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Cytologic and Histologic Correlation of Atypical Glandular Cells of Undetermined Significance

To determine the cytologic and histologic correlation of atypical glandular cells of undetermined significance (AGUS) in Papanicolaou smears, a cytology file from January 1998 to May 1999 was reviewed. Surgical pathology files were searched to determine which patients received subsequent biopsies. One hundred thirty-two patients with AGUS were identified. Corresponding biopsies were available for 82 of these cases. AGUS has been sub-classified into 3 subtypes: 1) AGUS, favor reactive; 2) AGUS, not otherwise specified; and 3) AGUS, favor neoplasia. The pathologic findings for the respective Papanicolaou smears with the diagnosis of each subtype of AGUS through the follow-up period were as follows: benign lesions in 56.1%, 0%, and 1.2%; squamous intraepithelial lesions 2.4%, 0%, and 1.2%; glandular intraepithelial lesions 0%, 0%, and 17.1%; endometrial simple hyperplasia 1.2%, 0%, and 0%; and carcinoma 0%, 9.8%, and 11%, respectively. In conclusion, AGUS, on cervical cytologic screening, was correlated with significant pathologic findings in 41.5% of the patients (37.8% with preinvasive or invasive glandular lesions and 9.6% with combined squamous intraepithelial lesions). It is thought that intensive follow-up studies, including colposcopy, cervical biopsy, and curettage, should be recommended for complete evaluation of AGUS.

Key Words: *Atypical Glandular Cells of Undetermined Significance; Cytology; Cervix Uteri; Vaginal Smears*

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INTRODUCTION

In 1988 the Bethesda System (TBS) for a Papanicolaou smear classification proposed the concept of atypical glandular cells of undetermined significance (AGUS) as a diagnostic subcategory of glandular epithelial cytologic abnormalities (1). This cytologic category includes a morphologic spectrum ranging from a possibly benign reactive process to in situ adenocarcinoma. Several investigators have established the value of using key cytologic criteria in differentiating benign atypical glandular cells of undetermined significance (AGUS) on Papanicolaou smears from clinically significant lesions (2-5). However, benign conditions, such as cervical endometriosis, tubal metaplasia, previous cone biopsy, Gardner's ducts, microglandular hyperplasia, deciduosis, and even endometrial glands in the upper cervical canal can make the differential diagnosis difficult (2-7).

The frequency of squamous cell carcinoma of the uterine cervix has been decreasing due to early detection of its precursor lesion by cervicovaginal smears and early treatment. However, this is not the case with cervical adenocarcinoma, which has demonstrated a steady increase in frequency. In the general population, the incidence of atypical squamous cells is significantly different from the incidence of atypical glandular cells, the former being 10 times more frequent (5%) than the latter (0.16%-0.5%) (8-13). The higher incidence of atypical squamous cell of undetermined significance (ASCUS) has led to numerous articles describing the significance of these diagnoses. On the other hand, only a few authors have investigated the clinical significance of AGUS, and as a result, this cytologic diagnosis is not completely understood (11). However, the percentage of serious abnormalities found in patients with AGUS is much higher than in patients with ASCUS. In this study we analyzed the cytologic and histologic correlation of AGUS on Papanicolaou smears to recognize the clinical significance of AGUS. In addition, we focused on guidelines for management of the patients with a diagnosis of AGUS.

MATERIALS AND METHODS

A total of 449,431 Papanicolaou smears were obtained at Gachon Medical School, Gil Medical Center, and its

affiliated clinics between January 1, 1998, and May 30, 1999: 42,214 samples were obtained at the Obstetrics and Gynecologic Clinic in Gil Medical Center and 407,217 samples were from mass screening. During that period, a diagnosis of AGUS was made in 132 patients. Each overall incidence of AGUS was 0.03%; 0.09% from the Gil Medical Center and 0.02% from mass screening. Fifty patients were excluded from further analysis due to drop-out during the follow-up period or absence of subsequent histologic studies. Eighty-two Papanicolaou smears were available for the analysis.

The patients were subclassified into 1 of 3 subtypes on the basis of the diagnosis or comment in the cytopathology report: 1) AGUS, favor reactive, when a reactive or inflammatory process was favored: These cells demonstrate nuclear enlargement three to five times normal and slight hyperchromasia. A honeycomb pattern with distinct cell borders is often contained. 2) AGUS, not otherwise specified (NOS), when no other qualification was present, and 3) AGUS, favor neoplasia, when a glandular neoplasia of endocervical (or, less frequently, endometrial) origin was suspected but could not be definitively diagnosed. The method by which tissue was obtained in the evaluation of these smears varied and included ectocervical biopsy, endocervical curettage, cervical conization, loop electrosurgical excision procedure, polypectomy, endometrial biopsy, and hysterectomy. All histopathologic specimens were correlated with the cytologic diagnoses.

RESULTS

The average age of the patients was 44.2 yr (range 24-76). The number and percentage of AGUS for cytologic subtypes were as follows: 49 favor reactive (59.8%), 8 NOS (9.8%), and 25 favor neoplasia (30.4%).

Benign lesion in histologic diagnosis

Of 82 AGUS cases, forty-four (53.7%) had chronic cervicitis with or without squamous metaplasia. Four patients (4.9%) had benign endometrial lesion; 3 of endometrial polyp, and one of simple endometrial hyperplasia.

Preinvasive or invasive carcinoma in histologic diagnosis

Overall, 34 (41.5%) of 82 patients in whom AGUS was diagnosed and who had subsequent follow-up were found to have important clinical changes. Table 1 shows the results of histologic evaluation subclassified by the Papanicolaou smear subtypes. AGUS was associated with pathologic conditions in the final diagnosis of between 12.2% (favor reactive) and 100% (favor NOS). According to the classification, the subtype interpreted as favor reactive, representing approximately 59.8% of smears in our study, had the lowest incidence of pathologic conditions (6.1%). In contrast, the subtype favoring NOS, comprising approximately 9.8% of smears had the highest incidence of pathologic conditions (100%). Three cases (3.7%) had squamous epithelial lesions such as in situ squamous cell carcinoma with glandular involvement. Glandular intraepithelial lesion in uterine cervix is consisted with 14 cases, nine (11%) of which had low and high grade glandular dysplasia. In situ adenocarcinoma of the cervix was diagnosed in 5 cases (6.1%) (Fig. 1). Endometrial pathologic changes, except endometrial adenocarcinoma, were found in 4 cases: polyps were found in 3 cases (3.7%), and simple hyperplasia in 1 case (1.2%). Adenocarcinoma was found in biopsy samples as follows: 8 cervical adenocarcinomas (1 NOS or 7 favor neoplasia), 6 endometrial adenocarcinomas (5 NOS or 1 favor neoplasia), 2 ovarian carcinomas (1 NOS or 1 favor neoplasia), and one metastatic adenocarcinoma

Table 1. Correlation between histologic diagnosis in patients with AGUS by cervicovaginal cytologic findings

Histologic Diagnosis	Favor reactive	Not otherwise specified	Favor neoplasia	Total (%)
Benign lesion	46		1	47 (57.3)
Chronic inflammation	43		1	44
Endometrial polyp	3			3
Preinvasive	3		15	18 (22.0)
Squamous intraepithelial lesion	2		1	3
Glandular intraepithelial lesion			14	14
Simple endometrial hyperplasia	1			1
Invasive carcinoma		8	9	17 (20.7)
Adenocarcinoma of cervix		1	7	8
Endometrial adenocarcinoma		5	1	6
Clear cell carcinoma of ovary		1	1	2
Adenocarcinoma of colon		1		1
Total (%)	49 (59.8)	8 (9.8)	25 (30.4)	82 (100)

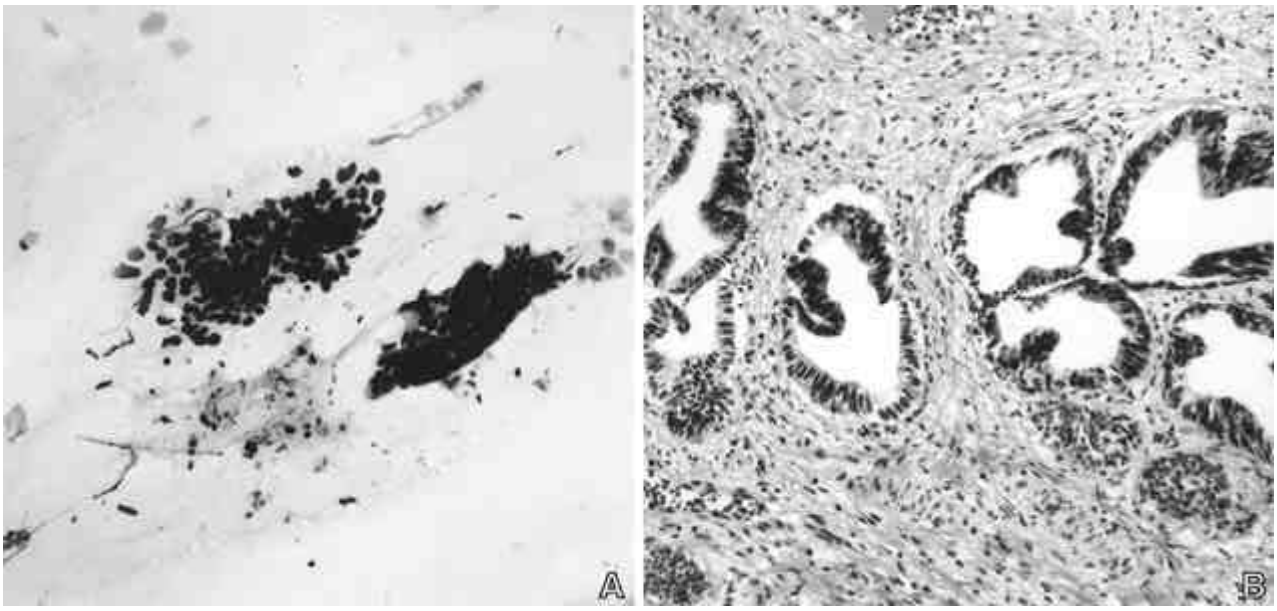

Fig. 1. Cytologic and histologic findings of AGUS, favor neoplasia: Cervical smear **(A)** diagnosed as AGUS, favor neoplasia. It shows palisading and crowded sheets: most nuclei are in a relatively uniform oval shape (Papanicolaou stain, ×200). Histologic section **(B)** shows nuclear stratification, crowding, and hyperchromatic enlarged nuclei (H&E, ×200).

from the colon (NOS).

DISCUSSION

The Bethesda System (TBS) was developed in 1988 to provide uniform diagnostic terminology that would facilitate communication between cytopathology laboratories and clinicians (14). One of the goals of TBS was to require cytopathologists to make the specific diagnosis in the classification of cellular atypias. As with its squamous counterpart ASCUS, AGUS applies to glandular cells that demonstrate changes beyond those encountered in usual benign reactive processes, but are insufficient for a diagnosis of invasive adenocarcinoma. The diagnosis should be further qualified, if possible, to indicate whether the cells are thought to be of endocervical or endometrial origin. Because AGUS is a relatively new term and there is a lack of conformity among laboratories as to the meaning of "glandular atypia", the exact incidence of AGUS is difficult to assess. Our study focuses on the diagnostic rate of AGUS and guidelines for management of patients with a diagnosis of AGUS by Papanicolaou smear, for the purposes of mass screening.

In our study, the diseases of the uterine cervix were more common in younger women and endometrial lesions were found more frequently in older women. The incidence of AGUS of approximate 0.03% was lower than the 0.2% previously reported by others including the most recent publications in United States which reported a diagnosis rate of 0.16-0.5% (8-13). In our opinion, this differences in incidence can be explained in three ways. First, the rate of endocervical lesions in Korea (6.1%) is actually lower than that in United States (9.4%) (15-17). The frequency of squamous cell carcinoma of the uterine cervix has been decreasing due to early detection of its precursor lesions by cervicovaginal smears (16). However, this is not the case with cervical adenocarcinoma, which has shown a steady increase in frequency (16, 17). Second, most cases might have been identified by mass screening at the primary care unit, which means selection bias. As a result, the incidence of AGUS might be relatively lower than that in university hospitals (tertiary care unit). Third, the patients enrolled in this study failed to represent the general population for other reasons, with a resultant underestimated incidence.

It is clear from the results of this study that the presence of AGUS on a routine cytologic specimen is a marker for important clinical change in large percent of women (46.3%). There are the incidence of preinvasive and invasive lesions (squamous intraepithelial lesions, glandular dysplasia, in situ adenocarcinoma, endometrial hyperplasia, and cancer) and benign lesions (polyps or benign ovarian lesions) according to the AGUS subtype (Fig. 2). Seventeen of 82 cases biopsied (20.7%) had invasive cancer, and 18 who were biopsied (22.0%) were found to have significant cancer precursors.

A higher incidence of preinvasive or invasive lesions was associated with the subtypes NOS or favored neo-

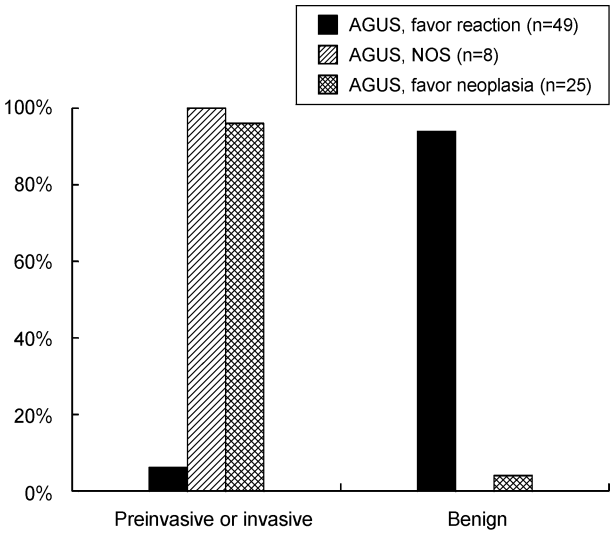

Fig. 2. Incidence of preinvasive or invasive lesions and benign lesions: Bar graph depicting percentage of each subtype of AGUS on Papanicolaou smear associated with preinvasive or invasive versus benign findings through follow-up biopsy. NOS, not otherwise specified. Preinvasive or invasive: Squamous intraepithelial lesion, glandular dysplasia, adenocarcinoma in situ, endometrial hyperplasia or cancer; benign: polyp or chronic inflammation.

plasia rather than the benign subtype favor reactive. However, it is noteworthy that even in the group of women in whom the Papanicolaou smear was interpreted as representing a benign process, there still existed a 6.1% incidence of preinvasive or invasive lesions confirmed by histopathologic analysis.

We found an approximate 7.3% incidence of endometrial adenocarcinoma among patients with AGUS. This finding is consistent with Zweizig et al. (11) and shows higher incidence compared with 2% in previous publications (8, 10, 13). The higher incidence of endometrial adenocarcinoma found in patients with AGUS might reflect the older ages of these patients compared with patients who had other abnormalities. The mean age of 54 yr in our study is older than that of 45 yr in other studies (8, 13). This is also significantly older than those patients with cervix lesions who had a mean age of 38.9 yr (11). It is noteworthy in our study that 3 cases with previously undiagnosed extrauterine malignancies were found to have AGUS based on vaginal smears. Two cases were ovarian clear cell carcinoma (Fig. 3). Another case was colonic adenocarcinoma. The presence of nonuterine malignancies in our series indicates the need to provide further diagnostic study in patients with otherwise unexplained AGUS after colposcopy and cervical biopsy.

The literature supports the premise that AGUS represents a cytologic diagnosis associated with a high probability of underlying pathologic conditions (18). The association between squamous lesions and glandular lesions of the cervix is undoubtedly related to two factors. First, cases of AGUS may be misclassified because of difficulty in seeing cellular detail due to poor preservation or obscuring inflammation (18). Second, probably more important, both cervical glandular and squamous neo-

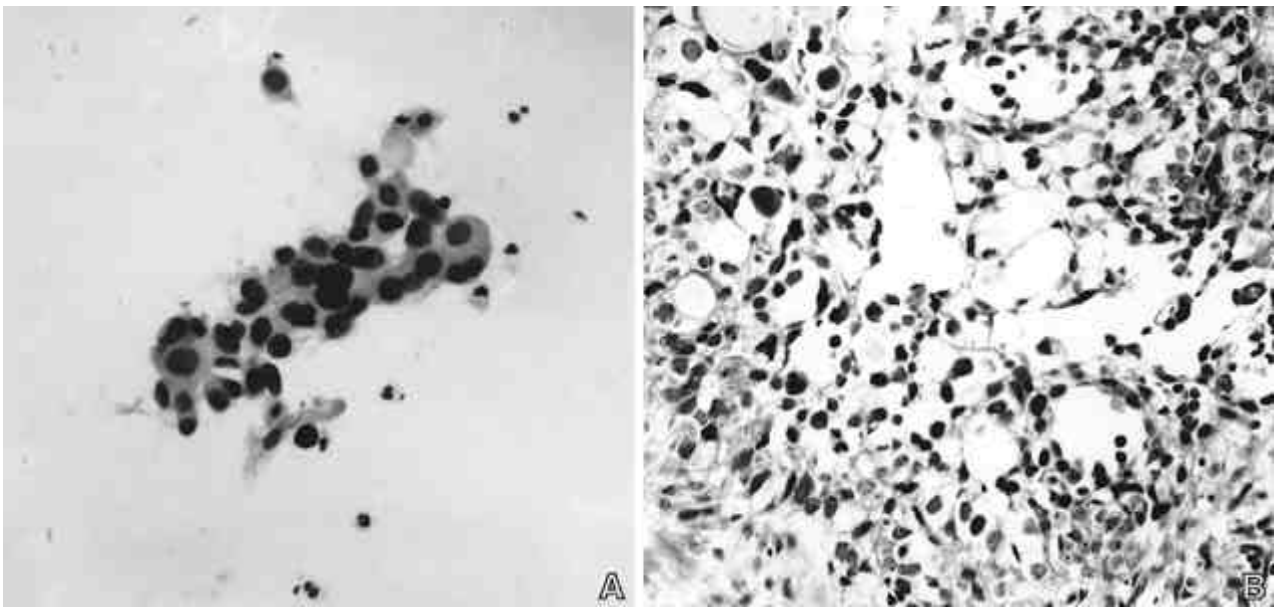

Fig. 3. Cytologic and histologic findings of AGUS, NOS: Cervical smear diagnosed as AGUS, NOS (A) shows sheets of slightly enlarged cells with abundant eosinophilic cytoplasm and pleomorphic nuclei (Papanicolaou stain, ×400). Histologic section (B) shows solid pattern of clear cell carcinoma of ovary (H&E, ×200).

Table 2. Comparison of incidence of atypical glandular cells of undetermined significance and prevalence of pathologic finding on follow-up in literature

Study	Total Papanicolaou smear	AGUS Papanicolaou smear	Incidence (%)	No.	SIL (%)	AIS (%)	EMH (%)	CA (%)
Goff et al. (1992) (10)	21,930	100	0.46	63	39.7	7.9	3.2	3.2
Nasu et al. (1993) (26)	34,384	620	1.8	277	43.7	3.3		4
Taylor et al. (1993) (27)	17,000	30	0.18	30	37			
Kennedy et al. (1996) (8)	68,368	136	0.20	77	9.1	3.9		3.9
Zweizig et al . (1997) (11)	46,804	127	0.27	85	21.2	1.2	11.8	9.4
Eddy et al. (1997) (28)	177,715	1,117	0.63	531	27	1.9	1.1	6
Duska et al. (1998) (12)	120,338	201	0.17	73	26			8.2
Veljovich et al. (1998) (18)	84,442	345	0.53	199	22.6	2.5	2.5	4
Total	570,981	2,676	0.47	1,335	28.3	3.5	4.7	5.5
Present study (1999)	449,431	132	0.03	82	9.6	6.1	1.2	10.9

AGUS, atypical glandular cells of undetermined significance; Incidence, incidence of atypical glandular cells of undetermined significance on Papanicolaou smear; No., number of patients evaluated with biopsy specimens; SIL, squamous intraepithelila lesion; AIS, adenocarcinoma in situ; EMH, endometrial hyperplasia; CA, cancer

plasia are etiologically linked to human papillomavirus infection (19-24); hence the two lesions tend to coexist although squamous lesions are diagnosed and confirmed approximately 20% to 100% more frequently than are true glandular neoplasia (18).

Table 2 shows findings of previous investigators and of this study with respect to the number of total Papanicolaou smears evaluated and the number of Papanicolaou smears with AGUS evaluated, the incidence of AGUS, and the prevalence of pathologic findings on follow-up evaluation (8, 10, 11, 18, 25-28). The number of invasive cancers in this study is sufficiently high to suggest that complete evaluation of all women with AGUS on smear is warranted. Aggressive workup of Papanicolaou smears with these glandular cells is recommended to rule out potential pathologic conditions in endocervical, endometrial, and, much more rarely, extrauterine lesions such as gastrointestinal, tubal, ovarian, or breast. The American Society for Colposcopy and Cervical Pathology recently published guidelines for management of patients with AGUS on Papanicolaou smears (18). All the women with this diagnosis should undergo cervical and vaginal colposcopy and endocervical curettage. Those patients with unqualified AGUS who have negative colposcopic examinations and endocervical curettage should have repeated Papanicolaou smears every 4 to 6 months until 4 consecutive normal smears have been obtained.

This study contributes to the understanding of AGUS in two ways. First, our study reinforces the previously published concept that AGUS on Papanicolaou smears represents a cytologic diagnosis associated with high incidence of underlying malignant or premalignant lesions on follow-up histologic examination. Thus, the patient with this diagnosis should be followed up appropriately in accordance with the guidelines of the American Society for Colposcopy and Cervical Pathology. Second, the classifications of AGUS by subtype may be valuable in assessing the risk of underlying pathologic conditions. Development of well-defined criteria for the diagnosis of various subtypes of AGUS could identify women at higher or lower risk for significant pathologic conditions and thus, assist in triage of patients on the basis of subtypes. Careful discussion with the interpreting cytopathologists is crucial, however, in any situation when a management plan is being developed.

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