Clinicopathological Characteristics of Atypical Glandular Cells Determined by Cervical Cytology in Japan: Survey of Gynecologic Oncology Data from the Obstetrical Gynecological Society of Kinki District, Japan

Shinji Toyoda^a Ryuji Kawaguchi^b Hiroshi Kobayashi^b

^aDepartment of Obstetrics and Gynecology, Nara Prefecture General Medical Center, Nara, Japan;

^bDepartment of Obstetrics and Gynecology, Nara Medical University, Kashihara, Japan

Keywords

Atypical glandular cells · Bethesda system · Cervical cytology · Uterus

Abstract

Background: The purpose of this study was to clarify the clinicopathological characteristics of, and the clinical approach used to identify, atypical glandular cells (AGCs) in Japan based on cervical cytology screening. **Objectives:** This study included 1,254 patients with AGCs who underwent cervical cytology. **Method:** Data from patients with AGCs were used to examine the practical management of AGCs and the histological results. **Results:** The incidence of AGCs was 0.20% (1,254/614,791). The 1,254 AGC cases included 859 endocervical cells not otherwise specified (NOS), 3 glandular cells NOS, 91 endocervical cells favor neoplasia (FN), and 301 atypical endometrial cells (AEMCs). Among the 1,254 AGC patients, the histological diagnosis was benign in 666 (53.1%), cervical intraepithelial neoplasia (CIN) 1 in 60 (4.8%), CIN2 in 31 (2.5%), CIN3 in 52 (4.1%), squamous cell carcinoma in 19 (1.5%), adenocarcinoma in situ in 39 (3.1%), cervical adenocarcinoma in 106 (8.5%), endometrial carcinoma in 209 (16.7%), ovarian cancer in 26 (2.1%), other malig-

nancy in 4 (0.3%), and other under follow-up in 42 (3.3%). When the 1,254 AGC patients were divided into three medical intervention degrees according to histology, AGC-NOS, AGC-FN, and AEMC required no medical intervention in 78.7, 13.2, and 25.9% (678, 12, and 78) of the patients, cervical cone resection in 13.0, 9.9, and 0.3% (112, 9, and 1) of the patients, and radical laparotomy for invasive cancer in 8.3, 76.9, and 73.8% (72, 70, and 222) of the patients, respectively. **Conclusions:** Our histological results supported the medical interventions applied for AGC diagnosis and treatment. AGC cases require careful histological evaluation.

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Introduction

Cervical cytology screening has considerably reduced the incidence of cervical cancer in many countries [1–3]. The risk of cervical cancer associated with abnormalities in cervical squamous cells is widely accepted [4–6], although uncertainty remains about the risk associated with abnormalities in cervical glandular cells [3]. Correspondingly, the incidence of cervical adenocarcinoma

Fig. 1. Age distribution. The age distribution was as follows: 64 patients (5.1%) were in their 20s, 250 patients (19.9%) were in their 30s, 428 patients (34.1%) were in their 40s, 261 patients (20.8%) were in their 50s, 151 patients (12%) were in their 60s, and 100 patients (8%) were in their 70s.

has not decreased to the same extent as the incidence of cervical squamous cell cancer in many countries [3, 7, 8].

The terminology of the field, from “atypical glandular cell of undetermined significance (AGUS)” to “atypical glandular cells” and including subcategory specifications, was defined and modified by the Bethesda system [9–11]. Atypical glandular cells (AGCs) are cytological abnormalities that are diagnosed when glandular cells exhibit changes but lack the features of adenocarcinoma in situ (AIS) or invasive adenocarcinoma of the uterine cervix. Therefore, AGCs present various histological types. Although the Bethesda system has been used globally for more than 20 years, Japanese physicians only started to utilize the system in 2008, and no evaluation of AGCs in Japan has been conducted.

The purpose of this study was to clarify the clinicopathological features of, and clinical approaches used to identify, AGCs based on cervical cytology screening in Japan.

Subjects and Methods

This study included 1,254 patients with AGCs who underwent cervical cytology screening between June 2008 and March 2017. Sixteen gynecological institutions provided their cervical cytology information. These 16 organizations were accredited by the Japanese Society of Gynecologic Oncology and the Japanese Society of Clinical Cytology. Additionally, these 16 institutions belonged to the Oncology Research Department Committee of the Obstetrical and Gynecological Society of Kinki District, Japan. The cytoprepa-

ration methods used in these 16 organizations included conventional smears at 10 institutions, liquid-based cytology at 4 institutions, and both methods at 2 institutions. All clinicians followed the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines for the management of cervical cytology results [12]. Our article reports a cohort study. We obtained Ethics Review Board permission from our institution.

The present study evaluated the incidence, age distribution, subclassification, histological evaluation methods used during diagnosis, diagnostic techniques, histological results, presence of invasive cancer, degree of medical intervention, period to a definitive diagnosis, and human papillomavirus (HPV) status. As determined by the histological analysis, benign lesions included reactive changes, polyps, and standard histology.

Results

Cervical cytology data were obtained for 614,791 cases, including a total of 1,254 AGC cases. Thus, the AGC incidence rate was 0.20%. The age distribution was as follows: 64 patients (5.1%) were in their 20s, 250 patients (19.9%) were in their 30s, 428 patients (34.1%) were in their 40s, 261 patients (20.8%) were in their 50s, 151 patients (12%) were in their 60s, and 100 patients (8%) were in their 70s (Fig. 1).

The origins of the 1,254 AGC cases included endocervical cells in 950 cases (75.8%), glandular cells in 3 cases (0.2%), and endometrial cells in 301 cases (24.0%) (Fig. 2a). The subclassifications of the 1,254 AGC cases included AGCs not otherwise specified (AGC-NOS) in 862 cases (68.7%), AGCs favor neoplasia (AGC-FN) in 91 cases (7.3%), and atypical endometrial cells (AEMCs) in 301 cases (24.0%) (Fig. 2b).

The primary histological evaluation methods used during diagnosis were a colposcopic cervical biopsy in 882 cases (70.3%), cervical canal curettage in 370 cases (29.5%), endometrial biopsy in 511 cases (40.7%), and direct endometrial cytology in 578 cases (46.1%) (Fig. 3).

The diagnostic techniques used for the histological diagnosis of AGCs were a colposcopic cervical biopsy in 354 cases (28.3%), cervical canal curettage in 155 cases (12.3%), endometrial biopsy in 154 cases (12.3%), cervical cone resection in 117 cases (9.3%), radical laparotomy in 268 cases (21.4%), repeat cervical cytology in 154 cases (12.3%), and endometrial direct cytology alone in 10 cases (0.8%); in addition, there was difficulty concerning the diagnosis in 42 cases (3.3%) (Table 1).

The definitive diagnoses for the 1,254 AGC patients included endocervical cells NOS in 859 cases, endocervical cells FN in 91 cases, glandular cells NOS in 3 cases, and AEMCs in 301 cases. Among the 1,254 AGC patients, the

Fig. 2. Origin and subclassifications of AGCs. **a** The origins of the 1,254 AGC cases included endocervical cells in 950 cases (75.8%), glandular cells in 3 cases (0.2%), and endometrial cells in 301 cases (24.0%). **b** The subclassifications of the 1,254 AGC cases included AGC-NOS in 862 cases (68.7%), AGC-FN in 91 cases (7.3%), and AEMCs in 301 cases (24.0%). AGCs, atypical glandular cells; AEMCs, atypical endometrial cells; FN, favor neoplasia; NOS, not otherwise specified.

Table 1. Diagnostic techniques used for the histological diagnosis

Diagnostic technique	Patients, <i>n</i> (%)
Cervical colposcopic biopsy	354 (28.3)
Cervical canal curettage	155 (12.3)
Endometrial biopsy	154 (12.3)
Conization	117 (9.3)
Radical laparotomy	268 (21.4)
Cervical cytology	154 (12.3)
Endometrial cytology	10 (0.8)
Diagnostic difficulty	42 (3.3)
Total	1,254 (100)

Fig. 3. Primary histological evaluation methods used during diagnosis. The histological evaluation methods were colposcopic cervical biopsy in 882 cases (70.3%), cervical canal curettage in 370 cases (29.5%), endometrial biopsy in 511 cases (40.7%), and endometrial cytology in 578 cases (46.1%).

histological diagnosis was benign in 666 (53.1%), cervical intraepithelial neoplasia (CIN) 1 in 60 (4.8%), CIN2 in 31 (2.5%), CIN3 in 52 (4.1%), squamous cell carcinoma (SCC) in 19 (1.5%), AIS in 39 (3.1%), cervical adenocarcinoma in 106 (8.5%), endometrial carcinoma in 209 (16.7%), ovarian cancer in 26 (2.1%), other malignancy in 4 (0.3%), and other under follow-up in 42 (3.3%) (Table 2).

The definitive diagnoses for the 862 AGC-NOS patients were benign lesions in 580 patients (67.3%), CIN1 in 58 patients (6.7%), CIN2 in 31 patients (3.6%), CIN3 in 48 patients (5.6%), SCC in 8 patients (0.9%), AIS in 33 patients (3.8%), cervical adenocarcinoma in 47 patients (5.5%), endometrial carcinoma in 7 patients (0.8%), ovarian cancer in 9 patients (1.1%), other malignancy in 1 patient (0.1%), and other under follow-up in 40 patients (4.6%) (Table 3).

The definitive diagnoses for the 91 AGC-FN patients were benign lesions in 11 patients (12.1%), CIN1 in 1 patient (1.1%), CIN3 in 4 patients (4.4%), SCC in 11 patients (12.1%), AIS in 5 patients (5.5%), cervical adenocarcinoma in 49 patients (53.8%), and endometrial carcinoma in 10 patients (11.0%) (Table 4).

The definitive diagnoses for the 301 AEMC patients were benign lesions in 75 patients (24.9%), CIN1 in 1 patient (0.3%), AIS in 1 patient (0.3%), cervical adenocarcinoma in 10 patients (3.3%), endometrial carcinoma in 192 patients (63.8%), ovarian cancer in 17 patients (5.7%), including 1 case of tubal carcinoma, other malignancy in 3 patients (1.0%), and other under follow-up in 2 patients (0.7%) (Table 5).

The 666 patients with benign lesions had cervical polyps in 25 cases, endometrial polyps in 9 cases, and benign endometrial hyperplasia in 24 cases.

The AGC-NOS, AGC-FN, and AEMC classifications included 72, 70, and 222 of the 364 invasive carcinomas out of the AGC cases, respectively. The 72 total cases of invasive carcinoma of the AGC-NOS category included 47 cases of cervical adenocarcinoma (12.9%), 8 cases of SCC (2.2%), 7 cases of endometrial carcinoma (1.9%), 9

Table 2. Definitive diagnoses for the 1,254 patients with AGCs

Histology	Patients with AGCs (<i>n</i> = 1,254), <i>n</i>				Total, <i>n</i> (%)
	endocervical cells		glandular cells NOS	endometrial cells	
	NOS	FN			
Benign lesions	578	11	2	75	666 (53.1)
CIN1	58	1	0	1	60 (4.8)
CIN2	31	0	0	0	31 (2.5)
CIN3	48	4	0	0	52 (4.1)
SCC	8	11	0	0	19 (1.5)
AIS	33	5	0	1	39 (3.1)
Cervical adenocarcinoma	47	49	0	10	106 (8.5)
Endometrial carcinoma	7	10	0	192	209 (16.7)
Ovarian cancer	8	0	1	17	26 (2.1)
Other malignancy	1	0	0	3	4 (0.3)
Diagnostic difficulty	40	0	0	2	42 (3.3)
Total	859 (68.5)	91 (7.3)	3 (0.2)	301 (24.0)	1,254 (100)

CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma; AIS, adenocarcinoma in situ; AGCs, atypical glandular cells; NOS, not otherwise specified; FN, favor neoplasia.

Table 3. Definitive diagnoses for the 862 patients with AGC-NOS

Histology	Patients with AGC-NOS (<i>n</i> = 862), <i>n</i>		Total, <i>n</i> (%)
	endocervical cells	glandular cells	
Benign lesions	578	2	580 (67.3)
CIN1	58	0	58 (6.7)
CIN2	31	0	31 (3.6)
CIN3	48	0	48 (5.6)
SCC	8	0	8 (0.9)
AIS	33	0	33 (3.8)
Cervical adenocarcinoma	47	0	47 (5.5)
Endometrial carcinoma	7	0	7 (0.8)
Ovarian cancer	8	1	9 (1.1)
Other malignancy	1	0	1 (0.1)
Diagnostic difficulty	40	0	40 (4.6)
Total	859	3	862 (100)

CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma; AIS, adenocarcinoma in situ; AGCs, atypical glandular cells; NOS, not otherwise specified.

cases of ovarian cancer (2.5%), and 1 case of other malignancy (0.4%). The 70 cases of invasive carcinoma of the AGC-FN category included 49 cases of cervical adenocarcinoma (13.5%), 11 cases of SCC (3.0%), and 10 cases of endometrial carcinoma (2.7%). The 222 invasive carcino-

mas of the AEMC category included 10 cases of cervical adenocarcinoma (2.8%), 192 cases of endometrial carcinoma (52.7%), 17 cases of ovarian cancer (4.7%), and 3 cases of other malignancy (0.8%) (Table 6). The subtypes in the 106 cases of cervical adenocarcinoma included endocervical adenocarcinoma usual type in 96 cases, lobular endocervical glandular hyperplasia in 4 cases, serous carcinoma in 3 cases, clear cell carcinoma in 2 cases, and endometrioid type in 1 case. The other malignancy category contained 4 cases of other malignancy (1.1%) including 2 cases of breast cancer and 2 cases of malignant lymphoma.

According to the degree of medical intervention, the final diagnosis was divided into one of three categories: (1) no surgical intervention, (2) cervical cone resection, or (3) radical laparotomy. The “no surgical intervention” category included cases of benign lesions, those under follow-up, and CIN1. The cone resection category included cases of CIN2, CIN3, and AIS. Radical laparotomy was required for invasive carcinoma.

When we determined the required medical interventions based on histology, the 862 AGC-NOS cases resulted in nonintervention in 78.7% of the patients (678 cases), cervical cone resection in 13.0% of the patients (112 cases), and radical laparotomy for invasive cancer in 8.3% of the patients (72 cases). The 91 AGC-FN cases resulted in nonintervention in 13.2% of the patients (12 cases), cervical cone resection in 9.9% of the patients (9 cases), and

Table 4. Definitive diagnoses for the 91 patients with AGC-FN

Histology	Patients with AGC-FN (<i>n</i> = 91), <i>n</i>		Total, <i>n</i> (%)
	endocervical cells	glandular cells	
Benign lesions	11	0	11 (12.1)
CIN1	1	0	1 (1.1)
CIN2	0	0	0
CIN3	4	0	4 (4.4)
SCC	11	0	11 (12.1)
AIS	5	0	5 (5.5)
Cervical adenocarcinoma	49	0	49 (53.8)
Endometrial carcinoma	10	0	10 (11.0)
Ovarian cancer	0	0	0
Other malignancy	0	0	0
Diagnostic difficulty	0	0	0
Total	91	0	91 (100)

CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma; AIS, adenocarcinoma in situ; AGCs, atypical glandular cells; FN, favor neoplasia.

Table 5. Definitive diagnoses for the 301 patients with AEMCs

Histology	Patients with AEMCs, <i>n</i> (%)
Benign lesions	75 (24.9)
CIN1	1 (0.3)
CIN2	0
CIN3	0
SCC	0
AIS	1 (0.3)
Cervical adenocarcinoma	10 (3.3)
Endometrial carcinoma	192 (63.8)
Ovarian cancer	17 (5.7)
Other malignancy	3 (1.0)
Diagnostic difficulty	2 (0.7)
Total	301 (100)

AEMCs, atypical endometrial cells; CIN, cervical intraepithelial neoplasia; SCC, squamous cell carcinoma; AIS, adenocarcinoma in situ.

Table 6. Definitive diagnoses for the 364 patients with invasive carcinoma in the AGC group

Histology	Patients with invasive carcinoma (<i>n</i> = 364), <i>n</i> (%)			Total, <i>n</i> (%)
	AGC-NOS (<i>n</i> = 72)	AGC-FN (<i>n</i> = 70)	AEMCs (<i>n</i> = 222)	
Cervical adenocarcinoma	47 (12.9)	49 (13.5)	10 (2.8)	106 (29.1)
SCC	8 (2.2)	11 (3.0)	0	19 (5.2)
Endometrial carcinoma	7 (1.9)	10 (2.7)	192 (52.7)	209 (57.4)
Ovarian cancer	9 (2.5)	0	17 (4.7)	26 (7.2)
Metastasis	1 (0.3)	0	3 (0.8)	4 (1.1)
Total	72 (19.8)	70 (19.2)	222 (61.0)	364 (100)

AGCs, atypical glandular cells; NOS, not otherwise specified; FN, favor neoplasia; AEMCs, atypical endometrial cells; SCC, squamous cell carcinoma.

radical laparotomy for invasive cancer in 76.9% of the patients (70 cases) (Fig. 4). The 301 AEMC cases resulted in nonintervention in 25.9% of the patients (78 cases), cervical cone resection in 0.3% of the patients (1 case), and radical laparotomy for invasive cancer in 73.8% of the patients (222 cases) (Fig. 5).

The period to definitive diagnosis from initial consultation was under 1 month for 363 cases, 1–3 months for 227 cases, 4–6 months for 69 cases, 7–12 months for 38 cases, and over 12 months for 515 cases. In all, 1,212 cas-

es were evaluated; the remaining 42 cases were shown as under follow-up with diagnostic difficulty (Fig. 6).

An HPV test was performed in 73 cases, yielding 38 positive claims and 35 instances of contrary evidence (Fig. 7). The negative results of HPV testing were benign lesions in 20 cases, CIN1 in 5 cases, a cervical polyp in 2 cases, cervical adenocarcinoma usual type in 2 cases, cervical endometrioid carcinoma in 1 case, an endometrial polyp in 3 cases, and endometrial hyperplasia in 2 cases.

Fig. 4. Degree of medical intervention in AGC-NOS and AGC-FN. The “no surgical intervention” category included cases of benign lesions, those under follow-up, and CIN1. The cone resection category included cases of CIN2, CIN3, and AIS. Radical laparotomy was required for invasive carcinoma. When we determined the required medical interventions based on histology, the 862 AGC-NOS cases resulted in nonintervention in 78.7% of the patients (678 cases), cervical cone resection in 13.0% of the patients (112

cases), and radical laparotomy for invasive cancer in 8.3% of the patients (72 cases). The 91 AGC-FN cases resulted in nonintervention in 13.2% of the patients (12 cases), cervical cone resection in 9.9% of the patients (9 cases), and radical laparotomy for invasive cancer in 76.9% of the patients (70 cases). AGC, atypical glandular cell; FN, favor neoplasia; NOS, not otherwise specified; CIN, cervical intraepithelial neoplasia; AIS, adenocarcinoma in situ.

Fig. 5. Degree of medical intervention in AEMCs. The 301 AEMC cases resulted in nonintervention in 25.9% of the patients (78 cases), cervical cone resection in 0.3% of the patients (1 case), and radical laparotomy for invasive cancer in 73.8% of the patients (222 cases). The definitions of the categories of degrees of medical intervention are the same as in Figure 4. AEMCs, atypical endometrial cells.

Fig. 6. Time until definitive diagnosis. The time to definitive diagnosis from initial consultation was <1 month in 363 cases, 1–3 months in 227 cases, 4–6 months in 69 cases, 7–12 months in 38 cases, and >12 months in 515 cases. In all, 1,212 cases were evaluated; the remaining 42 cases were shown as under follow-up with diagnostic difficulty.

Discussion and Conclusion

AGCs are cytological abnormalities diagnosed when glandular cells exhibit changes but lack the features of AIS or invasive adenocarcinoma of the uterine cervix. Clinical studies investigating the histological results for women with a diagnosis of AGCs have encompassed a broad

range of reactive changes, from mild changes and cervical precursor lesions of glandular or squamous origins to invasive cervical cancer and other gynecological cancers [13]. A previous study also demonstrated poor reproducibility between observers when interpreting AGC Pap smears [14]. In the literature, AGCs have been reported to have a 2.8–9.7% malignancy rate [3, 15, 16].

Fig. 7. HPV status. An HPV test was performed in 73 cases, yielding 38 positive claims and 35 instances of contrary evidence. HVP, human papillomavirus.

The vagueness of the AGC definition, uncertainty in the diagnosis, low incidence, minimal malignancy, multiple histological evaluation methods required, and malignant onset after an initial benign lesion are problematic for physicians. Few physicians manage persistent AGCs as recommended [12, 17, 18]. Thus, further physician education appears to be warranted [17].

The incidence of AGCs, or AGUS, has been reported to be 0.08% [19], 0.2% [20], 0.29% [13], 0.48% [3], and 5.9% [21]. Our result of 0.20% is not significantly different from these reported rates. Our data showed that 428 patients were in their 40s, 261 were in their 50s, and 250 were in their 30s. This age distribution did not reveal any striking characteristics. However, in one recent report, Wang et al. [3] described a higher risk of cervical cancer among women with AGCs aged 30–39 years and that this increased risk was primarily derived from an increased risk of adenocarcinoma. Therefore, the 30s might be an essential age range for follow-up. When organized by subclassification, AGC-FN comprised 7.3% of the 1,254 total AGC cases, which was consistent with recent reports showing rates of 14.7–34.5% [22–25]. The reason for the low occurrence of AGC-FN was that the AEMC ratio was high in AGCs, but further details were unknown.

In a comprehensive evaluation of women with cytological AGCs, various techniques were applied, including pelvic examination, ultrasonography, colposcopy, endocervical curettage, cervical biopsy, and endometrial biopsy [3, 13, 26, 27]. Cervical biopsy and endometrial sampling are the principal early tests [12]. The detection rates of abnormal lesions reported by Kim et al. [19] were 3.1% with repeated Pap smears, 28.4% with colposcopy-directed biopsy, 63.6% with cone biopsy, and 29.7% with endo-

metrial curettage. The authors recommend that patients with AGUS by Pap smear undergo immediate intensive diagnostic assessment, including colposcopy-directed biopsy with endocervical curettage or cone biopsy, to detect cervical lesions and endometrial curettage to detect endometrial lesions. In our study, the canal curettage rate was meager compared with the rate in the data collected by Kim et al. [19]. This low canal curettage rate might be due to lack of recognition of the hidden and latent malignant tendency of AGCs by Japanese gynecological physicians. Moreover, 13.1% of the diagnostic techniques, including cervical and endometrial cytology alone, showed little diagnostic ability for AGCs. Importantly, various types of procedure, including endometrial cytology, are needed to evaluate the endometrial sample for AGCs.

Schnatz et al. [13] reported that 6,829 AGUC cases explained 71.0% of benign findings including reactive changes, polyps, and normal histology, 8.5% of low-grade squamous intraepithelial lesions (LSILs), 11.1% of high-grade squamous intraepithelial lesions (HSILs), 2.9% of AIS, and 5.2% of malignancies. Our AGC-NOS data showed 67.3% benign findings, 6.7% LSILs (CIN1), 9.2% HSILs (including 6.7% of CIN2 and 3.6% of CIN3), 3.8% AIS, and 8.4% malignancies (Table 3). Our study found high rates of HSIL, AIS, and malignancy but low rates of benign findings and LSIL compared with those found by Schnatz et al. [13]. However, neither their nor our study recognized a significant difference in histology. Therefore, our AGC-NOS data demonstrated that many benign lesions were included. There was another report that invasive cancer did not occur in 91 AGC-NOS cases [28], whereas we showed a frequency of 8.4%. The reason why our rate of malignancy was high was not apparent, but an improvement in accuracy of the cytological diagnosis might be required. Our data showed that 12.1% of the AGC-FN cases were benign, 1.1% were LSILs (CIN1), 4.4% were HSILs (CIN3), 5.5% were AIS, 53.8% were cervical adenocarcinomas, and 11.0% were endometrial carcinomas (Table 4). AIS and cervical adenocarcinoma accounted for 59.3% of the total AGC-FN cases. Therefore, the AGC-FN data demonstrated that many cervical glandular lesions were included. Glandular neoplasia had a frequency of 27% in a report on 15 AGC-FN cases [28], whereas our data showed a high frequency of 59.3%. As with the cases of AGS-NOS, we might need more careful control of the cytological accuracy for AGC-FN. Our data showed that 24.9% of the AEMC cases were benign, 0.3% were LSILs (CIN1), 0.3% were AIS, 3.3% were cervical adenocarcinomas, 63.8% were endometrial carcinomas, 5.7% were ovarian cancer, and 1.0% were some other ma-

lignancy (Table 5). Therefore, the AEMC data demonstrated that many endometrial carcinomas were included. In summary, AGC-NOS encompasses numerous benign lesions and a few cervical glandular lesions, AGC-FN encompasses many cervical glandular malignancies, and AEMCs encompass a large number of endometrial cancers. Therefore, a clear distinction between these three groups is required for clinical management.

The reported rates of dysplasia and malignancy that are associated with AGCs vary widely and range from 17 to 59% [15, 20, 21, 29]. A total of 364 malignancies accounted for 29.0% of the AGC cases in this study. We examined malignancies divided into AGC-NOS, AGC-FN, and AEMCs. Out of the 72 cases of malignancy in the AGC-NOS group, 47 (65.3%) were diagnosed as cervical adenocarcinoma, 8 (11.1%) were diagnosed as SCC, 7 (9.7%) were diagnosed as endometrial carcinoma, 9 (12.5%) were diagnosed as ovarian cancer, and 1 (1.4%) was diagnosed as some other malignancy. Out of the 70 cases of malignancy in the AGC-FN group, 49 (70.0%) were diagnosed as cervical adenocarcinoma, 11 (15.7%) were diagnosed as SCC, and 7 (9.7%) were diagnosed as endometrial carcinoma. Out of the 222 AEMC cases, 10 (65.3%) were diagnosed as cervical adenocarcinoma, 192 (57.4%) were diagnosed as endometrial carcinoma, 17 (4.7%) were diagnosed as ovarian cancer, and 3 (1.1%) were diagnosed as another malignancy. In summary, in the subclasses, malignant cervical lesions were characteristic among the cases of AGC-NOS and AGC-FN, and endometrial carcinoma was distinctive among AEMCs.

When the AGC cases were divided into three medical intervention degrees according to histology, AGC-NOS required radical laparotomy for invasive cancer in 8.3% of the cases, cervical cone resection in 13.0% of the cases, and nonintervention in 78.7% of the cases. AGC-FN required radical laparotomy for invasive cancer in 76.9% of the cases, cervical cone resection in 9.9% of the cases, and nonintervention in 13.2% of the cases. AEMCs required radical laparotomy for invasive cancer in 73.8% of the cases, cervical cone resection in 0.3% of the cases, and nonintervention in 25.9% of the cases. These results supported the clinical approach applied for AGCs in Japan. This study is the first report of a simplified management rate for AGCs.

Gynecological malignancies comprise 16–84% of invasive cervical cancers, 4–77% of uterine cancers, and 4–8% of ovarian cancers [13, 20, 26, 30]. For endometrial cancer, Liao et al. [31] and Lee et al. [14] reported that the rate of endometrial cancer was up to 10% in AGC cases. Our data including AGC-NOS and AGC-FN showed an endometrial cancer rate of 1.8% among the patients (17/953). In

contrast, AEMCs showed an endometrial cancer rate of 63.8%. Clinically, AEMCs should be instrumental in the detection of endometrial lesions. So as not to misunderstand that endometrial cancer is determined by cervical sampling, we chose endometrial cytology or endometrial biopsy when endometrial malignancies were suspected.

We focused on results related to initial testing for AGCs in this study. Cheng et al. [26] reported that AGC cases had an approximately 18-fold higher incidence of cervical cancer, a 6-fold higher incidence of uterine cancer, and a 2-fold higher incidence of ovarian cancer than the general screening population. Women with AGCs found at screening should immediately be adequately assessed by histological analysis and must not be lost to follow-up [3]. Therefore, an intent approach to histological analysis at the initial visit is critical [15, 19]. Our study focused on histology at the initial visit and showed a rate of early diagnosis (<4 months) of only 47.0% (590/1,254 cases), which might indicate that early diagnosis of AGCs is difficult.

A total of 622 cases (49.6%) from our data received a diagnosis more than 3 months after initial testing. In these 622 cases, the difficulty in differentiating false negatives from a newly originated lesion during follow-up limited our study. In the literature, the false negative rate was 4.7% in initial testing [18], and 12 of 42 AGC cases (29%) were diagnosed more than 1 year after the initial AGUS Pap test [18]. A missed or ineffectively eliminated glandular lesion during or after the initial histological identification of AGCs would not be as visible and accessible as squamous lesions using colposcopic methods [3, 32–34]. Therefore, follow-up testing is also significant [3, 19]. A recent practical suggestion for follow-up is a more aggressive assessment strategy, such as including an additional histological analysis at 1 year and close surveillance for many years [3]. A cytology result of AGCs may require long-term management for final histology.

High-risk HPV DNA is found in 9.0–34.0% of AGC cases [16, 24, 35]. HPV testing may improve prediction of the risk of cancer after detection of AGCs, because cervical adenocarcinoma and its precursor lesions are also related to HPV infection [3, 24, 36]. In 2006, consensus guidelines for managing AGCs released by the ASCCP included high-risk HPV testing for women with AGC-positive Pap test results [11, 16]. In our analysis, 38 cases included an HPV test with a positive result and 35 included an HPV test with contrary findings. This low number of submitted HPV-tested AGC cases came about because health insurance did not approve HPV testing for AGC cases in Japan. In addition to the small number of cases, HPV typing was not considered in this paper. Al-

though endocervical adenocarcinomas of the usual type are etiologically related to infection with oncogenic HPVs [37], rarer endocervical adenocarcinoma subtypes, i.e., clear cell, serous, endometrioid, and gastric type, showed much lower rates in relation with HPV [38]. These reports suggested that special attention should be given to specific rarer endocervical adenocarcinoma subtypes, as most appear to be unrelated to HPV [37, 38]. In this article, 1 HPV-negative case in AGCs was an endometrioid-type endocervical adenocarcinoma. By increasing the number of cases, we must pay close attention to the histological diagnosis of HPV-negative cases in AGCs. The incorporation of HPV testing in AGC smears for clarification might be an important strategy in Japan.

This study has two limitations. The first limitation is that although in many cases, histological results were received after 1 year or more, this study did not provide any diagnostic interval description of the period. Therefore, an examination of the appropriate interval of visits for patients with AGCs should be performed in the future. The second limitation is that there were 42 follow-up cases of diagnostic difficulty, which may have affected frequencies of histological types that may be determined in the future.

In conclusion, our data show the necessity of using various techniques for the histological analysis of AGCs, and our histological results support the medical intervention provided. This study is the first to evaluate a large number of AGC patients in Japan. However, unanswered questions remain concerning histology in follow-up cases.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

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