Incidence and Evaluation of an AGUS Papanicolaou Smear in Primary Care

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Background: **The category atypical glandular cells of undetermined significance (AGUS) occurs in about 0.5% of Papanicolaou smears. Although recent case series report a great many dysplastic, cancerous, and precancerous lesions of the cervix and endometrium associated with AGUS, little attention has been focused on this issue in primary care literature.**

Methods: **We report a case series of 52 women with AGUS Papanicolaou smears in a family health center during 2 years (1997 to 1998), along with colposcopy and biopsy results and 18 months of follow-up findings. These results were compared with findings of recent reports.**

Results: **The incidence of AGUS was 0.5%, 52 of 10,564 Papanicolaou smears. Colposcopy was performed in 45. Biopsy (n = 46) showed 2 adenocarcinomas of the endometrium, and 6 high-grade dysplastic lesions, including 1 squamous cell carcinoma in situ. Nineteen women had cervical intraepithelial neoplasia stage I-changes of human papillomavirus effect, and 4 had endocervical polyps. Three women were lost to follow-up. The frequency of dysplastic and cancerous lesions in our population (17.4%) is consistent with series findings from cytology and obstetrics and gynecology literature, reporting that 19.5% of women with AGUS have either cancer—adenocarcinoma of the endometrium, squamous cell carcinoma, or extrauterine (8%)—or high-grade lesions—cervical intraepithelial neoplasia II-III, carcinoma in situ, or cervical adenocarcinoma in situ, (11.5%).**

Conclusions: **A relatively large percentage of women with AGUS on Papanicolaou smears have cancerous and dysplastic squamous and glandular lesions of the exocervix, endocervix, and endometrium. Clinical practice guidelines recommend patients with AGUS should be evaluated with colposcopy and endocervical curettage. Consensus supports endometrial sampling in women 35 years and older and in those with a laboratory report of AGUS, favors neoplasia or suggests an endometrial source.(J Am Board Fam Pract 2001;14:172–7.)**

The term, *atypical glandular cells of undetermined significance* (AGUS), was added to Papanicolaou smear categories by the Bethesda classification system in 1988.[1] The importance of the term AGUS is not always recognized because of confusion with the similar-sounding category of atypical squamous cells of undetermined significance (ASCUS), the use of the word "undetermined," and its rarity. AGUS is reported in approximately 0.5% of the US Papanicolaou smears.[2]

Although several retrospective studies[2–9] have shown that a notable percentage of patients with an AGUS finding have clinically important lesions, until recently the issue has received inadequate attention. The most worrisome associated lesions are adenocarcinoma of the endometrium or endocervix or, rarely, carcinoma from an extrauterine source.[10] Additionally, squamous intraepithelial lesions occur in patients who have AGUS Papanicolaou smears and are reported with nearly three times greater frequency than are glandular cell abnormalities.[3]

The cytologic diagnosis of AGUS is challenging for the pathologist because it can be confused with atypical squamous cells of undetermined significance, high-grade squamous intraepithelial lesion, or glandular involvement by a squamous process. Misclassification of AGUS occurred in 9 of 114 smears in one series.[5] Added to the challenge of diagnosis for the cytopathologist is that of the primary care provider, who receives the AGUS result and needs to make clinical decisions regarding evaluation and follow-up. To help guide subsequent evaluation, some pathology laboratories will include further description favoring a benign or ma-

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lignant result, ie, "AGUS: favor reactive" or "AGUS: favor neoplasia,"[11,12] and "the origin of atypical cells, either endocervical or endometrial."[13]

Most studies regarding AGUS Papanicolaou smears have been reported in the pathology and obstetrics and gynecology literature; little information has been published in the primary care literature. We reviewed 2 years' experience with AGUS Papanicolaou smear results in an urban family health center to determine their importance in a primary care practice. We report a case series of 52 women with biopsy results and 18 months' subsequent follow-up. Outcomes are compared with those previously reported. Recommendations are given for patient evaluation and follow-up.

Methods

Setting and Population

The Greater Lawrence Family Health Center (GLFHC) is an urban community health center 30 miles north of Boston. During the study period the GLFHC served a population of approximately 30,000 (78% Medicaid insured), mostly of Caribbean Hispanic-Dominican or Puerto Rican heritage. Sixty-one percent of the patients were female; of these 37% were aged between 0 to 19 years, 48% were 20 to 49 years, and 15% were older than 50 years. The center provides obstetric care (more than 600 births per year). Papanicolaou smear screening was performed by the entire provider staff of 23 family physicians, 9 nurse practitioners, 3 internists, 6 pediatricians, and 24 family practice residents. Residents' patients (approximately 3,000) are included in the analysis.

Case Selection

We conducted a hand review of the GLFHC Papanicolaou smear log at the pathology laboratory in the Lawrence General Hospital to select all AGUS Papanicolaou smear results reported between 1 January 1997 and 31 December 1998. As a check mechanism, we asked providers at GLFHC to indicate which patients in their panels had an AGUS Papanicolaou smear result and reviewed our in-house (GLFHC) colposcopy logs. These data sets were combined to yield 52 cases of AGUS Papanicolaou smear results for review. Follow-up and outcome data were obtained by the authors, who reviewed the office and consultants' medical records, colposcopy notes, and biopsy reports. Eight women had colposcopy after their primary provider was contacted by study staff during chart review. Electronic retrieval of these data was not possible, as neither the hospital laboratory nor the Family Health Center coded for AGUS.

Evaluation and Follow-up

Our routine evaluation for AGUS included a careful colposcopic examination of the cervix with endocervical curettage and biopsy of any abnormal areas. Endometrial sampling and pelvic sonography were optional. Patients who had high-grade cervical intraepithelial neoplasia (CIN II–III) were referred for loop electrosurgical excision procedure (LEEP) or cone biopsy, and those who had endometrial lesions (adenocarcinoma) were referred for hysterectomy. Patients with low-grade lesions of the cervix (CIN I-HPV [human papillomavirus] changes) had follow-up Papanicolaou smears. Endocervical polyps were removed at the time of colposcopy. Patient follow-up was noted by chart review through July 2000.

Patient's age when AGUS was reported, time elapsed from Papanicolaou smear until colposcopy, cervical biopsy and repeat Papanicolaou smear results, other histologic findings, and procedures were abstracted from record review. Several women had follow-up care at outside gynecology clinics, and the results of their cases were verified by medical record review from those consultant sources. We used Microsoft Excel to create a database of the findings regarding workup of the AGUS Papanicolaou smear results in this population.

Comparison Group

After a careful electronic search of the National Library of Medicine database, we retrieved five series of AGUS Papanicolaou smear findings that met the following criteria: (1) they were published in refereed journals coincidentally with the study period (1997 to 1998), (2) prevalence of AGUS was reported, (3) there were biopsy results on 40 or more cases, and (4) any associated pathologic diagnosis was delineated, including differentiation of squamous dysplastic lesions into high (CIN II-III), and low (CIN I) grades. We then combined the case series, summing the number of cases in each category to arrive at frequencies for the group (Table 1). The largest series from this period[3] (with 531 biopsies) was excluded based on criterion 4.

Table 1. Comparison of Histologic Findings After Atypical Glandular Cells of Undetermined Significance (AGUS) Found on Papanicolaou Smears: Greater Lawrence Family Health Center (GLFHC) vs Five Recent Case Series.

Study Characteristics	GLFHC Case Series 1997–1998 Number	GLFHC Case Series 1997–1998 Percent	5 Case Series 1997–1998[2,4–7] Number	5 Case Series 1997–1998[2,4–7] Percent
Total Papanicolaou smears	10,564	100.0	312,536	100.0
Total with AGUS findings	52	0.5	1,124	0.4
Patients with biopsy*	46	88.0	572	50.9
Cancer	2 endometrial adenocarcinoma	4.3	46	8.0
Cervical intraepithelial neoplasia II, III	6 including 1 squamous cell carcinoma in situ	13.0	66	11.5
Cervical intraepithelial neoplasia I, changes of human papillomavirus	19	41.3	57	10.0
Endometrial hyperplasia†	0	NA	29	5.1
Endocervical polyps	4	8.6	35	6.1
Ectopic decidua	1		NA	
Ectopic endometrium	1		NA	
Vaginal postoperative granuloma	1		NA	
No cause of AGUS determined	11	23.9	NA	
No biopsy	3		552	
Lost to follow-up	3		NA	

*Frequency calculations for cancer, high-grade squamous intraepithelial lesions, low-grade squamous intraepithelial lesions–changes of human papillomavirus, polyps, and no cause determined are based on cases evaluated with colposcopy and biopsy.
†Not all women were evaluated with endometrial sampling.

Results

Study Group Description

From 1 January 1997 to 31 December 1998, the practice performed 10,564 Papanicolaou smears. Fifty-two patients (0.5%) had AGUS Papanicolaou smears. The average age of the AGUS group was 35 years (range 18–64 years). Forty-five patients had colposcopy. Of the remaining 7 patients, 3 were lost to follow-up. One had a hysterectomy before colposcopy was performed. Pathologic examination of her (removed) cervix and uterus showed a myometrial ectopic pregnancy with decidual invasion of the cervix. No cancer or dysplasia was found. These histologic findings are included in our calculations and Table 1. The remaining 3 patients not lost to follow-up had Papanicolaou smears after the initial AGUS finding; in 2 women cytologic findings have been normal during the year's follow-up. In the third, the Papanicolaou smear after the AGUS Papanicolaou smear was a high-grade squamous intraepithelial lesion. She, unfortunately, refused further evaluation. Her high-grade cytologic result is not included in our frequency calculations. Average time from AGUS Papanicolaou smear to colposcopy was 7 months, with a range of 1 to 29 months.

Biopsy Results

The routine evaluation for AGUS is described in the Methods section. The following procedures were performed on women in the study group: 45 had cervical biopsy at colposcopy (the 46th cervical biopsy was obtained at hysterectomy), 35 had endocervical curettage, 26 had endometrial biopsy, 9 had LEEP or cone biopsy, and 3 had hysterectomy (1 for ectopic pregnancy). These evaluations yielded the following findings: CIN I-HPV changes were found in 19 women, and high-grade dysplasia was found in 6 women, including 1 with squamous cell carcinoma in situ, as a result of cervical biopsy. Endocervical curettage showed that 2 women had endocervical atypia and 4 women had benign cervical polyps that were believed to be the source of the AGUS. Endometrial biopsy showed two cases of adenocarcinoma, and hysterectomy confirmed two cases of cancer of the endometrium. Ages of women with endometrial adenocarcinoma were 39 and 54 years.

LEEP and cone biopsies showed pathologic diagnoses of koilocytosis-atypia in 4 women, high-grade dysplasia in 2 women, low-grade lesion in 1 woman, and adenocarcinoma (previously seen on endometrial sampling) in 1 woman. Table 1 displays colposcopy-biopsy findings, listing the highest grade lesion found. For 1 woman the AGUS Papanicolaou smear was believed to be due to a vaginal granuloma found after a vaginal hysterectomy; in 2 others AGUS was believed to be due to ectopic (cervical) endometrium and ectopic decidua, respectively. The remainder of the women with AGUS Papanicolaou smears had evaluation and treatment for benign diagnoses, with the five exceptions noted below.

Follow-up Papanicolaou smear results were available for 48 of 52 women. With the exception of 1 woman who had persistent AGUS (and subsequently had a cone biopsy), 2 had atypical squamous cells of undetermined significance, 1 had a high-grade squamous intraepithelial lesion and incomplete evaluation (mentioned above), and 1 was being observed for a persistent low-grade squamous intraepithelial lesion. After treatment, none had progressed to higher grade lesions in the subsequent 18 months. Twenty-three women had pelvic ultrasound examinations; no extrauterine pathologic changes were found. The usefulness of measuring endometrial thickness cannot be addressed from this small sample.

A comparison group of a combined five series of women with AGUS Papanicolaou smears[2,4–7] (n = 1,124, and 572 evaluated with colposcopy) had a prevalence of 7.5% adenocarcinomas (predominantly of the endometrium, but including extrauterine). Less than 1% had squamous cell carcinomas; 11.5% had high-grade dysplasias including CIN II–III, carcinoma-in-situ, and adenocarcinoma in situ; 10% had CIN I; and 5.1% had (potentially precancerous) endometrial hyperplasia.

Discussion

Our findings of 2 cancers and 6 high-grade dysplastic lesions from 52 AGUS Papanicolaou smears indicate that this diagnostic category is to be taken seriously. Although AGUS Papanicolaou smears are not common, findings in this category are troubling. First, there is a frequent (19.5%) association of AGUS with cancer and high-grade dysplastic lesions.[2,4–7] Second, in contrast with squamous cell cancers, glandular lesions of the endocervix are more difficult to visualize and sample with a colposcope because of endocervical location, multicentricity, and small size.[11] Third, a precise cytologic diagnosis is subject to "difficulties in microscopic interpretation."[5,11,12] Fourth, cervical adenocarcinoma is becoming more common in young women.[10] Fifth, glandular cell abnormalities can occur from the squamocolumnar junction proximal to the endocervical canal, involving endometrium, fallopian tubes, and ovaries, and can even include glandular nonuterine cancers, including ovarian, colon, and breast.[10]

A comparison group of 572 women with AGUS Papanicolaou smears investigated with biopsy had the following diagnoses: cancer (8%), high-grade dysplasia (11.5%), low-grade dysplasia (10%), endometrial polyps (6.1%), and endometrial hyperplasia (5.1%).[2,4–7] We found a similar prevalence of these more serious diagnoses in our series (Table 1). The frequency of women with CIN I-HPV changes in our series (41%) was much greater than that reported in the comparison group (10%). The younger age of our study group (average age 35 years compared with mid-40-year-olds where reported in the comparison group)[5,7] could partially explain the increased finding of CIN I-HPV. Another series of women[14] with a mean age of 39 years also had a higher proportion of low-grade (16%) to high-grade (9%) dysplasias. Endocervical polyps, rarely occurring ectopic endometrium,[15] and atypical reparative process after hysterectomy[5] have previously been described as the cause of AGUS.

The importance of an AGUS Papanicolaou smear is established by comparison with atypical squamous cells of undetermined significance. In 1993 Taylor et al[8] used colposcopy and biopsy to investigate women with these two Papanicolaou smear findings. High-grade dysplasia was found in 20% of those with AGUS compared with 6% of those with atypical squamous cells of undetermined significance. Additionally, the most common cellular abnormalities detected on biopsy after cytologic diagnosis of AGUS are squamous.[2–4,6,7,9] Although atypical squamous cells of undetermined significance is 10 times more prevalent, AGUS is more likely to have a dangerous cause.

Evidence that not all providers of gynecologic primary care are aware of the importance of an AGUS Papanicolaou smears is given by a recent series in which less than one half of the women

Management Guidelines for Patients with AGUS (Atypical Glandular Cells of Undetermined Significance) Papanicolaou Smears

- All women with AGUS should have colposcopy with ECC (endocervical curettage), even if the endocervical canal looks normal through the colposcope.
- The entire vagina should be colposcopically evaluated.
- All women with negative colposcopy examination and ECC should be followed up closely, with Papanicolaou smears every 4 to 6 months until a minimum of four follow-up negative Papanicolaou smears have been obtained.
- Cone biopsy or electrosurgical loop excision is undertaken if the ECC is positive for neoplasia, unless invasive cancer is diagnosed on the curettings or on biopsy, which requires a radical hysterectomy or radiotherapy or both.
- Endometrial biopsy, hysteroscopy, or a dilation and curettage is undertaken if atypical cells appear to be of endometrial origin.
- Consider conization or electrosurgical loop excision when colposcopy and ECC are negative in AGUS favoring neoplasia, or unexplained persistent AGUS when the cellular type is most likely of endocervical origin.
- A cervical conization for glandular atypia should be long (2.0–2.5 cm) and should contain the entire cervical transformation zone.

Figure 1. American Society for Colposcopy and Cervical Pathology–ASCCP Management guidelines for patients with Papanicolaou smears that have atypical glandular cells of undetermined significance (AGUS). From Cox JT. ASCCP practice guidelines and management of glandular abnormalities in the cervical smear. J Lower Gen Tract Dis 1997;1:41–5, by permission.

were evaluated with colposcopy.[3,6,7] "AGUS is still a relatively new diagnosis that has no widely accepted protocol for patient evaluation among general medical providers. . . ," commented Chin et al[16] on the results of a year 2000 population-based study.

The American Society for Colposcopy and Cervical Pathology management guidelines for patients with AGUS Papanicolaou smears are summarized in Figure 1.[10] The question of which women with AGUS need endometrial sampling has yet to be answered. Those with cytologic changes suggestive of endometrial lesions and neoplasia clearly do require endometrial evaluation. In contrast, "AGUS: unqualified," and "AGUS: favor reactive," are significantly less often associated with adenocarcinoma of the endometrium.[3,5] The National Cancer Institute, in its *Interim Guidelines for Management of Abnormal Cervical Cytology*[17] agrees that management of AGUS –unqualified or favor reactive, "is not established." Their guidelines list Papanicolaou smears with a cytology sampling brush, endocervical curettage, and hysteroscopy, along with endometrial sampling, as "procedures that may resolve the diagnosis."

Patient age also plays a role in deciding which women should have endometrial sampling. Some sources[4,18] suggest that women less than 35 years old with AGUS are unlikely to have endometrial disorders. Medalie found "squamous lesions and endocervical gland lesions on aggregate occurred in younger patients (mean age 39 years) than did endometrial lesions (mean age, 63 years)."[5] Because of irregular shedding, repeat cytologic examination has poor sensitivity to detect endometrial lesions. The risk of missing a rare cancer in a young woman with a "favor reactive" or unqualified AGUS must be weighed against the risks of endometrial sampling. The patient should be included in this decision.

Limitations

That we had to hand search the Papanicolaou smear logs makes it possible that some AGUS Papanicolaou smears were missed. If this were true, our findings would underestimate the prevalence of AGUS. Additionally, endometrial sampling was left to the discretion of the colposcopist (26 of 45 women) and could have contributed to an underestimation of endometrial lesions as well. Although we had more than 10,000 Papanicolaou smears for review, AGUS is an infrequent diagnosis. Thus, we did not have the quantity of AGUS Papanicolaou smears available to ascertain the frequency of some diagnoses, eg, cervical adenocarcinoma in situ and endometrial hyperplasia, in our primary care setting.

We questioned whether the prevalence of AGUS and its associated pathologic changes found in our populations would be similar to that of an institution-based comparison group. The 0.5% prevalence of AGUS in our study group is consistent with 0.4% in a comparison group of 312,536 Papanicolaou smears. Our findings of dysplastic and cancerous lesions in 17.4% of women with AGUS undergoing biopsy is also consistent with 19.5% similar lesions found in comparison group of women who had biopsy for AGUS. We acknowledge, however, that our case series cannot prove equivalence. To achieve a credible 95% confidence interval of 14% to 23% around the 19.5% frequency of expected dangerous lesions, the sample size would need to be increased to 300 biopsies

from 70,000 Papanicolaou smears. Nevertheless, this series is the only one we know that is solely from a primary care, non-obstetrics-gynecology setting. There was considerable delay in evaluation of some patients, with a maximum interval of 29 months. While low-grade squamous intraepithelial lesions often regress, the time delay made it more likely that serious underlying pathologic changes, if present, would be found.

In conclusion, this series collected during a 2-year period in a large, urban, family health center affirms that AGUS is potentially dangerous and occurs in about 1 in 200 Papanicolaou smears. Clinical practice guidelines recommend that patients with AGUS should be evaluated with colposcopy and endocervical curettage.[10] Although guidelines for endometrial sampling are undetermined, consensus supports it in women 35 years old and older and in those with the laboratory result of AGUS, favor neoplasia or suggestive of endometrial source. AGUS does have clinical importance in primary care, heralding dysplastic lesions in both 17.4% of the patients evaluated in our series and 19.5% of those in a comparison group of 572 women with AGUS and biopsy.[2,4–7]

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