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Concurrent endometrial carcinoma following hysterectomy for atypical endometrial hyperplasia☆

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ABSTRACT

Objective: To evaluate the prevalence of concurrent endometrial carcinoma in women diagnosed with atypical endometrial hyperplasia (AEH) by endometrial biopsy.
Study design: We retrospectively analyzed the medical records of 126 patients who underwent hysterectomies for AEH diagnosed by endometrial biopsy from 1999 to 2008. AEH was initially diagnosed by dilatation and curettage (98 cases) or endometrial biopsy with a Z-sampler (24 cases). The remaining four cases were diagnosed by hysteroscopic polypectomy. The results of the endometrial biopsies were graded on an ordinal scale and were compared with pathologic features obtained at the hysterectomy.
Results: In patients preoperatively diagnosed with AEH by biopsy, hysterectomy specimens revealed a rate of simple or complex endometrial hyperplasia without atypia of 27% with AEH and normal proliferative phases found in 54.7 and 7.9% of specimens, respectively. The incidence of endometrial carcinoma was considerably high (13/126, 10.3%). Eleven of 13 cases were confined to the endometrium and the remaining two were located at the adenomyosis without myometrial invasion. All patients with endometrial carcinoma displayed coexisting atypical complex hyperplasia following hysterectomy.
Conclusions: Biopsy specimens showing AEH, particularly atypical complex hyperplasia, are associated with a risk of coexisting endometrial carcinoma. When considering management strategies for women with a biopsy diagnosis of AEH, clinicians should take into account the considerable rate of concurrent endometrial cancer and the discrepancy with pathologic diagnosis. Treatment modalities may differ depending on population as the rates of concurrent endometrial cancer with AEH and myometrial invasion vary by geographical location.

1. Introduction

Endometrial hyperplasia is classified into four categories according to the World Health Organization (WHO) system, including simple hyperplasia, complex hyperplasia, simple hyperplasia with atypia, and complex hyperplasia with atypia [1]. While the Endometrial Collaborative Group has proposed a new term, endometrial intraepithelial neoplasia (EIN), for superior reproducibility, this classification has not yet undergone the necessary prospective evaluation or assessment of reproducibility [2]. Miller et al. classified endometrial hyperplasia based on the WHO classification system with additional qualifying comments that could potentially identify patients at high risk for endometrial cancer. The intent was to better predict increased risk for coexistent carcinomas that may require surgical staging. However, several limitations, including the retrospective nature and the absence of expert pathologic review, compromise its utility [3]. Atypical endometrial hyperplasia (AEH) has a well-known role in the progression to endometrial carcinoma, providing the link from proliferative endometrium to well-differentiated adenocarcinoma. Although they fall along the same spectrum, the diagnosis of AEH versus endometrial carcinoma carries different significance, as endometrial carcinoma requires a different clinical approach compared with its predecessor. Despite the significance of the differentiation between AEH and carcinoma, a pathologic review by the Gynecologic Oncology Group (GOG) in 2006 failed to

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demonstrate diagnostic consistency [4]. In the study, the diagnosis agreement between the referral and the study groups was only 39%, suggesting that morphological differences may be nearly indistinguishable.

Many previous studies have reported that approximately 17–52% of cases of AEH may be associated with coexistent endometrial carcinoma [4–11]. Moreover, the rate of concurrent endometrial carcinoma following hysterectomy is increasing, and therefore, in recent studies the rates are even higher, reaching 40–50% [4,11]. In order to ensure appropriate management and patient safety, it is essential to have a better understanding of the rate of concurrent endometrial carcinoma among women with AEH as diagnosed by endometrial biopsy. The purpose of this study was to examine the relationship between the diagnoses of AEH by endometrial sampling and endometrial carcinoma with the postoperative pathology reports from hysterectomy specimens serving as the definitive results.

2. Materials and methods

We retrospectively analyzed the medical records of 712 patients with endometrial hyperplasia who were diagnosed at Cheil General Hospital and Women's Healthcare Center from January 1999 to December 2008 through pathologic databases based on endometrial preoperative sampling. Among patients with endometrial hyperplasia, 141 patients with AEH were included for the present study. This group was further divided into two subgroups, one with surgical treatment (hysterectomy) and the other without. We excluded 15 patients who did not receive surgical intervention, and thus a total of 126 patients were included in the final data analysis (Fig. 1). The excluded patients did not undergo hysterectomy; instead, they were medically treated with progestin. The interval between AEH diagnosis and subsequent hysterectomy was less than 12 weeks and there was no interval medical treatment. We performed all endometrial biopsies at the midluteal phase of the ovulatory cycle.

The parameters included in the evaluation were patient age, body mass index, gravidity, parity, indication for endometrial biopsy (EMB), preoperative diagnostic method and the definitive results of the hysterectomy specimen preoperatively diagnosed as AEH by dilatation & curettage (D&C), EMB or hysteroscopic polypectomy. We evaluated the relationship between preoperatively diagnosed AEH and the pathologic results from the hysterectomy by further dividing preoperatively diagnosed AEH into simple and complex AEH.

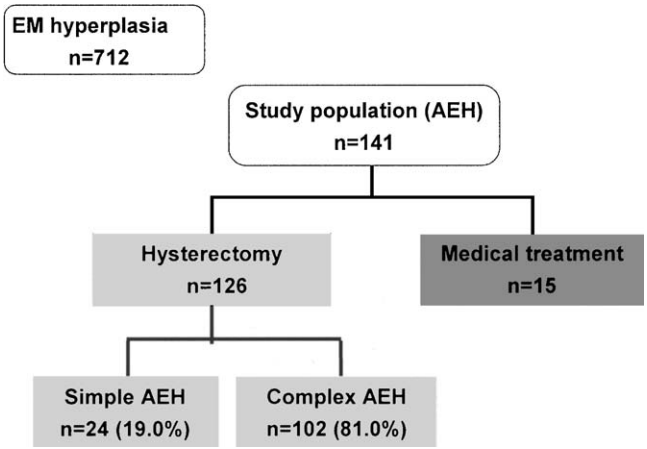

Fig. 1. An illustration of the study design. EM, endometrium; AEH, atypical endometrial hyperplasia.

Table 1
Characteristics of the women in this study with atypical endometrial hyperplasia.

Characteristic	*n*	%
Age (years)	Mean 45.44 ± 6.62 (range 25–65)	
25–30	1	0.8
31–35	9	7.1
36–40	13	10.3
41–45	35	27.8
46–50	45	35.7
51–55	17	13.5
56–60	3	2.4
60<	3	1.6
Body mass index (kg/m^2)	Mean 24.9 ± 3.6 (range 18.2–37.1)	
Weight (kg)	Mean 61.2 ± 9.65 (range 45–95)	
Height (cm)	Mean 156.8 ± 4.11 (range 146–169)	
Gravidity	Mean 3.3 ± 2.1 (range 0–10)	
Parity	Mean 1.8 ± 1.0 (range 0–5)	
Indication for EMB		
Abnormal uterine bleeding	122	96.8
Infertility evaluation	3	2.4
HRT work-up	1	0.8
Diagnosis method		
D&C	98	77.8
Office EMB[a]	24	19.0
H/S polypectomy	4	3.2

D&C, dilatation and curettage; EMB, endometrial biopsy; H/S, hysteroscopy; HRT, hormone replacement therapy.
[a] Endometrial biopsies were performed by Z-sampler.

At the time of hysterectomy, the endometrial tissue was immediately fixed in 10 mM citrate buffered formalin and sent to the pathologist. Slides were produced within 24 h following endometrial sampling. All pathologic diagnoses of initial biopsies and hysterectomies were conducted by three pathologists at Cheil General Hospital and Women's Healthcare Center according to the standard WHO classification system. The three pathologists read all AEH slides and a consensus diagnosis was defined as agreement among at least two of the three pathologists. The pathologic results obtained from the hysterectomy specimens were classified into six groups: simple endometrial hyperplasia, complex endometrial hyperplasia, simple AEH, complex AEH, endometrial carcinoma and proliferative phase.

3. Results

Of the 126 patients who underwent hysterectomy for preoperatively diagnosed AEH, 24 patients (19.0%) were diagnosed with simple AEH by pathologic review and the remaining 102 patients (81.0%) with complex AEH (Fig. 1).

The mean patient age was 45.44 ± 6.62 years with a range of 25–65 years (Table 1). Ninety-eight patients (77.8%) were diagnosed by D&C, 24 patients (19.0%) by EMB and four cases (3.2%) were diagnosed by hysteroscopic polypectomy. Mean body mass index was 24.9 ± 3.6 kg/m^2 and mean gravidity and parity were 3.3 ± 2.1 and 1.8 ± 1.0. The major indication for EMB was abnormal uterine bleeding (96.8%), three cases of EMB (2.4%) were conducted for infertility evaluation and one case (0.8%) for work-up of hormone replacement therapy.

Table 2 shows the pathologic results from the hysterectomy specimens which were preoperatively diagnosed as AEH. The rate of complex AEH was 48.3% and that of concurrent endometrial carcinoma was 10.3%. All patients with endometrial carcinoma demonstrated concurrent AEH, and 11 of 13 cases had carcinomas

Table 2
Results of hysterectomy specimens preoperatively diagnosed as atypical endometrial hyperplasia ($n = 126$).

Hysterectomy specimen	n	%
Simple EM hyperplasia	21	16.7
Complex EM hyperplasia	13	10.3
Simple AEH	8	6.3
Complex AEH	61	48.4
Endometrial carcinoma[a]	13	10.3
Proliferative phase	10	7.9

EM, endometrium; AEH, atypical endometrial hyperplasia.
[a] Eleven of 13 cases were confined to the endometrium and the other two cases were located within adenomyosis lesions without myometrial invasion. All patients with endometrial carcinoma showed coexisting complex AEH. Eleven of 13 patients with AEH concurrent with endometrial carcinoma were grade I and the remaining two were grade II.

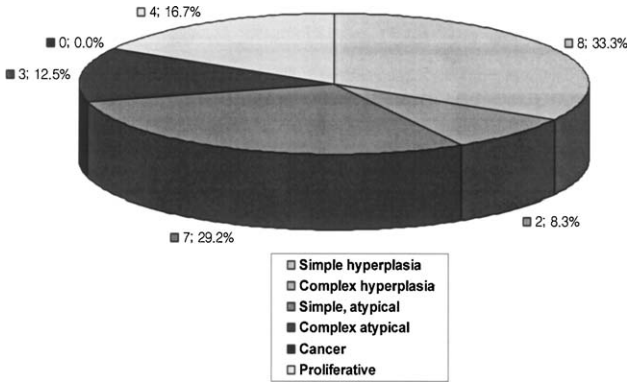

Fig. 2. Pathologic results from hysterectomy for those cases preoperatively diagnosed as simple AEH ($n = 24$).

confined to the endometrium and the other 2 cases had carcinomas located within adenomyosis lesions without myometrial invasion. There was no evidence of myometrial or lymphovascular invasion in any case. With respect to cancer cell differentiation, 11 of 13 patients with endometrial carcinoma were grade I and the remaining 2 were grade II. Ten of 13 patients with endometrial cancer were initially diagnosed as AEH by EMB, and the remaining three patients were diagnosed by D&C.

Figs. 2 and 3 depict data analyses as diagrams which divide preoperatively diagnosed AEH into two groups, simple and complex AEH. There were no patients with evidence of carcinoma

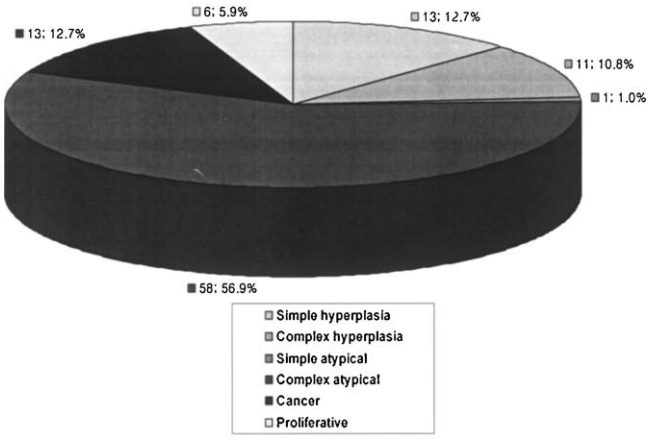

Fig. 3. Pathologic results from hysterectomy for those cases preoperatively diagnosed as complex AEH ($n = 102$).

in the pathologic results of hysterectomy who carried a preoperative diagnosis of simple AEH. Simple endometrial hyperplasia and simple AEH constituted 62.5% of the pathologies in the current population. With respect to a preoperative diagnosis of complex AEH, 12.7% demonstrated concurrent endometrial carcinoma, with complex AEH constituting 56.9% of the pathologies observed.

The relatively lower rate of concurrent carcinoma with AEH found in the current study is related to the higher preoperative detection rate of coexisting malignancies. Thirty-three patients were identified as coexisting cases before and after hysterectomy, and thus, adding these cases to the 13 patients who were diagnosed with AEH preoperatively and ultimately found to have concurrent cancer, the incidence rate of concurrence reaches 28.9% (46 out of 159).

4. Comment

The present study was designed to evaluate the prevalence of concurrent endometrial carcinoma in women who were diagnosed with AEH by endometrial biopsy. The increasing rate of concurrent endometrial carcinoma following hysterectomy seems to be partially due to increasing rates of patients with endometrial carcinoma. Endometrial carcinoma is the most common gynecological malignancy in Western countries [12,13], and the incidence of endometrial cancer in Korean women has also increased by five times in the past 10 years [14]. Endometrial hyperplasia, particularly the atypical type, may be mediating this increase.

The GOG study [4] reported the rate of concurrent carcinoma with AEH to be 42.6% and Giede et al. [15] reported an incidence of 35.7%. In the present study, the rate was found to be 10.3%, and it was 12.7% in patients with preoperatively diagnosed complex AEH, excluding the cases of simple AEH, which showed no concurrent endometrial carcinoma after hysterectomy. Although the incidence rate of uterine cancer in Korea has increased, it remains considerably lower than that reported in the United States. The age-standardized incidence rate (ASR) of uterine cancer in Korea was 9.12, while that of American women was 24.79 per 100 000 females in 2000 [16,17]. With the lack of studies, it is not clear whether the lower incidence of uterine cancer in Korean women is responsible for the lower coincident rates of endometrial cancer with AEH, and further studies in Korea are required.

Until the present, most studies regarding concurrent endometrial cancer with AEH were performed on Western populations, with no studies based in Asian countries. However, endometrial cancer is one of the most rapidly increasing gynecological malignancies in Asian countries. The present study is significant in that it presents Korean data on concurrent endometrial cancer with AEH. Further studies with Asian populations, including multicenter studies based in Korea, are necessary for better understanding this relationship.

One possible reason for the relatively lower rate of concurrent carcinoma with AEH found in the current study involves the higher preoperative detection rate of coexisting malignancies as mentioned previously in the results. This presumption is in accordance with the fact that the rates of concurrent endometrial carcinoma with AEH increase to 28.9% (46 out of 159) if we include the data of 33 patients who were diagnosed preoperatively with both afflictions. As preoperative identification of many cases was possible, only 13 additional cases were detected following hysterectomy.

Of note, a preoperative endometrial diagnosis was established in 77.8% of patients by D&C and only 19.0% by office-based EMB. Most previous studies used office-based EMB more frequently for preoperative diagnosis than they did D&C [3,4]. However, office-based EMB carries a higher possibility for missing cancerous

lesions, such as in cases of focally originating small volume tumors, and D&C reflects more accurately the final pathology [18,19]. Therefore, more frequent use of D&C could have decreased the possibility of missing cancerous lesions. In the current study, 10 of 13 patients with endometrial cancer were initially diagnosed as AEH by EMB. On the other hand, only three patients with endometrial cancer were diagnosed as AEH by D&C. This result supports that D&C reflects more accurately the final pathology and shows the consistency of the result. We conducted four cases (3.2%) of hysteroscopic endometrial resection for polypectomy and all the cases were diagnosed as having the pathology of AEH, with no concurrent cancer after hysterectomy. It is impossible to determine the role of hysteroscopic endometrial resection in improving preoperative prediction with these small numbers of cases. To determine the role of hysteroscopic endometrial biopsy, more studies with larger cases would be required.

In the present study, no myometrial invasion was detected in the cases of concurrent carcinoma with AEH, and the malignant cells were localized to the endometrium or adenomyosis lesions without myometrial invasion in all cases. This result differs from those of previous studies, in which approximately 30–90% of cases involved myometrial invasion [4–11]. It is not clear whether the lack of myometrial invasion is related to the lower incidence rates of uterine cancer in Korea. However, the higher rates of stage Ia disease in our institution could be involved. Creasman et al. reported 71% of 8807 patients with endometrial cancer treated between 1999 and 2001 had stage I disease when surgically staged, and 14% of patients had no myometrial invasion (stage Ia) [20]. Compared with these data, 69% of 465 patients with endometrial cancer treated in our hospital between 1996 and 2007 had stage I disease, and 43% of patients lacked myometrial invasion. These differences between Western populations and Korean women have implications for varying treatment modalities. In Western countries, the rates of concurrent endometrial cancer with AEH and myometrial invasion are relatively high, and thus clinicians should be cautious with conservative management, such as medical treatment with progestin. Conversely, in Korean populations, the rates are relatively low, and thus conservative treatment may be considered as a comparatively safe therapeutic option for patients who wish to preserve their fertility. For the appropriate management of patients with AEH, further studies regarding endometrial hyperplasia coexisting with endometrial cancer in other countries are required.

Although there was no myometrial invasion in the present study, the rate of concurrent endometrial carcinoma with AEH indicates that 1 of 10 patients who undergo surgery for AEH is a cancer patient. Thus, it is important to warn patients with AEH about the possibility of concurrent malignancy and that comprehensive surgical staging depends on an intra-operative frozen biopsy. Given the possibility of myometrial invasion with more than half of endometrial cancer grade III, an intra-operative frozen biopsy is necessary to avoid possible suboptimal surgery under the preoperative diagnosis of AEH.

In conclusion, the present study demonstrated that biopsy specimens revealing AEH were associated with a risk of coexisting endometrial carcinoma. Given the considerable rate of concurrent cancer, clinicians should take into account the risk of malignancy and share this information with their patients.

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