Clinical evaluation of atypical glandular cells of undetermined significance

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OBJECTIVE: This study was undertaken to determine the clinical implications of the finding of atypical glandular cells of undetermined significance in cervical cytologic specimens in our patient population.

STUDY DESIGN: A retrospective study was performed. All cervical cytologic examinations with the diagnosis of atypical cells of undetermined significance between January 1992 and June 1997 were identified by means of a computerized database. Medical records were reviewed to identify patient demographic characteristics and to determine the presence or absence of associated pathologic conditions of the cervix and endometrium. The χ² test and analysis of variance were applied to dichotomous and continuous variables, respectively, to determine the implications of a cytologic evaluation of atypical glandular cells of undetermined significance.

RESULTS: Cytologic results reported as atypical glandular cells of undetermined significance were obtained in a patient cohort of 492. Atypical glandular cells of undetermined significance was the only cytologic diagnosis in 224 patients; 268 patients had both atypical glandular cells of undetermined significance and an additional squamous abnormality, including atypical squamous cells of undetermined significance and cervical intraepithelial neoplasia I, II, or III. Two patients were excluded because of a history of endometrial cancer. A histologic evaluation was obtained within 1 year in 353 cases. Among the 353 patients who had a histologic evaluation performed, 227 (64%) had benign cervical and endometrial findings. There were 18 glandular lesions (5%), including complex hyperplasia with atypia, adenocarcinoma in situ of the cervix, adenocarcinoma of the cervix, and adenocarcinoma of the endometrium. A squamous lesion was present in 108 patients (31%). Most squamous lesions (81%) were found in patients with atypical glandular cells of undetermined significance associated with a squamous abnormality, whereas only 19% were found in patients with atypical glandular cells of undetermined significance as the only diagnosis. Women <35 years old had a much higher frequency of histologic abnormalities than did women >50 years old (P < .0001), with most of these lesions being squamous. Women >50 years old had a much higher frequency of glandular histologic abnormalities (P < .001).

CONCLUSION: More than a third of women with Papanicolaou smears reported as showing atypical glandular cells of undetermined significance will be found to have a histologic abnormality. Women <35 years old with a cytologic evaluation of atypical glandular cells of undetermined significance have a higher frequency of histopathologic findings, with most being squamous lesions. Women with a cytologic evaluation of atypical glandular cells of undetermined significance who are >50 years old have more glandular lesions than do younger women. The term atypical glandular cells of undetermined significance is a misnomer. The significance of this cytologic finding has been defined and represents a marker for serious pathologic processes.

Key words: Atypical glandular cells of undetermined significance, Bethesda System, cervical intraepithelial neoplasia

In 1988 the National Cancer Institute developed the Bethesda System for the reporting of cytologic diagnoses to provide uniform diagnostic terminology. It was at this time that the term atypical glandular cells of undetermined significance (AGUS) and its squamous counterpart, atypical squamous cells of undetermined significance (ASCUS) were first used in cytologic diagnoses.1,2

The term AGUS is used to describe "cells showing either endometrial or endocervical differentiation displaying nuclear atypia that exceeds obvious reactive or reparative changes but lack unequivocal features of invasive adenocarcinoma."3 Determining whether the abnormality arises from the endocervix or endometrium proves challenging for the pathologist and often is impossible. Sampling technique, timing of the menstrual cycle, and coexisting infec-
tion can all hinder the pathologist’s ability to make the correct diagnosis. Once the diagnosis of AGUS has been made, it then presents a management dilemma for the physician. Many studies have demonstrated an association between a cytologic evaluation of AGUS and significant cervical and endometrial pathologic conditions. AGUS is a rare diagnosis, representing <1% of all Papanicolaou smears, and this rarity limits our study populations. Because of this limitation, coupled with the multiplicity of diagnostic and management strategies used by physicians, no accepted guidelines have been established for a rational approach in managing the care of the patient with a diagnosis of AGUS. In fact, the only AGUS management guidelines published to date are the recent recommendations of the American Society of Colposcopy and Cervical Pathology, which advocate cervical and vaginal colposcopy and endocervical curettage.

We conducted this study to determine the clinical implications of AGUS in our patient population and to identify risk factors for serious pathologic conditions. Our purpose was to establish appropriate evaluation and treatment guidelines at our institution.

Material and methods

A retrospective study performed by means of a computerized database included all women with cervical cytologic specimens with a cytologic diagnosis of atypical endocervical cells, atypical endometrial cells, or AGUS (the last is the diagnosis that is given if site of origin cannot be determined) between January 1992 and June 1997 at the Medical University of South Carolina. Of the 8221 Papanicolaou smears reviewed at our institution during this period, 492 met these diagnostic criteria. All cytologic diagnoses were made by staff pathologists according to standard Bethesda System criteria.

The medical records were reviewed to identify patient demographic characteristics, including age, parity, history of abnormal bleeding, smoking, use of oral contraceptives and hormone replacement therapy, and history of previous gynecologic cancer. The presence or absence of associated pathologic conditions of the cervix or endometrium, clinical follow-up, and the most significant histologic diagnosis from all biopsy and hysterec-
omy samples from each patient within 1 year of the AGUS diagnosis were recorded. Two patients were excluded because of a history of endometrial cancer. The \( \chi^2 \) test and analysis of variance were applied to dichotomous and continuous variables, respectively, to determine the clinical implications of a cytologic evaluation of AGUS.

Results

A cytologic evaluation of AGUS as the only diagnosis was found in 223 cases, and 267 patients had AGUS and also a squamous abnormality, including ASCUS or cervical intraepithelial neoplasia (CIN I, CIN II, or CIN III). The mean age of our study population was 37 years, with a mean parity of 2. A recorded history of abnormal bleeding was seen in 6.5% of patients, 12% were smokers, and 23% were receiving some form of hormonal treatment (oral contraceptives, hormone replacement therapy, or medroxyprogesterone acetate depot). Each of the 490 patients were seen and evaluated by different residents and attending faculty, and different evaluation schemes were therefore used. There were 353 patients (72%) who had a histologic follow-up within 1 year of the diagnosis, whereas 57 (12%) had repeated cytologic examination only within 1 year of the diagnosis, and 80 (16%) had no follow-up. There were 227 patients (64%) with benign results of biopsy, 108 (31%) with biopsy-proven squamous abnormalities, and 18 (5%) with glandular abnormalities (Fig 1). Of the 156 patients with AGUS as the only cytologic result who underwent histologic evaluation, only 29 (19%) had a biopsy-proven abnormality found at this
In contrast, among the 197 patients who had AGUS and an additional squamous pathologic condition according to cytologic evaluation who underwent histologic evaluation, 97 (49%) had an abnormality identified at histologic examination (Table I).

Colposcopy with directed biopsy and endocervical biopsy with or without endometrial biopsy were performed in almost two thirds of the cases. The other third of the patients underwent various diagnosis procedures (Table II).

Eighteen patients had glandular histologic abnormalities: 8 (44%) had hyperplasia with atypia, 7 (39%) had adenocarcinoma in situ, 2 (11%) had adenocarcinoma of the cervix, and 1 (6%) had adenocarcinoma of the endometrium. No other glandular abnormalities were identified.

The glandular abnormalities associated with cytologic evaluation of AGUS alone were compared to those associated with AGUS and a squamous abnormality (Table III). Eight glandular abnormalities (44%) were in patients with AGUS alone, versus 10 (56%) in patients with AGUS and a squamous abnormality. Most glandular lesions were identified in patients with AGUS as the only cytologic result or in patients with AGUS and an additional high-grade squamous abnormality.

There were 108 patients with biopsy-proven squamous abnormalities among our patients with a cytologic evaluation of AGUS. Most were cases in which there was a coexisting squamous abnormality identified on the Papanicolaou smear. Forty-nine patients (45%) had CIN I, 30 (28%) had CIN II, 28 (26%) had CIN III, and 1 (1%) had vaginal intraepithelial neoplasia I. Only 21 patients (19%) had AGUS as the only cytologic diagnosis, versus 87 (81%) with AGUS and a squamous cytologic abnormality \( (P < .0001) \). The relationship between the squamous cytologic diagnosis and the final histologic diagnosis is shown in Table IV.

Age was examined for correlation with the frequencies of all histologically detected abnormalities among women with cytologic evaluation of AGUS. More lesions were found histologically in patients <35 years old than among women 35 to 50 years old \( (P = .03) \) or >50 years old \( (P = .005) \). No statistical difference was found when women aged 35 to 50 years were compared with women >50 years old. There were abnormal histologic diagnoses in 71 (43%) of women < 35 years old with 66 (41%) of
these showing a histologic squamous abnormality of CIN I, II, or III (Table V). There were 5 patients (3%) in this age group with cytologic glandular abnormalities, including 4 adenocarcinomas in situ of the cervix and 1 adenocarcinoma of the cervix (Table VI). In the 128 patients aged 35 to 50 years who underwent biopsy for histologic examination 36 (28%) had squamous intraepithelial lesions including CIN I through CIN III. There were 3 patients (2%) with glandular lesions, including 2 patients with adenocarcinoma in situ and 1 with endometrial hyperplasia with atypia. Among those patients >50 years old 63 underwent biopsy for histologic examination, with 6 (10%) having squamous lesions that included CIN II, CIN III, and vaginal intraepithelial neoplasia 1. There were 10 (16%) with histologic glandular lesions, including 7 (11%) with endometrial hyperplasia with atypia, 1 (2%) with adenocarcinoma in situ, 1 (2%) with adenocarcinoma of the cervix, and 1 (2%) with adenocarcinoma of the endometrium.

The distributions of histopathologic diagnoses in each age group are noted in Fig 2. Most histologic findings in each age group were benign. More than 90% of all abnormalities among women <50 years old were squamous in origin, versus only 40% among women >50 years old. Fig 3 illustrates the specific squamous and glandular lesions found among women in each age group.

For the 18 histologic glandular abnormalities, the site of origin of the glandular atypia assigned on cervical cytologic examination (endocervical vs endometrial) was compared with the final histologic diagnosis to determine the accuracy of determination by cytologic studies alone of the origin of glandular atypias. The origin of the glandular abnormality could not be determined for 8 specimens by cytologic means alone. Seven were noted to have atypical endocervical cells according cytologic diagnosis. Six of these patients had squamous histologic abnormalities of the ectocervix, and 1 patient had adenocarcinoma in situ of the cervix. Furthermore, 3 patients were noted to have atypical endometrial cells according to cytologic evaluation. Only 1 had an abnormality of the endometrium according to histologic evaluation (adenocarcinoma of the endometrium), whereas 1 had adenocarcinoma in situ of the cervix and the other had a squamous abnormality of the ectocervix.

Other demographic parameters, including parity, history of abnormal uterine bleeding, smoking history, and use of oral contraceptives and hormone replacement therapy, were not found to be of significance.

**Comment**

The optimal evaluation and management of AGUS have still not been determined a decade after the creation of this category. Some physicians choose a conservative approach to AGUS and treat it much like ASCUS, with repeated cytologic examination alone, whereas others are taking a more comprehensive approach, performing colposcopy and biopsy of the endocervix and endometrium. In previous studies, as well as this one (Table VII), AGUS has been associated with histologic abnormalities in a third of all cases. Most of these abnormalities associated with a cytologic evaluation of AGUS have been found to be squamous in nature. CIN I represents an appreciable number of these lesions; however, high-grade squamous intraepithelial lesions represent >50% of these abnormalities. Our findings therefore support the need to evaluate patients with a cytologic diagnosis of AGUS further at least with colposcopy, directed biopsy, and endocervical curettage.

Age does appear to be a risk factor for squamous and glandular lesions associated with a cytologic diagnosis of AGUS. There was a much higher frequency of lesions

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**Table V. Squamous lesions according to age among patients with AGUS evaluations**

<table>
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<tr>
<th></th>
<th>&lt;35 y</th>
<th>35-50 y</th>
<th>&gt;50 y</th>
<th>&lt;35 y</th>
<th>35-50 y</th>
<th>&gt;50 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN I</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>33</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>CIN II</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>16</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>CIN III</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>10</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>TOTAL</td>
<td>7</td>
<td>10</td>
<td>4</td>
<td>59</td>
<td>26</td>
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among women <35 years old; however, most of these were low-grade intraepithelial abnormalities. Of the glandular abnormalities found among women <35 years old, all were confined to the cervix. No endometrial pathologic conditions were found in the women of this age group.

Women >35 years of age had fewer overall lesions, but most of the high-grade intraepithelial squamous abnormalities and glandular lesions of the cervix and endometrium were found among these women.

Our data suggest that colposcopic evaluation with appropriate cervical biopsy and endocervical curettage is warranted for all women with a cytologic evaluation of AGUS, regardless of age. Women >35 years of age should also undergo endometrial biopsy because of the increased risk of endometrial disease in that age group. This should be done regardless of the site of origin of the atypical cells reported by the pathologists. Our data suggest that the reliability in predicting the origin of disease and the degree of abnormality on the basis of cytologic results alone are not satisfactory. Determination of the extent of evaluation on the basis of a cytologic determination alone of whether a reparative process or a more significant lesion is present does not appear reliable.

On the basis of this report and a review of the literature, we suggest that the term AGUS is a misnomer. The significance of a cytologic evaluation of AGUS has now been defined and represents a marker for serious pathologic conditions.
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