
27	Endometrial stromal sarcoma, high grade	IIIC	Comprehensive staging	Death	Yes
28		IIIA	Comprehensive staging	Death	No
29	Endometrial stromal sarcoma, low grade	IA	Lost		

BSO bilateral salpingo-oophorectomy

Table 2 Predictors of gynecologic malignancies

	Benign lesions	Malignancy	Univariate analysis		Multivariate analysis	
			OR (95%)	*P*	OR (95%)	*P*
Age (years) median (range)	65 (49–88)	69 (52–90)	1.1 (1.0–1.1)	0.001		
Menopausal periods (years) median (range)	14 (1–38)	20 (1–40)	1.1 (1.0–1.1)	0.001		
Endometrial thickness (mm) median (range)	8 (1–20)	15 (1–25)	1.1 (1.0–1.2)	< 0.001	1.1 (1.0–1.2)	0.037
Lesions in the uterine cavity (%)			7.6 (3.4–17.4)	< 0.001	18.8 (6.0–59.1)	< 0.001
No ($n = 212$)	201 (94.8%)	11 (5.2%)				
Yes ($n = 61$)	43 (70.5%)	18 (29.5%)				
Doppler signals of lesions in the uterine cavity (%)			6.6 (2.0–22.1)	0.001		
No ($n = 39$)	33 (84.6%)	6 (15.4%)				
Yes ($n = 22$)	10 (45.5%)	12 (54.5%)				
Symptoms *n* (%)			16.1 (2.2–120.2)	< 0.001	16.2 (1.9–129.3)	0.011
No ($n = 90$)	89 (98.9%)	1 (1.1%)				
Yes ($n = 183$)	155 (84.7%)	28 (15.3%)				
Low abdominal pain *n* (%)			3.7 (1.2–11.3)	0.030		
No ($n = 255$)	231 (90.6%)	24 (9.4%)				
Yes ($n = 18$)	13 (72.2%)	5 (27.8%)				
Vaginal bleeding *n* (%)			6.1 (1.8–20.8)	0.001		
No ($n = 104$)	101 (97.1%)	3 (2.9%)				
Yes ($n = 169$)	143 (84.6%)	26 (15.4%)				
Abnormal CA125 n (%)			10.6 (4.5–24.8)	< 0.001	14.5 (4.5–46.5)	< 0.001
No ($n = 221$)	207 (93.7%)	14 (6.3%)				
Yes ($n = 36$)	21 (58.3%)	15 (41.7%)				
History of colorectal cancer *n* (%)			4.4 (1.4–13.8)	0.018		
No ($n = 257$)	233 (90.7%)	24 (9.3%)				
Yes ($n = 16$)	11 (68.8%)	5 (31.3%)				

include patient-reported symptoms ($P = 0.011$, OR 16.2, 95% CI 1.9–139.3), abnormal serum CA125 ($P < 0.001$, OR 14.5, 95% CI 4.5–46.5), lesions in the uterine cavity ($P < 0.001$, OR 18.8, 95% CI 6.0–59.1) and endometrial thickness ($P = 0.037$, OR 1.1, 95% CI 1.0–1.2). Only 1.1% (1/90) of the asymptomatic patients had gynecologic cancer (stage IA, well-differentiated endometrial endometrioid cancer).

Follow-up

Thirty patients were lost during follow-up, and 243 patients (89.0%) had definite survival outcomes. The median follow-up time was 54 months (6–114). We detected nine new cases of uterine cancer during the follow-up period, and the pathology results indicated that all the patients had endometrioid carcinoma, six of whom had vaginal bleeding but benign pathology at initial enrollment. During the follow-up, 57 (57/243, 23.5%) patients died, 11 of whom died of cancer. Among the 29 patients with gynecological cancer at initial enrollment, 4 patients were lost to follow-up and 16 patients died, 10 of whom died of malignancies.

In the patients with and without gynecologic malignancies at initial enrollment, the median OS rates were 29 months (range 6–106) and 55 months (range 6–114), respectively ($P = 0.003$), the 5-year OS rates were 28% and 78%, and the 5-year cancer-specific OS rates were 39% and 99%. Among the patients with gynecologic malignancies, the univariate analysis indicated that menopause periods ($P = 0.001$), endometrial thickness ($P = 0.003$) and abnormal serum CA125 ($P = 0.024$) were risk factors related to cancer-specific OS. However, the multivariable analysis did not determine any independent risk factors related to cancer-specific OS.

Discussion

The presence of EFC in postmenopausal women and its management are still controversial. In our study, patient-reported symptoms, TVS findings (endometrial thickness and lesions in the uterine cavity) and abnormal CA125 were independent factors predicting gynecologic malignancies, highlighting the importance of a detailed evaluation in

patients with EFC. The results in our study are supported by other reports.

Patient-reported symptoms are critical indicators of the risk of malignancies. In our study, in patients with and without symptoms, the incidences of malignancy were 15.3% and 1.1%, respectively. In postmenopausal women, cervical stenosis caused by genital atrophy was considered the main cause of EFC [10, 11]. All previous reports showed that EFC in asymptomatic postmenopausal women is a benign condition [8, 12–14]. Thus, asymptomatic women with EFC may avoid invasive examinations if they have a thin, regular endometrium and normal CA125 level.

TVS provides a noninvasive and invaluable evaluation that enables detection of EFC. It is reported that the surrounding endometrial lining is more important than fluid accumulation alone, and patients with a regular thin endometrium do not need further examination [5, 15, 16]. If the endometrial echo complex (EEC), or the combined thickness of the two separated endometrial layers, is 3 mm or less, the pathology finding is highly likely to be benign [5, 15, 16]. Goldstein stated that when the endometrial layer peripheral to the fluid collection is no more than 3 mm, the endometrial pathology revealed inactive endometrium [5]. The endometrial thickness as well as the smoothness and symmetry of the endometrial lining are influencing factors, the lack of which may render an overall thin endometrium as conspicuous. Similarly, Schmidt et al. [15] reported that 4 of 74 (5.4%) women with an endometrial carcinoma (endometrial thickness 9–15 mm) presented with a highly conspicuous endometrium on sonography, i.e., an asymmetric and irregular mucosa, such that the endometrial fluid had no impact on the diagnosis. Debby et al. [16] reported that of the 82 postmenopausal women, no case of endometrial cancer was found and only one premalignant patient with an endometrial polyp in the postmenopausal group was diagnosed. If the EEC is greater than the threshold (3.0–4.5 mm depending on the study) or if the fluid is echogenic [11], there is a risk of malignancy, and further investigation to obtain a tissue sample is recommended [17]. However, several investigators reported endometrial cancer in the absence of a thickened endometrial lining with an incidental finding of fluid collection [3, 11, 18, 19]. Krissi et al. [19] recommended endometrial investigation regardless of endometrial thickness and suggested that the fluid could mask pathology because of the exertion of pressure on the endometrium. Doctors must keep in mind that postmenopausal bleeding, intrauterine sonolucent fluid, and an EEC of 3 mm or less could still indicate the presence of a carcinoma in the cervical canal [11]. Few studies have focused on predictors of malignant tumors in postmenopausal patients with EFC. Takacs et al. reported that echogenic fluid in the endometrial cavity was the only significant risk factor for nonbenign disease in postmenopausal women with EFC [11].

CA125 has been proven to be a practical tool in the diagnosis and follow-up of gynecologic malignancies. For symptomatic postmenopausal women with an endometrial thickness > 4 mm, Giannella [20] proposed a risk-scoring model that included recurrent vaginal bleeding, hypertension, endometrial thickness > 8 mm and age > 65 years. Knific [21] developed a model based on the preoperative serum CA125 level, human epididymis protein (HE4) level and BMI, which had good diagnostic accuracy for separating patients with endometrial cancer and control patients (prolapsed uterus or myoma). Savelli [22] stated that polyps were commonly believed to be a risk factor for endometrial cancer because of the hyperplastic and neoplastic lesions found in this context. All of this evidence supports the application of CA125 analysis in the management of EFC.

This study has several limitations. First, it is prone to recall and selection bias because of its retrospective nature. The study lacked a comprehensive review of medical records on family history and history of smoking and alcohol usage, all of which significantly impact the risk of endometrial cancer. Second, the standards for hysteroscopy may not have been consistent during the 8 years, therefore, resulting in heterogeneity of pathological outcomes. Third, more than one-third of the patients received only D and C, which decreased the reliability of pathological exploration. Finally, the role of other imaging evaluations and comparison with TVS were not clear in our study.

Conclusions

In postmenopausal patients with EFC, patient-reported symptoms, abnormal serum CA125, endometrial thickness, and lesions in the uterine cavity detected by TVS were independent factors predicting gynecologic malignancies. Compared with D and C, hysteroscopy has superior accuracy of histopathological diagnosis. Long-term follow-up is essential for symptomatic patients with EFC.

Author contributions LL: protocol/project development, data management, data analysis, and manuscript editing. ZL: data collection, data analysis, and manuscript writing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest and nothing to disclose.

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