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ORIGINAL ARTICLE

Clinical Significance of Atypical Glandular Cells in the Bethesda System 2001: A Comparison with the Histopathological Diagnosis of Surgically Resected Specimens

Tadahiro Shoji,[1] Eriko Takatori,[1] Satoshi Takeuchi,[1] Akira Yoshizaki,[1] Noriyuki Uesugi,[2] Tamotsu Sugai,[2] and Toru Sugiyama[1]

[1]Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Iwate, Japan [2]Department of Diagnostic Pathology, Iwate Medical University School of Medicine, Iwate, Japan

Forty-one patients diagnosed with atypical glangular cells (AGC) underwent surgery, and the histopathological diagnosis results for the resected specimens and the clinical features were analyzed. Out of 41 patients, final pathological diagnosis was endometrial cancer in 13 patients, cervical adenocarcinoma in 8, AIS in 7, CIN3 in 6, others in 2, and no lesions in 5. In comparison with previous reports, malignant or premalignant lesions were detected more frequently in patients with AGC who underwent surgery. We believe that conization or hysterectomy aimed at diagnosis and treatment, as well as endometrial histodiagnosis, should be carried out aggressively in patients with AGC.

Keywords: Cervical cytology, Atypical glandular cells, Cervical intraepithelial neoplasia, Diagnostic accuracy, The Bethesda System 2001

INTRODUCTION

Atypical glandular cells (AGC) represent a diagnostic category with features suggestive of adenocarcinoma but which are not sufficient for a definitive diagnosis in the Bethesda System (TBS) 2001. In the TBS 2001, the AGC category is divided into two groups, i.e., AGC not otherwise specified (AGC-NOS) and favoring neoplasia (AGC-FN). The AGC-NOS category is further divided into atypical endocervical cells (AGC-EC, NOS), atypical endometrial cells (AGC-EM, NOS), and simple atypical glandular cells (AGC, NOS). On the other hand, the AGC-FN category is further divided into atypical endocervical cells (AGC-EC, FN) and simple atypical glandular cells (AGC, FN). Glandular dysplasia as specified in the WHO classification (2003) has not been adopted in the TBS 2001 (1). The AGC-NOS category is a diagnostic item pertaining to glandular cells that show atypism beyond reactive or reparative changes, including endocervical adenocarcinoma *in situ* (AIS) and glandular cells that do not meet the criteria for adenocarcinoma (2). The AGC-FN category consists of glandular cells that are abnormal in terms of cellular morphology but do not meet the criteria for AIS or adenocarcinoma in terms of quality and quantity.

Premalignant lesions that require treatment are more frequently detected in cases with AGC than in those with atypical squamous cells (ASC), and thus a diagnosis of AGC is positioned as an index of risk for adenocarcinoma. In this regard, we examined the histopathological diagnosis of only surgically resected specimens in patients who had been diagnosed with AGC by cervical cytology in order to determine the clinical significance of the AGC designation.

SUBJECTS AND METHODS

The subjects of this study were 41 patients who underwent surgery among 66 women diagnosed with AGC based on cervical cytology at the Department of Obstetrics and Gynecology of Iwate Medical University Hospital between July 2010 and April 2012. For these 41 patients, the histopathological diagnosis of the surgical specimen was compared with the cytological diagnosis. The detection rates of malignant or premalignant lesions were examined based on division of the AGC cases into AGC-NOS and AGC-FN and age groups. In addition, the lesions were examined in relation to patient age, focusing on whether they were in the uterine cervix or corpus, and whether they were squamous epithelial or glandular. The malignant lesions were included invasive lesions, AIS and carcinoma *in situ* (CIS), while the premalignant lesions were included another noninvasive lesions, respectively. Cervical samples were obtained employing Cervex-Brush, and specimens were prepared by conventional methods. The results of preoperative cervical biopsy were not considered in this study. The Mann–Whitney test and the Chi-square test were used for statistical analyses, and differences were regarded as statistically significant at $p < 0.05$.

Correspondence to: Tadahiro Shoji, Department of Obstetrics and Gynecology, Iwate Medical University, Uchimaru 19-1, Morioka, Iwate 020-8505, Japan, e-mail: tshoji@iwate-med.ac.jp

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Table 1. Final Histopathological Diagnosis of AGC Patients Stratified by Subtype of Smear and Age

						CIN 3				
	CA	AIS	LEGH	EC	OC	CIS	SD	NEM	Premalignant/Malignant	Malignant
ACG NOS ($N = 35$)	6	6	1	11	1	4	1	5	85.7%	80.0%
ACG FN ($N = 6$)	2	1	0	2	0	1	0	0	100%	100%
Total	8	7	1	13	1	5	1	5	87.8%	82.9%

Abbreviations: CA, cervical adenocarcinoma; LEGH, lobular endocervical glandular hyperplasia; EC, endometrial cancer; OC, ovarian cancer; CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma *in situ*; CIS, carcinoma *in situ*; SD, severe dysplasia; NEM, no evidence of malignancy.

RESULTS

Detection rate of AGC

Cytological diagnosis of the uterine cervix was carried out in 8,316 patients between July 2010 and April 2012. Among these patients, 66 were diagnosed with AGC, for a detection rate of 0.79%. AGC-NOS was diagnosed in 59 (0.71%) patients, and AGC-FN in 7 (0.08%). None of the patients experienced the detection of AGC more than once. At our institution during the study period, the detection rate of AIS and adenocarcinoma were 0.05%, 0.24%, respectively.

Backgrounds and courses of AGC cases

The 59 patients diagnosed with AGC-NOS had a median age of 47 (range, 28–87) years. Of these 59 patients, the 35 (59.3%) who underwent surgery had a median age of 45 (range, 31–87) years. Twenty-one (35.6%) patients were followed without surgery. Three (5.1%) received chemotherapy or radiation therapy because they were inappropriate candidates for surgery.

The median age of seven patients diagnosed with AGC-FN was 47 (range, 26–75) years. Of these seven patients, six (85.7%) who underwent surgery had a median age of 47 (range, 26–75) years. One (14.3%) patient was followed without surgery.

Among the 41 patients who underwent surgery, conization was performed in 14 (34.1%), and total hysterectomy (including radical hysterectomy) in 27 (65.9%). The 35 patients with a diagnosis of AGC-NOS comprised 13 (37.1%) treated by conization and 22 (62.9%) treated by total hysterectomy (including radical hysterectomy). Of the six patients with a diagnosis of AGC-FN, conization was carried out in one (16.7%), total hysterectomy (including radical hysterectomy) in five (83.3%).

Comparison with the histopathological diagnosis of the surgical specimen

Among the 35 patients diagnosed with AGC-NOS who underwent surgery, 6 (17.1%) had cervical adenocarcinoma, 11 (31.4%) endometrial cancer, 1 (2.9%) ovarian cancer, 6 (17.1%) AIS, 5 (14.3%) CIN3, [4 (11.4%) carcinoma *in situ* (CIS), 1 (2.9%) severe dysplasia], 1 (2.9%) lobular endocervical glandular hyperplasia, and 5 (14.3%) no lesions. The six patients with AGC-FN comprised two (33.3%) with cervical adenocarcinoma, two (33.3%) with endometrial cancer, one (16.7%) with AIS, one (16.7%) with CIN3 (CIS). The detection rates of malignant or premalignant lesions in patients with AGC-NOS and AGC-FN were 85.7% and 100%, respectively. The detection rate of malignant lesions was 80.0% for patients with AGC-NOS and 100% for those with AGC-FN.

Of the 41 patients diagnosed with AGC, 36 had malignant or premalignant lesions as identified by pathological examination of the resected specimen, yielding a detection rate of 87.8%. Malignant lesions were identified in 34 patients, for a detection rate of 82.9% (Table 1).

FIGO stage in patients whose lesions were histopathologically diagnosed as malignant

Among the 41 patients diagnosed with AGC who underwent surgery, 22 (53.7%) had malignant lesions, including 8 with uterine cervical cancer, 13 with endometrial cancer, and 1 with ovarian cancer. Among patients with uterine cervical cancer, the FIGO stage was IA1 in one, IB1 in six, and IIB in one. In the 13 patients with endometrial cancer, the FIGO stage was IA in 10, IB in 2, and IIIC1 in 1. The patient with ovarian cancer had stage IA disease. Therefore, 21 (95.5%) of the 22 patients had I or II stage of cancer (Table 2).

Comparison of patient age by lesion type

The median age of the 35 patients with AGC-NOS who underwent surgery was 45 (range, 31–87) years. The median age of the six patients with AGC-FN was 47 (range, 26–75) years. There was no significant difference in age between these two groups of patients (N.S.).

Uterine cervical lesions were found in 22 (53.7%) of 41 patients, and the median age of these 22 patients was 40.5 (range, 26–74) years. Endometrial lesions were found in 13 (31.7%) patients, with a median age of 56 (range, 41–87) years. Thus, patients with endometrial lesions were significantly older than those with cervical lesions ($p = 0.008$). All endometrial lesions, found in 13 patients, were endometrial cancer. Only one patient with ovarian cancer was excluded from the analysis.

Squamous epithelial lesions were detected in 6 (14.6%) of the 41 patients, and the median age of these 6 patients was

Table 2. FIGO Stage of Invasive Cancer Diagnosed as AGC

	Stage	No of Patients
Cervical cancer	IA1	1
	IB1	6
	IIB	1
Endometrial cancer	IA	10
	IB	2
	IIIC1	1
Ovarian cancer	IA	1

Table 3. Statistical Analyses Between Age and AGC Subtype, Lesion Type

	Median age (range)	*p* Value
AGC-NOS ($N = 35$)	45 (31–87)	
AGC-FN ($N = 6$)	47 (26–75)	N.S.
Cervical lesions ($N = 22$)	40.5 (26–74)	
Endometrial cancer ($N = 13$)	56 (41–87)	$p = 0.008$
Squamous lesions ($N = 6$)	37 (35–52)	
Glandular lesions ($N = 30$)	48.5 (26–87)	$p = 0.04$

Abbreviation: N.S., not significant.

37.5 (range, 33–52) years. Glandular lesions in the cervix, endometrium, and ovary were detected in 30 (73.2%) of the 41 patients, and in the endometrium and ovary in 14 (34.1%) of the 41 patients, with a median age of 48.5 (range, 26–87) years. Patients with glandular lesions were significantly older than those with squamous epithelial lesions ($p = 0.04$) (Table 3).

DISCUSSION

The frequencies of AGC according to the TBS 2001 reportedly range from 0.2% to 0.85% (3–5). The discrepancies among reports are derived from differences in the method of collecting samples, methods of preparing specimens (the conventional versus the liquid-based cytology (LBC) method), the scale of screening, and the subject population screened. In general, the AGC detection rate is higher for specimens prepared by the LBC method than for those prepared by the conventional method (5). Despite our institution using the conventional method for preparing specimens, the AGC detection rate was 0.79%. The detection rate was high in our institution probably because many patients with AGC were referred to our institution, a tertiary care center for cancer patients. In fact, 62 (93.9%) of 66 patients diagnosed with AGC had been referred from other institutions.

Goff *et al*. reported that a diagnosis of AGC was obtained in 100 (0.46%) of 21,930 patients, and that malignant or premalignant lesions including invasive adenocarcinoma (2 cases), AIS (5 cases), CIS (6 cases), severe dysplasia (6 cases), and moderate dysplasia (5 cases) were detected in 24 (38%) of 63 patients who were followed (6). Tam *et al*. reported that malignant or premalignant lesions were detected in 19% of patients with AGC-NOS, while malignant or premalignant lesions such as cervical intraepithelial neoplasia, endometrial cancer, uterine cervical adenocarcinoma, and ovarian cancer were detected in 68% of patients with AGC-FN (7). According to Krane *et al*., the detection rate of malignant or premalignant lesions was 34.3% in 108 specimens from 106 patients with AGC, and malignant or premalignant lesions were detected in 7 (27%) of 26 patients with AGC-EC, NOS, including high-grade squamous intraepithelial lesions (HSIL) (3 cases), AIS and invasive adenocarcinoma (2 cases), and uterine cervical cancer/fallopian tube cancer (2 cases). AIS (12 cases), concurrent HSIL and AIS (2 cases) and invasive adenocarcinoma (1 case) were detected in 15 (94%) of 16 patients with AGC-EC, FN (8). Sawangsang *et al*. carried out colposcopy and biopsy in 63 patients diagnosed with AGC, and reported that malignant or premalignant lesions were found in 7 (15.2%) of 46 with AGC-NOS and 7 (41.2%) of 17 with AGC-FN (9). Jadoon *et al*. reported that out of 85 women in the study group, 29 (34%) were maintained under cytological surveillance and 56 (66%) were referred for colposcopic examination. By histological diagnosis, they detected CIN1-3, squamous cell carcinoma, and AIS or more malignant lesions in 21 (38%) of 56 patients judged to be in the borderline glandular change category according to the British Society of Clinical Cytology classification (10). On the other hand, Lai *et al*. reported that malignant lesions were detected in all 7 patients with AGC-FN (11). Thus, the detection rates of malignant or premalignant lesions ranged from 15% to 43% for AGC-NOS, whereas the corresponding range was 41%–100% for AGC-FN. For patients with AGC as a whole, the detection rates of malignant or premalignant lesions ranged from 22% to 53% (12). Table 4 presents a comparison between these previous reports and our present study, in which the detection rate of malignant or premalignant lesions was 87.8%. Previous reports included many patients in whom the results of cervical or endometrial biopsy were compared. Thus, a comparison with histopathological diagnosis using the surgical specimen was not made in all patients. We speculate that uterine cervical biopsy has limitations in the detection of malignant or premalignant lesions if it is the only diagnostic method employed. In our study, the detection rate was high, at 87.8%, because comparisons were made with the histopathological diagnosis after conization or total hysterectomy. Although the TBS 2001 divides squamous epithelial abnormalities into many types, it divides glandular abnormalities into only three types, i.e., AGC, AIS, and adenocarcinoma. This may also account for the high-detection rate of malignant or premalignant lesions in AGC patients.

Table 4. Published Detection Rate of Malignant or Premalignant Lesions With AGC Subtype

Author	Year	AGC-NOS	ACG-FN	AGC total
Tam	2003	19% (20/104)	68% (23/34)	31.6% (43/138)
Krane	2004	27% (7/26)	94% (15/16)	34.3% (37/108)[#]
Lai	2008	43% (31/72)	100% (7/7)	48% (38/79)
Westin	2008	28% (21/91)	54% (8/15)	27% (27/106)
Jadoon[*]	2009			38% (21/56)
Sawangsang	2011	15.2% (7/46)	41.2% (7/17)	22.2% (14/63)
Our study		85.7% (30/35)	100% (6/6)	87.8% (36/41)

[#] Includes 35 cases of favor reactive and 21 cases of endometrial type and 10 cases of site not specified.
[*] British Society of Clinical Cytology classification.

A final histopathological diagnosis of malignant lesions was obtained in 22 patients, comprising 8 with uterine cervical cancer, 13 with endometrial cancer, and 1 with ovarian cancer. Among these cases, 21 (95.5%), excluding one with endometrial cancer at stage IIIc, had I or II stage of cancer.

The rates of detection of CIN2 or CIN3 in cases with atypical squamous cells of undetermined significance (ASC-US) and ASC – cannot exclude high squamous intraepithelial lesion (ASC-H) are reported about 21% and 27%, respectively (13,14). In contrast, in cases of ACG-NOS and AGC-FN, the frequency of detecting high-grade lesions that require treatment is higher than in ASC cases (6–11). According to the management guidelines from the American Society for Colposcopy and Cervical Pathology (15,16), colposcopy and biopsy are recommended for both AGC-NOS and AGC-FN, and implementation of human papillomavirus testing alone or repeated cytological diagnosis can thereby be avoided. In patients aged 35 years or older or in those younger than 35 years at risk for endometrial lesions, it is desirable to consider endometrial cytology. In our study, 13 patients were diagnosed as having endometrial cancer, and all were 40 years of age or older. Therefore, it seems that cytology or biopsy of the endometrium is necessary when a diagnosis of AGC is made in any patient aged 40 years or older. When patients with cervical lesions and those with endometrial lesions were compared in terms of age, the median age of patients with endometrial lesions was 56 years, which was higher than the median age, 40.5 years, of those with cervical lesions. All 13 patients with endometrial lesions had endometrial cancer, with the youngest being 41 years of age. While a review of the literature shows that 75%–88% of uterine body lesions in AGC are endometrial cancer (9,17), all lesions detected in our study were endometrial cancer. Moreover, Haidopoulos *et al*. reported that endometrial cancer was detected in AGC lesions in eight patients, all of whom were at least 45 years of age (18).

This finding also provides a rationale for close examination of the endometrium in patients 40 years of age or older who are diagnosed with AGC.

In AGC cases, squamous epithelial lesions are often detected, with the detection rate of such lesions reportedly reaching 57% in TBS 2001 (19). Kumar *et al*. reported that glandular lesions and squamous epithelial lesions of the uterine cervix are coexistent at a frequency of 62% (20). In our study, squamous epithelial lesions were detected in 6 (14.6%) of 41 patients. This is probably because the cytological features of HSIL accompanied by glandular involvement resemble that of AGC and because glandular lesions themselves often coexist with squamous epithelial lesions. The median age of patients with squamous epithelial lesions was 37.5 years, which was significantly lower than the median age, 48.5 years, of patients with glandular lesions. We believe that it is necessary to always keep in mind the potential presence of squamous epithelial lesions when a patient diagnosed with AGC is younger than 40 years of age.

The detection rate of malignant lesions was 82.9% among patients with AGC who underwent surgery and were examined in this study. Including premalignant lesions, the detection rate was 87.8%. These figures are higher than the corresponding rates reported in previous studies. In particular, the detection rate of malignant lesions was 80% for patients diagnosed with AGC-NOS, showing a higher frequency of malignant lesions than in other reports. Based on these findings, it is assumed that patients with AGC should undergo conization of the uterine cervix or total hysterectomy for diagnostic or therapeutic purposes. It is also necessary to closely examine the endometrium prior to surgery in patients 40 years of age or older because endometrial cancer is frequently detected in this age group. This finding indicates that a diagnosis of AGC can facilitate detection of early cervical or endometrial cancer lesions and thereby contributes to prognostic improvement by allowing surgical treatment at an early stage.

The future clinical courses of the 22 patients who are currently being followed without surgery are of particular interest. We intend to report the outcomes of these patients in a subsequent publication.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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