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CLINICAL ARTICLE

Factors predicting pathologic significance among women with atypical glandular cells on liquid-based cytology

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ABSTRACT

Objective: To determine incidence, originating organ, and factors predicting significant histopathology (premalignant and malignant lesions) among women with atypical glandular cells (AGCs) on liquid-based cytology (LBC). *Methods:* In a retrospective study at Siriraj Hospital, Bangkok, Thailand, clinical and histologic data were reviewed for women with AGCs who underwent appropriate examinations from January 2007 to December 2010. *Results:* There were 284 women with AGC cytology (mean age, 51.2 years). The incidence of significant pathology and invasive cancer was 43.3% and 34.5%, respectively. The most common malignant organ was the uterus (64/123, 52%). Predictors of serious pathology were AGC favor neoplasia (AGC-FN) endocervical (odds ratio [OR], 5.64; 95% confidence interval [CI], 1.62–19.57), AGC-FN endometrial (OR, 4.11; 95% CI, 1.27–13.32), AGC-FN glandular (OR, 8.23; 95% CI, 2.02–33.49) subtypes, and bleeding (OR, 2.88; 95% CI, 1.47–5.65). Combining patient age and AGC subtype, there were no serious cervical lesions among women aged 50 years or younger with AGC-FN glandular subtype, or serious non-cervical neoplasia among women aged 50 years or younger with AGC not otherwise specified (AGC-NOS) or AGC-FN endocervical subtypes. *Conclusion:* AGC subcategories defined from LBC, alone or combined with patient age, might be predictors of significant histopathology, cancer incidence, and originating organ.
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1. Introduction

Atypical glandular cells (AGCs) are glandular cells that show changes beyond reactive or reparative alterations, but lack the unequivocal features of invasive adenocarcinoma [1,2]. AGCs are frequently caused by benign conditions such as reactive changes and polyps, or significant underlying neoplastic conditions of the cervix, endometrium, ovary, or fallopian tube.

The percentage of significant neoplasia among women with AGCs has been reported to vary from 9% to 38% [2]. A retrospective study of 71 liquid-based cytology (LBC) and 114 conventional cytology AGC samples revealed that the LBC method determined a higher incidence of significant pathology, as compared with a conventional smear method (33.8% versus 15.3%), which mostly originated from cervix [3]. A retrospective study of 63 cases of AGCs on conventional smears determined the incidence of significant pathology and cancer to be 22% and 8%, respectively [4]. In addition, women with AGC favor neoplasia (AGC-FN) had a higher incidence of significant pathology and cancer than women with AGC not otherwise specified (NOS) (41.2% and 23.5% versus 15.2% and 2.2%, respectively) [4]. A study of 92 LBC and conventional cytology samples found that the incidence of significant pathology and invasive cancer was 38% and 17%, respectively [5]. The risk of cancer was found to be higher in women older than 40 years [5].

Because of the wide differences in incidence and the variety of serious underlying diseases, AGC cytology is a diagnostic challenge. To the best of our knowledge, previous studies of women with AGCs on LBC have had a small sample size. In particular, there are no data on specific AGC subcategories, and data on predictors of significant pathology have been inconclusive.

The Siriraj Hospital, Mahidol University, Bangkok, Thailand, has used LBC for cervical cancer screening for all women since 2006, and its screening efficacy has been approved with high cost-effectiveness [6]. The aim of the present retrospective study was to evaluate the final histopathology of women found to have AGCs on LBC in terms of both the incidence of cancer and the malignant organ. A second aim was to determine factors predicting significant lesions.

2. Materials and methods

The present study was a retrospective analysis of data from women with AGC detected by LBC screening at the Siriraj Hospital, Bangkok, Thailand, between January 1, 2007, and December 31, 2010. Data, including completely documented examinations for definite pathologic diagnoses, were collected from the medical records

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of all women who met the study criteria. Women with a history of gynecologic malignancy or hysterectomy were excluded. The study was approved by Siriraj Institutional Review Board.

At Siriraj Hospital, AGCs were interpreted by 1 gynecologic cytologist in accordance with the 2001 Bethesda System [7]. Women with AGC results were managed according to the American Society for Colposcopy and Cervical Pathology (ASCCP) recommendations [2]. Colposcopic examination and pathologic interpretation were performed by gynecologic oncologists and pathologists, respectively.

The medical records of the study women were reviewed including demographic data, investigation methods, pathologic results, diagnoses, treatment modalities, and follow-up outcomes. The pathologic results were obtained from 1 or more of the following sources: tissue biopsy of suspected lesions seen with the naked eye or under colposcopy, endocervical or endometrial curettage, conization, and surgical specimens (e.g. cervix, uterus, adnexa, colon, and peritoneum). Each final diagnosis was decided by consideration of the pathologic results from all of the investigations, on the basis of the severity of lesions and the correlation between the organ sites favored by 1 cytologist and histologic reports. Significant pathologic results included cervical intraepithelial neoplasia grade 2–3 (CIN 2–3), adenocarcinoma in situ, endometrial hyperplasia, and cancer of any primary site such as cervix, uterine body, adnexa, and colon. Body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) was categorized in accordance with the National Institutes of Health guidelines [8] as follows: underweight, less than 18.5; normal weight, 18.5–24.9; overweight, 25–29.9; obesity, 30 or higher.

The data accumulated were analyzed using SPSS version 14.0 (IBM, Armonk, NY, USA). Descriptive statistics were used for the baseline characteristics. Two-sided χ^2 and Fisher exact tests were calculated as appropriate to compare the variables with significant pathologic results and organ sites. Variables with a P value of less than 0.1 were included in a multivariable regression analysis to determine their association with overall significant pathology by estimated odds ratio (OR) and 95% confidence interval (CI). A P value of less than 0.05 was considered to be statistically significant.

3. Results

Over the 4-year study period, 125 839 LBC records were reviewed. The number of records with AGC abnormalities was 346 (0.27%), of which 62 records were excluded from the study for the following reasons: 19 records owing to a previous history of gynecologic cancer; 3 records owing to hysterectomy for benign gynecologic disease; 19 records because further investigations after the AGC result were lost; and 1 record because the woman died from septicemia before further investigation. In addition, 20 records (5.8%) were excluded owing to management that was against the ASCCP 2006 recommendations or because there was no histologic report even though the guidelines had been followed. As a result, 284 records were included for analyses.

The mean age was 51.2 years (median, 50 years; range, 25–87 years). There were 217 parous women with a parity of 1–9 (mean, 1.8; median, 2), and 173 women (79.7%) who were multiparous. Two menopausal women (1.5%) were prescribed hormonal treatment. Data on history of sexually transmitted diseases, available for 95 records, showed that 9 women (9.5%) had a previous sexually transmitted disease. Approximately half of the study women (133 women, 46.8%) came for a check-up, and the most common symptoms among symptomatic women were vaginal bleeding (114/151 symptomatic women, 75.5%). The mean, median, and range of body mass index (BMI) were 24.5, 23.6, and 15.4–55.5, respectively.

Among 47 women (16.5%) who came to the hospital annually for a cervical cytology examination, 12 had abnormal cervical cytology results before the study period: 4 were classified as atypical squamous cells of undetermined significance (ASC-US); 3 as ASC, cannot exclude high-grade lesion (ASC-H); 1 as low-grade squamous intraepithelial lesion (LSIL); and 4 as high-grade squamous intraepithelial lesion (HSIL). However, no significant diseases were detected and normal cervical cytology was found after follow-up visits.

Overall, 186 cases were subclassified as AGC-NOS (65.5%), and 98 cases as AGC-FN (34.5%). In addition, 8 women had both AGC cytology and squamous cell abnormalities as follows: 2 had ASC-US, 3 had ASC-H, 2 had LSIL, and 1 had HSIL cytology. Eleven women had concomitant abnormal appearance of the cervix and received a cervical biopsy at the time of LBC sample collection.

The final pathologic results according to AGC subclassification are given in Table 1. The overall significant pathology was 43.3% (123 women): 22.5% (64 women) had uterine lesions, 16.6% (47 women) had cervical lesions, and 4.2% (12 women) had ovarian or non-gynecologic malignancies. Invasive cancer was diagnosed in 98 women (34.5%). The 26 cases of cervical cancer consisted of 18 adenocarcinoma, 7 squamous cell carcinoma, and 1 adenosquamous cell carcinoma. Sixty patients were diagnosed with endometrial carcinoma or uterine sarcoma, including 3 patients who had coexisting primary endometrial and ovarian carcinoma. The most common endometrial carcinoma was endometrioid type (41 cases). Ovarian

Table 1
Final pathologic outcome according to AGC subclassification.

Final pathology	AGC-NOS (n = 186)			AGC-FN (n = 98)			Total [a]
	EC (n = 71)	EM (n = 68)	Gland (n = 47)	EC (n = 32)	EM (n = 42)	Gland (n = 24)	
Normal histology	27	28	26	9	10	4	104 (36.6)
Cervical lesions							
Non-significant lesions [b]	17	8	8	3	1	3	40 (14.1)
High-grade lesions [c]	9	2	2	7	0	1	21 (7.3)
Cervical cancer	11	3	1	10	0	1	26 (9.1)
Uterine lesions							
Non-significant lesions [b]	3	8	2	0	3	1	17 (5.9)
EH	0	2	0	0	1	1	4 (1.4)
Endometrial cancer	4	13	3	2	25	8	55 (19.3)
Uterine sarcoma	0	1	1	1	0	2	5 (1.7)
Other organs							
Ovarian cancer	0	2	2	0	1	0	5 (1.7)
Non-Gyn cancer	0	1	2	0	1	3	7 (2.4)

Abbreviations: AGC-FN, atypical glandular cells, favor neoplasia; AGC-NOS, atypical glandular cells, not otherwise specified; EC, endocervical; EH, endometrial hyperplasia; EM, endometrial; Gland, glandular; Gyn, gynecologic.

[a] Values are given as number (percentage).

[b] Non-significant lesions included polyp, myoma, inflammation, and cervical intraepithelial neoplasia 1.

[c] High-grade lesions included cervical intraepithelial neoplasia 2–3 and adenocarcinoma in situ.

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