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Prognostic factors of regression and relapse of complex atypical hyperplasia and well-differentiated endometrioid carcinoma with conservative treatment

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HIGHLIGHTS

- Conservative treatment may be recommended in selected women with endometrial tumors.
- None of the factors studied was associated with higher regression probability.
- Obesity was associated with higher relapse probability.

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ABSTRACT

Objective. To evaluate possible prognostic factors regarding regression and relapse of complex atypical hyperplasia (CAH) and well-differentiated endometrioid adenocarcinoma (WDC) treated with conservative treatment.

Methods. The retrospective study reviewed clinicopathologic, treatment, regression and relapse data from patients diagnosed with CAH or WDC who were treated with conservative treatment at 4 institutions. Potential factor evaluation was performed. SPSS 16 was used for statistical analyses.

Results. Eighty-eight patients were included (51 had WDC, and 37 had CAH). Regression was evaluated in 88 patients, with a median follow-up of 61 (range 15–95) months. Seventy-seven (87.5%) patients regressed, and 11 (12.5%) had persistent or progressive disease. Univariate and multivariate analyses showed no factors associated with regression. Relapse was evaluated in 71 patients, with median follow-up of 54 (range 8–86) months. Twenty-five/71 (35.2%) patients experienced relapse. On univariate analysis, body mass index (BMI) 30 or higher ($p = 0.001$), WCD at initial biopsy ($p = 0.017$) and positive expression of post-treatment ki67 ($p = 0.033$) were associated to a higher relapse probability. However, only BMI 30 or higher was significant on multivariate analysis ($p = 0.012$). The Kaplan–Meier analysis revealed a higher relapse probability in the patients with BMI 30 or higher ($p = 0.001$).

Conclusion. Obesity seems to be a risk factor for relapse of CAH or WDC with conservative treatment.

1. Introduction

Endometrioid adenocarcinoma (EC) is a common gynecologic malignancy worldwide. Complex atypical hyperplasia (CAH) is the immediate precursor of EC because of its high risk of progression to carcinoma. Its progression risk is up to 29% [1]. For patients with CAH or EC, surgical management is the standard treatment. However, it may not be possible for younger patients wishing to preserve their fertility or those who are unfit for surgery. Thus, conservative treatment, which mainly comprises hormonal therapies involving progestins and progestin-releasing intrauterine devices, etc., may be recommended as an alternative to hysterectomy in such cases.

Numerous reports show regression of CAH or early-stage, well-differentiated endometrial adenocarcinoma (WDC) in majority of patients treated with conservative therapy. Complete regression varies from 50% to 100% for CAH [2–8] and from 33% to 100% for WDC

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[2,4–6,8–11]. However, some patients experience disease recurrence after their initial regression. The relapse rate ranges from 0% to 50% for CAH [6,8,12–14], and from 0% to 67% for WDC [6,8,10,11,15,16]. To improve the result of conservative treatment for CAH or WDC and prolong disease-free survival, it is important to elucidate possible factors associated with regression and relapse of CAH or WDC. It was reported that obesity [11], chronic anovulation [11],lack of response within 2 months of initiating progestin treatment [17] and progesterone receptor (PR) expression [18] seem to be signs of lower likelihood of achieving regression of CAH or WDC. Possible predictors of a lower risk of recurrence include successful subsequent pregnancy [19], use of maintenance progestin therapy [19], and use of medroxyprogesterone acetate (MPA) [19] and levonorgestrel-releasing intrauterine system (LNG-IUS) [14]. In contrast, none of live births [20], infertility [21] and polycystic ovary syndrome [21] were found to be associated with a higher risk of relapse. Although several studies have been conducted which identified possible factors affecting regression and relapse of CAH or WDC, there are still no reliable predictors available for use in routine practice. Hence, a clinicopathologic study is conducted to clarify which factors are associated with regression and relapse of CAH or WDC treated with conservative treatment and also to evaluate any differences in the prognostic factors for regression and relapse of CAH or WDC.

2. Materials and methods

2.1. Patients and follow-up

We performed a retrospective analysis of patients with CAH or EC who were treated with conservative treatment at 4 institutions between January 2001 and December 2010. Patients were included if they met the following three inclusion criteria: (1) histologically confirmed CAH or grades 1 EC, (2) diseases confined to the endometrium, (3) absence of myometrial invasion and extrauterine spread on diagnostic imaging. The study encompassed 88 patients for the assessment of regression of CAH or WDC, and 71 patients for the elevation of relapse of CAH or WDC. The retrospective study was approved by the Independent Ethics Committee of the 4 institutions.

The patients underwent regular review in our gynecology outpatient clinic and endometrial histologic surveillance by curettage or endometrial biopsy after the beginning of the hormonal therapy. Histologic examinations of the endometrium were performed on a 3-month basis for the first year, a 6-month basis for the second year and yearly thereafter for 5 years. For each patient, data on the clinicopathologic characteristics, treatment and patient outcomes were noted from the medical record. Moreover, we contacted patients included in our study for clarification and supplement of relevant information.

2.2. Material and evaluation

Histological material from initial and follow-up biopsies was sent to the Department of Pathology for routine procedure and assessment. The immunohistochemical expression of estrogen receptor (ER), PR, and ki67 was assessed before and after treatment.

Disease regression was defined as a lack of residual WCD or CAH at follow-up endometrial sampling. Disease persistence was defined as regression of WDC to CAH or persistence of CAH or WCD. Disease progression was defined as development of grade 2 or 3 adenocarcinoma from either CAH or WDC, or when myometrial invasion or any extrauterine lesions were recognized. The diagnostic criteria of CAH and WDC were based on the World Health Organization definitions [22]. Body mass index (BMI) ≥30 was considered obese.

Immunohistochemical results of ER, PR and ki67 (rabbit, rabbit and mouse monoclonal antibody, respectively; Clone No. SP1, SP2 and MIB-1, respectively; ZSGB-BIO, Beijing, China) were evaluated according to Yamazawa1 KJ et al. [18] Percentage of positive ER/PR cells was scored as negative (<10%) and positive (≥10%), respectively. Ki67 was evaluated in 1000 cells under the same observation conditions. Only strong nuclear immunostaining was regarded as positive, and weak nuclear or cytoplasmic stainings were regarded as negative.

All slides were re-examined independently by three experienced gynecologic pathologists. Regarding those cases with discordant diagnosis, three pathologists performed a consensus adjudication review using a multiheaded microscope. Therefore, the diagnostic errors and recall biases were kept as minimal as possible.

2.3. Statistical analysis

All data were presented descriptively as medians, means or proportions. Chi-square test was used to determine the relationship between categorical variables. Univariate and multivariate logistic regressions were performed to determine associations between possible prognostic factors and regression and relapse of CAH or WDC. The relapse curve for CAH and WDC was calculated by the Kaplan–Meier method and compared between groups using the log-rank test. $P < 0.05$ was considered statistically significant. All statistical analysis was performed using SPSS 16.0 software (Los Angeles, CA).

3. Results

Eighty-eight patients with CAH or WDE were treated with progestogens. The median age at initial diagnosis and median age at menarche were 33 years (range, 24–39) and 13 years (range, 11–15) respectively. Thirty-four/88 patients were obese, with a median BMI of 26.7 (range 17.5–44.9) kg/m^2. Table 1 details the baseline characteristics of all patients included in our study.

At initial diagnosis, 37 (42.0%) had CAH and 51 (58.0%) had WDC. Positive rates for ER, PR and Ki67 expression were 93.2% (82/88), 92.0% (81/88) and 81.8% (72/88), respectively. By comparing immunohistochemical results before and after treatment, 65 (73.9%) of 88

Table 1
Baseline clinical characteristics.

	Regression	No regression	Relapse	No relapse
Age at initial biopsy				
<35	46	6	15	28
≥35	31	5	10	18
Age at menarche				
<13	39	4	11	24
≥13	38	7	14	22
Body mass index (kg/m^2)				
≥30	31	3	15	14
<30	46	8	10	32
History of PCOS				
Yes	19	4	7	10
No	58	7	18	36
History of menometrorrhagia				
Yes	43	6	12	26
No	34	5	13	20
Previous pregnancy				
Yes	46	7	15	28
No	31	4	10	18
History of diabetes				
Yes	13	1	4	7
No	64	10	21	39
Smoking status				
Yes	20	3	5	12
No	57	8	20	34
Prior OCP use				
Yes	25	4	8	14
No	52	7	17	32

PCOS: polycystic ovary syndrome; OCP: oral contraceptive.