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Original article

Risk of endometrial cancer in patients with a preoperative diagnosis of atypical endometrial hyperplasia treated with total laparoscopic hysterectomy

Katsutoshi Oda [a,*], Kaori Koga [a], Tetsuya Hirata [a], Masanori Maruyama [b], Masako Ikemura [c], Yoko Matsumoto [a], Kazunori Nagasaka [a], Katsuyuki Adachi [a], Mayuyo Mori-Uchino [a], Kenbun Sone [a], Takahide Arimoto [a], Osamu Wada-Hiraike [a], Kei Kawana [a], Masashi Fukayama [c], Tomoyuki Fujii [a], Yutaka Osuga [a]

[a] Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo, Tokyo, Japan
[b] Department of Obstetrics and Gynecology, Maruyama General Hospital, Saitama, Japan
[c] Department of Pathology, Faculty of Medicine, The University of Tokyo, Tokyo, Japan

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ABSTRACT

Objective: Distinguishing atypical endometrial hyperplasia (AEH) and endometrial cancer (EC) is often difficult, and patients with a preoperative diagnosis of AEH are sometimes diagnosed with EC after hysterectomy. In this study, we assessed the risk factors for EC in patients who underwent total laparoscopic hysterectomy (TLH) with a preoperative diagnosis of AEH.

Patients and methods: We retrospectively analyzed 20 patients with a preoperative diagnosis of AEH using endometrial cytology, biopsy (fractional and total curettage), and hysteroscopic inspection.

Results: Four of 20 (20%) patients were diagnosed with EC after TLH, all of whom had endometrioid adenocarcinoma Grade 1 and Stage IA without lymph node metastasis. Four of seven (57%) patients who were highly suspected of having EC by three diagnostic modalities (cytology, fractional curettage, and by hysteroscopy) were diagnosed with EC after TLH, whereas none of the 13 without any suspicious findings in these examinations were diagnosed with EC ($p = 0.007$ by Fisher's exact test). Hysteroscopic findings were positive (suspicious of EC) in six of 11 patients tested, including all four EC patients. However, either endometrial cytology or fractional curettage alone failed to predict cancer in two EC patients. All four EC patients were also suspected of having EC by total curettage. Ovarian preservation was performed in 12 (60%) patients. Three of the four EC patients received subsequent surgery, including pelvic lymphadenectomy.

Conclusion: Careful preoperative examinations, including hysteroscopy, might be useful to evaluate the risk of EC. Accordingly, we should be still careful about the possibility of overdiagnosis in patients with AEH.

Introduction

Atypical endometrial hyperplasia (AEH) is considered a precancerous stage of endometrial cancer (EC), especially well-differentiated endometrioid endometrial cancer (Grade 1), and the ratio of concurrent EC and AEH in patients with a prediagnosis of EC is ~17–52%.[1–4] Laparoscopic surgery is broadly applied for early stage EC patients as well as AEH patients.[5,6] However, the type of surgery is not the same for AEH and EC. Hysterectomy and bilateral salpingo-oophorectomy (BSO) are considered to be minimally required as a standard surgical treatment in EC, even at Stage I/II (International Federation of Gynecology and Obstetrics staging), as ovarian metastasis was reported to be detected in 5–10% of EC patients with a preoperative evaluation of Stage I/II.[7–9] In addition,

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* Corresponding author. Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail address: katsutoshi-tky@umin.ac.jp (K. Oda).

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pelvic lymphadenectomy (PLA) is required to pathologically diagnose the presence or absence of lymph node metastasis. On the contrary, ovarian preservation can be considered for AEH patients, especially for premenopausal women, and lymphadenectomy is unnecessary. The ratio of premenopausal women is ~40–50% in AEH patients,[10,11] and most premenopausal women desire to preserve their ovaries. Thus, appropriate preoperative diagnosis is important to decide the surgical procedure. However, the pathological diagnosis of AEH and EC (Grade 1) is still challenging, even when using the samples obtained from total curettage.[7] Hysteroscopy has been reported to be useful for the diagnosis of AEH and EC, and is anticipated as another diagnostic modality in addition to pathological diagnosis (cytology of endometrium, endometrial biopsy, and total curettage).[12,13] In this study, we retrospectively analyzed patients with a preoperative diagnosis of AEH, and aimed to assess the correlation between preoperative diagnosis and postoperative diagnosis, by focusing on pathologic findings and hysteroscopy.

Patients and methods

We retrospectively analyzed 20 patients with a preoperative diagnosis of AEH, who were treated with total laparoscopic hysterectomy (TLH) at the University of Tokyo Hospital, Tokyo, Japan from 2013 to 2015. The study was performed under the approval of the Institutional Review Board of our hospital and with written informed consent. The AEH patients who underwent laparotomy due to severe obesity (body mass index > 32) and/or enlargement of the uterus, were not included in this study. Eight of 20 (40%) patients received BSO, and 12 patients (60%) received bilateral salpingectomy with ovarian preservation. All patients received cytologic evaluation of the endometrium and fractional endometrial curettage, followed by total endometrial curettage (dilatation of the cervix and curettage). Hysteroscopy was performed in 11 patients (55%), and transcervical resection was performed in five (25%) patients. Thickness of the endometrium was evaluated with magnetic resonance imaging and transvaginal ultrasonography. Final diagnosis was determined with pathological findings of the resected uterus. Nonatypical hyperplasia remaining in the hysterectomy specimen was diagnosed as AEH. For EC patients, we performed subsequent surgery with oophorectomy (if preserved during the initial surgery) and pelvic lymphadenectomy, except for one case who had received TLH and BSO and declined to receive lymphadenectomy. Fisher's exact test was used to evaluate the risk factors between the two groups of AEH and EC (final diagnosis). The p-values were considered to be significant at $p < 0.05$.

Results

The final diagnosis was EC in four (20%) and AEH in 16 (80%) of the 20 patients. All four patients with EC were diagnosed as Stage IA with well-differentiated adenocarcinoma (Grade 1). Three of four patients received pelvic lymphadenectomy, which revealed no lymph node metastasis. The patient characteristics, prepathological and postpathological diagnosis, and histeroscopic findings are listed in Table 1. The size of the uterus and absence of myometrial invasion were confirmed using magnetic resonance imaging in all 20 patients. The median age of the 20 patients was 47.6 years. Among 12 patients with ovarian preservation, one (8.3%) was diagnosed as EC, and 11 were diagnosed as AEH. In cytology of the endometrium before surgery, four (20%) patients were diagnosed as positive (EC was suggested), 11 (50%) patients were as suspicious (with atypical endometrial epithelium), and five (25%) patients were as negative (Table 1). By fractional endometrial curettage, three (15%) patients were diagnosed as suspicious of EC (unable to discriminate AEH and EC), 14 (70%) patients were as AEH, and two (10%) patients as endometrial hyperplasia, complex, or suspicious of AEH (Table 1). By total curettage (5 patients received concurrent

Table 1
Patient characteristics, findings of each examination, and final diagnosis in 20 patients with a prediagnosis of atypical endometrial hyperplasia (AEH).[a]

No.	Age	Gravidity	Parity	Menopause	BMI	Cytology[b]	Biopsy	Total curettage	Hysteroscopy[c]	Em (mm)	Ovaries	Uterine fiborid	TCR	Final diagnosis	Sequential surgery
1	45	0	0	–	<25	Suspicious	AEH	AEH		10	Preserved			AEH	
2	51	4	2	–	<25	Suspicious	AEH	AEH	AEH likely	10	Preserved	4 cm		AEH	
3	37	1	0	–	<25	Negative	AEH	AEH		7	Preserved	2 cm		AEH	
4	49	0	0	–	29	Suspicious	AEH	AEH		5	Preserved	4 cm		AEH	
5	47	4	2	–	25.7	Suspicious	AEH	AEH	AEH likely	6	Preserved		Done	AEH	
6	47	0	0	–	31.2	Suspicious	AEH	AEH	AEH likely	10	Preserved			AEH	
7	48	3	2	–	27.5	Suspicious	AEH	AEH		13	Preserved			AEH	
8	46	0	0	–	26	Negative	AEH	AEH		15	Preserved	3 cm		AEH	
9	43	1	1	–	<25	Suspicious	AEH	AEH		14	Preserved	3 cm		AEH	
10	45	1	0	–	<25	Suspicious	AEH	AEH		16	Preserved			AEH	
11	43	0	0	–	<25	Positive	AEH	AEH		7	Preserved			AEH	
12	51	3	1	–	<25	Suspicious	AEH	AEH	AEH likely	8	BSO	5 cm	Done	AEH	
13	54	3	3	51	<25	Negative	AEH suspected	AEH	AEH likely	5	BSO	2 cm	Done	AEH	
14	46	0	0	–	<25	Suspicious	AEH	AEH		15	BSO	2 cm		AEH	
15	59	0	0	55	25.2	Suspicious	AEH	AEH	EC likely	16	BSO	3 cm	Done	AEH	
16	47	2	2	–	<25	Positive	EC strongly suspected	AEH	EC likely	5	BSO			AEH	
17	55	2	2	50	<25	Positive	AEH or more	AEH	EC likely	10	BSO			G1, Ia	PLA
18	50	0	0	–	25.8	Positive	AEH or more	AEH or more	EC likely	8	BSO	3 cm	Done	G1, Ia	PLA
19	59	3	3	50	<25	Negative	EMH (without atypia)	AEH or more	EC likely	20	BSO			G1, Ia	
20	31	0	0	–	<25	Suspicious	AEH	AEH or more	EC likely	12	Preserved			G1, Ia	Laparo-BSO + PLA

AEH = atypical endometrial hyperplasia; BMI = body mass index; BSO = bilateral salpingo-oophorectomy; EC = endometrial cancer; EMH = extramedullary hematopoiesis; PLA = pelvic lymphadenectomy; TCR = transcervical resection.

[a] Null entries are either not analyzed (for examinations) or not observed (for uterine fibroids).

[b] Negative (no atypical endometrius), suspicious (atypical endometrial cells), and positive (adenocarcinomy, highly suspected cells).

[c] AEH likely (protruding lesion with mild to moderate atypical vessels); EC likely (papillary, irregular-shaped, and solid lesion with severe atypical vessels).

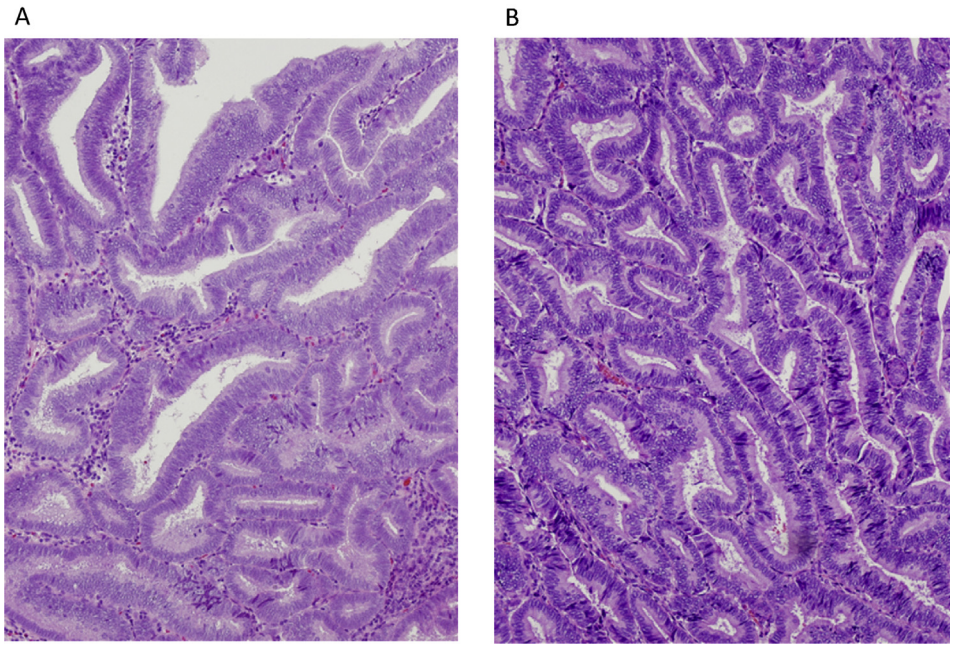

Figure 1. Microscopic findings of one typical patient (#17), whose prediagnosis is atypical endometrial hyperplasia and final diagnosis is endometrial cancer: (A) microscopic features (high power) by total curettage (the glands are irregular-shaped, and closely packed, but stromal tissue exists among the atypical glands). This was diagnosed as atypical endometrial hyperplasia with possibility of concurrent endometrial cancer; (B) microscopic features (high power) of the specimen obtained by total laparoscopic hysterectomy (a back-to-back glandular structure was observed with stromal disappearance). Solid growth was < 5%, and was diagnosed as endometrioid adenocarcinoma, Grade 1.

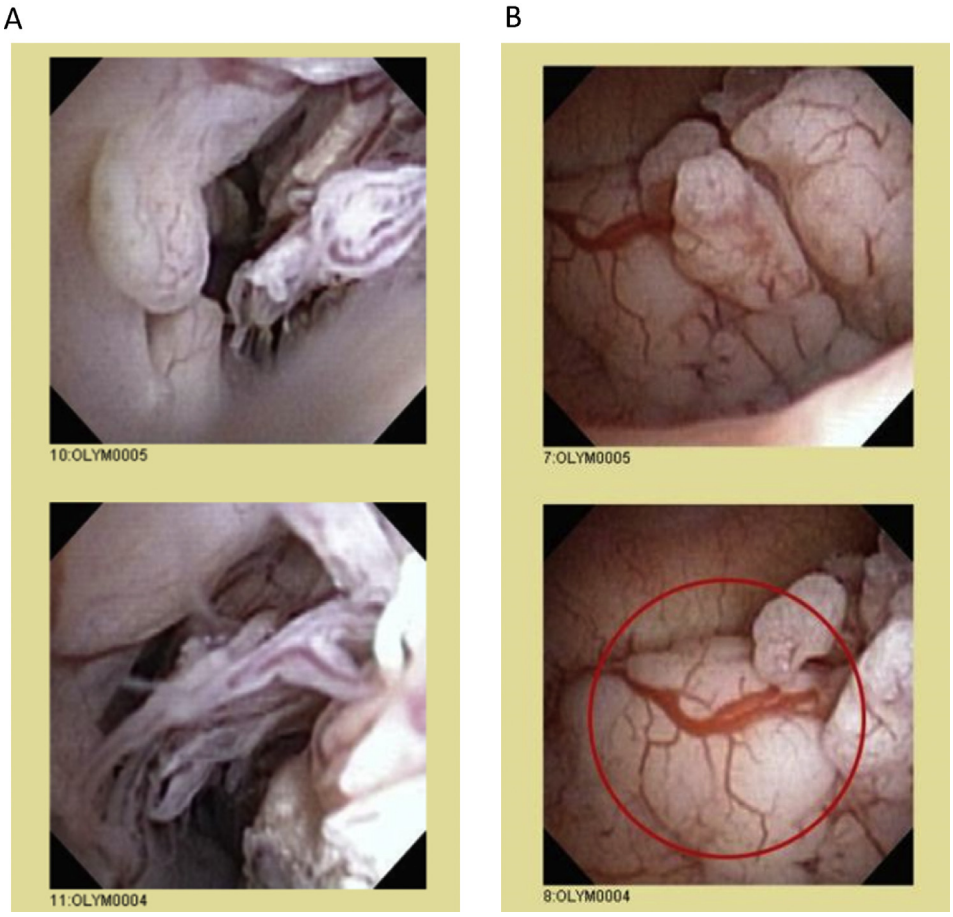

Figure 2. Hysteroscopic findings of two patients, whose prediagnosis was atypical endometrial hyperplasia and final diagnosis was endometrial cancer: (A) hysteroscopic features of patient #19 in Table 1. Irregular-shaped, broad solid lesion with atypical vascularization was observed, which was suspected of endometrial cancer; (B) hysteroscopic features of patient #20 in Table 1. Papillary solid lesions were spread in endometrial cavity with intermittent atypical vessels.

Table 2
Correlation between clinicopathological characteristics and final diagnosis.

	AEH	Endometrial cancer	*p*
Age			
<50	12	1	
≥50	4	3	0.10
Gravidity			
0	7	2	
≥1	9	2	1.0
Parity			
0	9	2	
≥1	7	2	1.0
BMI			
<25	10	3	
>25	6	1	1.0
Thickness of endometrium			
<10	7	1	
>10	9	3	0.62
Cytology			
Negative/suspicious	14	2	
Positive	2	2	0.16
Biopsy (fractional)			
AEH likely	15	2	
Cancer suspected	1	2	0.087
Hysteroscopy			
AEH likely	5	0	
Cancer highly suspected	2	4	0.022
Presence of risk factors[a]			
Negative	13	0	
Positive	3	4	0.007
Biopsy (fractional and Total curettage)			
AEH likely	15	0	
Cancer suspected	1	4	<0.001

AEH = atypical endometrial hyperplasia; BMI = body mass index.
[a] Risk factors by cytology, fractional biopsy, and hysteroscopy.

transcervical resection and total curettage) 17 (85%) patients were diagnosed as AEH, and three patients were as suspicious of EC (unable to discriminate AEH and EC; Table 1). Pathologically, AEH is characterized with atypical glands consisting of dyspolaric cells, eosinophilic cytoplasm, and rounded, enlarged nuclei with prominent nucleoli.[14] The histological findings of one case, in which EC cannot be ruled out and diagnosed as EC after hysterectomy, are shown in Figure 1. In the specimen of total curettage, the irregularly shaped glands are closely packed; however, no definitive stromal invasion was observed (EC was suspected but not definitely diagnosed; Figure 1A). In the specimen of TLH, back-to-back glands were clearly observed with stromal disappearance, which was diagnosed as EC (Figure 1B). Among 11 patients who received hysteroscopic inspection, five (45%) showed papillary protruding lesions with atypical vessels, which suggest the possibility of EC (especially Grade 1) and considered as positive in this study (Figure 2).

Next, we analyzed the association between clinical characteristics and final diagnosis (risk of EC). Twelve of 16 (75%) AEH patients were younger than 50 years, while one of four with EC were younger than 50 years ($p = 0.10$; Table 2). Gravidity, parity, body mass index, and thickness of the endometrium were not associated with the risk of EC (Table 2). Endometrial cytology alone or fractional curettage alone was not significantly associated with the risk of EC in this setting ($p = 0.16$ and $p = 0.087$, respectively; Table 2). Hysteroscopic findings with papillary swollen lesions with atypical vessels were significantly associated with the risk of EC ($p = 0.022$; Table 2). By combining these three examinations, the presence of any risk factors was also associated with the risk of EC ($p = 0.007$). By fractional and total curettage, all four patients with EC were suspected for EC, whereas only one (6%) of 16 AEH patients were suspected for EC ($p < 0.001$).

Discussion

Laparoscopic surgery is broadly performed in patients with AEH and early stage EC with Grade 1. Although laparoscopic surgery is less invasive than laparotomy,[5,15,16] the difficulty in the differential diagnosis of AEH and well-differentiated endometrioid EC may result in enforced secondary surgery or overtreatment. In this study, we focused on patients with preoperatively diagnosed AEH (after total curettage), and examined what kind of findings are associated with a final diagnosis of EC.

In this study, four out of 20 patients (20%) with preoperatively diagnosed AEH had a final diagnosis of EC (Grade 1). Our data are in agreement with previous reports that show 6–48% of patients with a preoperative diagnosis of AEH have concurrent EC.[4] These data support the difficulty and limitation of preoperative differential diagnosis of AEH and EC.[14] However, the presence of EC was suspected in all four cases where EC was diagnosed using histopathological examination. Moreover, hysteroscopy indicated the possibility of EC in all these patients, which revealed the findings of papillary protruding lesions with atypical vessels. The usefulness of hysteroscopy for EC has been reported.[12,17] Therefore, by using a combination of pathological and hysteroscopic findings, the risk of EC could be evaluated in patients with a preoperative diagnosis of AEH. Intraoperative diagnosis using frozen sections of the uterus might be informative for diagnosis of AEH and EC; however, the risk of EC still remains in patients with AEH.[18] In addition, we should be aware of the false–positive risk in both the preoperative and intraoperative pathological examination,[19] and be aware of the variation of diagnosis among pathologists. The risk of concomitant malignancy of the endometrium and ovaries should be also considered, even in AEH patients who desire ovarian preservation. It was reported that 26 of 102 (25%) women younger than 45 years who underwent hysterectomy for EC were found to have coexisting epithelial ovarian cancer (EOC), and four women lacked any abnormal intraoperative findings in the ovaries.[20] The overall rate of coexisting EOC in EC patients is ~7%, with the ratio at 6.3% in patients younger than 45 years and 8.4% in those older than 45 years.[21] Coexistence of AEH was also reported in EOC patients.[22] Therefore, the potential risk of latent EOC requires careful consideration for patients undergoing hysterectomy to treat endometrial malignancy. Lymph node metastasis is reported to be low (1.3–2.0% in Stage 1A and Grade 1 EC) and the effect of PLA on prognosis is still under debate.[23–25] If patients do not wish to receive (or physicians do not plan to perform) PLA, TLH and BSO might be a favorable option for patients with a preoperative diagnosis of AEH and high risk of EC, even in premenopausal women. This may allow patients to avoid an additional surgery (oophorectomy).

This study has several limitations. Firstly, the sample size is small and hysteroscopic inspection was not performed for all patients. Secondly, interpretation of hysteroscopic findings may vary among investigators. Thirdly, the data in this study may not apply to patients who received total abdominal hysterectomy because the preoperative diagnosis may be more difficult in those patients due to enlargement and/or deformation of the endometrial cavity.

In conclusion, although the preoperative differential diagnosis of AEH and EC (Grade 1) is still challenging, the risk of EC may be evaluated by a combination of pathological and hysteroscopic findings. Further study is warranted to improve the preoperative diagnosis and contribute to avoiding repetitive surgery by the postoperative diagnosis.

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