Original Article

Histological Follow-Up in Patients with Atypical Glandular Cells on Pap Smears

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Abstract

Context: Atypical glandular cells (AGCs) result in the Papanicolaou (Pap) smear may be associated with significant genital and nongenital neoplastic processes. **Aims:** To evaluate the underlying histopathology in women who had AGCs on Pap smears. **Settings and Design:** Retrospective cross-sectional study. **Patients and Methods:** Clinicopathological data of patients who had AGC on Pap smears and underwent histological workup between January 2004 and December 2014 were retrieved from the computerized database of a tertiary care center. Patients with a prior history of cervical intraepithelial neoplasia or gynecological cancer were excluded. **Statistical Analysis Used:** Chi-square test or Fisher's exact tests were used as appropriate. **Results:** Cytological examination of the uterine cervix was carried out in 117,560 patients. We identified 107 patients (0.09%) with AGC and 80 of those with histological follow-up were included in the study. The median age at diagnosis was 47 years (range, 18–79), and 32 women (40%) were postmenopausal, while 56 (70%) had gynecological symptoms. Significant preinvasive or invasive lesions on pathological examination were detected in 27 (33.8%) patients, including 12 endometrial adenocarcinomas (15%), 8 cervical carcinomas (10%), 3 cervical intraepithelial neoplasia II/III (3.75%), 2 ovarian adenocarcinomas (2.5%), and 2 metastatic tumors (2.5%). Univariate analysis showed that postmenopausal status ($P < 0.001$), age >50 years old ($P < 0.001$), having symptoms at the time of admission ($P = 0.041$), and AGC "favor neoplasia" smear results ($P = 0.041$) were the clinical factors associated with significant pathological outcome. **Conclusions:** Patients with AGC on Pap smears should be evaluated vigilantly with histological workup, especially if they are postmenopausal or symptomatic.

Keywords: Atypical glandular cells, carcinoma *in situ*, cervical intraepithelial neoplasia, neoplasms

Introduction

Cervical cytological evaluation with Papanicolaou (Pap) smear is the standard screening test for cervical malignant and premalignant lesions. Positive screening may reveal either squamous or glandular cell abnormalities. Glandular cell abnormalities are found far less commonly than squamous cell abnormalities.[1] According to the literature, glandular cell abnormalities are found in <1% of cervical cytology samples and atypical glandular cell (AGC) incidence varies from 0.1 to 2.1% in the literature.[2,3] AGCs are defined as cells that demonstrate changes beyond those encountered in benign reactive processes, still are not sufficient for the diagnosis of adenocarcinoma.[4] Although these cells usually originate from the glandular epithelium of the endocervix or endometrium, they may originate from various locations such as salpinges, ovary, or other intraperitoneal organs.[5] According to the Bethesda 2001 system, glandular cell abnormalities are subclassified into: (i) AGCs either endocervical (EC), endometrial (EM), or not otherwise specified (AGC–NOS); (ii) AGCs favor neoplastic (AGC-FN), either EC or not otherwise specified; (iii) EC adenocarcinoma *in situ* (AIS); and (iv) adenocarcinoma.[6,7]

The identification of AGCs in a Pap smear is clinically important due to its close association with premalignant and malignant diseases. In the literature, 9–38% of the women with AGC have cervical intraepithelial neoplasia (CIN) 2, CIN 3, and AIS; 3–17% have invasive carcinomas.[2] The commonly detected malignancies in patients with AGC cytology is EM adenocarcinoma, EC adenocarcinoma, and squamous cell

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cervical carcinoma. Occasionally, ovarian or fallopian tube malignancy could be detected. Ovarian cancer has been reported in 0.1–0.6% of women with AGC in the literature.[8,9] Thus, patients with AGC require further aggressive diagnostic evaluation for premalignant or malignant conditions of the cervix, endometrium, ovary, and fallopian tube. Colposcopic examination, cervical biopsy, EC curettage, EM biopsy, and gynecologic ultrasonography should be considered for women with AGC smear results to detect possible malignant or premalignant diseases.[5,10,11] Although a number of studies have addressed the incidence, clinical implications, and management of patients with AGC, the results have varied significantly. Therefore, this study was conducted to evaluate the significance of AGC by analyzing the final histologic diagnosis results attained via histologic follow-up.

Patients and Methods

Clinicopathological data of patients who had AGC on Pap smears between January 2004 and December 2014 were retrieved from the computerized database of a tertiary care center. Liquid-based cytology (ThinPrep or SurePath systems) system was used for liquid-based cytological analysis. Patients with AGC on cervical cytology who underwent histopathological workup at our Department of Obstetrics and Gynecology were included. Patients with previous personal history of CIN or any gynecological cancer were excluded. Relevant study flowchart is presented in Figure 1. Following AGC result, cervical colposcopy with directed cervical biopsies and sampling of the EC canal was performed by gynecologic oncologists in our department. We performed EM sampling for all patients aged 35 years or older. For younger patients EM sampling was done if they had risk factors for EM cancer, including abnormal uterine bleeding, obesity, or polycystic ovarian syndrome. The clinical and pathological characteristics including patient's age, symptoms, menopausal status, Pap test findings and subclassifications, EM, EC, or cervical biopsy results were evaluated.

The Institutional Ethical Committee approval was not sought as this study represented a retrospective database review.

Statistical Package for the Social Sciences, version 17 (SPSS Inc., Chicago, IL, USA) was used for the data record and statistical analyses. *P* value <0.05 was considered significant. Chi-square test or Fisher's exact tests were used, as appropriate.

Results

Cytological examination of the uterine cervix was carried out in 117,560 patients between January 2004 and January 2015. Of these patients, 107 were diagnosed with AGC at a detection rate of 0.1%. After exclusion of cases with previous history of gynecological cancer or cervical preinvasive disease and those without proper follow-up, 80 patients were included in the study with a median age at diagnosis as 47 years (range: 18–79 years). Of these women, 32 (40%) were postmenopausal and 56 (70.0%) had gynecological symptoms.

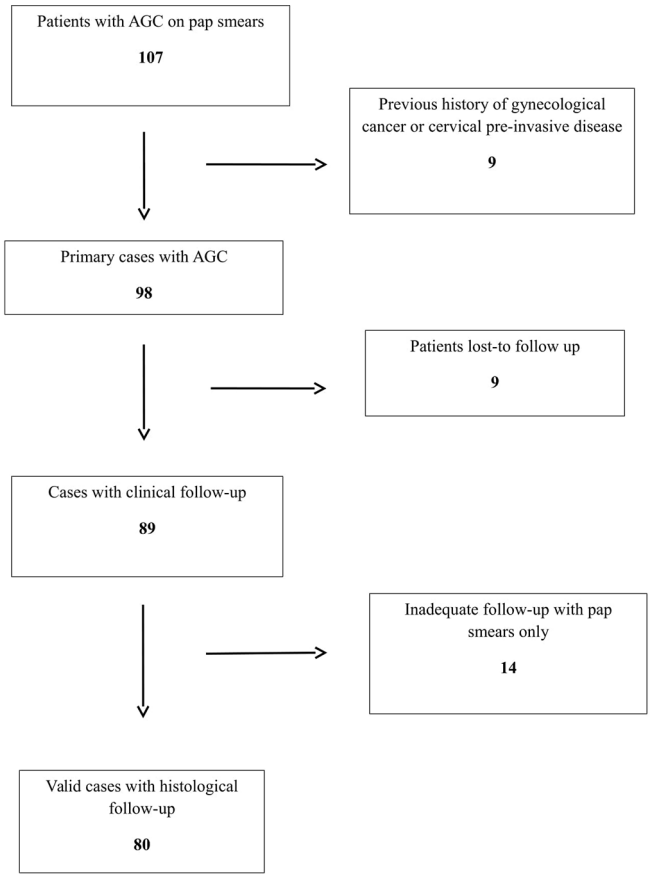

Figure 1: Study flowchart

The most frequent symptom was postmenopausal bleeding, which was found in 35% of study population. Menorrhagia was present in 22 patients (27.5%). Two patients (2.5%) had post coital bleeding and four (5.0%) had chronic pelvic pain. The remaining 24 (30%) AGC cases were detected on routine follow-up in asymptomatic women.

Among the 80 patients with AGC, 39 (48.8%) had AGC-NOS (not otherwise specified), 18 (22.5%) had AGC-EC (of endocervical origin), 14 (17.5%) had AGC-EM (of endometrial origin), 4 (5.0%) had AGC-FN, 3 (3.7%) had AGC-EX (from extragenital origin), 2 (2.5%) had AGC and atypical squamous cells of undetermined significance (ASC-US) [Figure 2].

Histopathologic evaluation confirmed a clinically significant pathology in 27 patients with AGC (33.8%) [Table 1]. Of these, endometrium was the most common (15%) site for significant pathology, including 10 cases with endometrioid EM adenocarcinoma, 1 with serous EM adenocarcinoma, and 1 with EM carcinosarcoma. A total of seven cases had cervical squamous lesions, which were squamous cell cervical carcinoma in four and CIN 2/3 in three patients. Four cases (5.0%) had invasive cervical adenocarcinoma.

When the association with significant pathology was evaluated according to different AGC subgroups, a diagnosis of AGC-FN was the most serious one that was associated

with invasive disease in all cases (P = 0.04). It was followed by AGC-EX (AGC of extragenitalial origin) which was associated with invasive malignancy in 2 out of 3 patients (66.7%) [Table 2].

In an attempt to demonstrate the risk factors for significant pathology in patients with AGC, univariate analysis was performed [Table 3]. Being postmenopausal, being aged 50 years or older, and having a gynecologic symptoms during initial presentation were found to be statistically significant risk factors for having such pathologies [$P < 0.001$, $P < 0.001$, and $P = 0.04$, respectively).

Discussion

The frequency of AGC according to the Bethesda system is reported to range from 0.1 to 2.1% in the literature.[2,3,12] In accordance with the literature, AGC was detected in approximately 0.1% of all cervical cytologies in our study. Although rarely reported, AGC diagnosis should raise the clinician's suspicion for significant pathologies either in the genital tract or in extragenital structures. In the literature, the rates of malignant or premalignant lesions ranged from 22 to 53% in patients with AGC.[13] Kim *et al.* reported that malignant diseases were found in 24 patients (28.9%) during histological follow-up among 83 patients with AGC on Pap smear. In their study group, cervical adenocarcinoma (8/24 patients, 33.3%) was the most frequently observed malignant disease, followed by EM cancer (6/24 patients, 25%), ovarian cancer (4/24 patients, 16.6%), breast cancer (3/24 patients, 12.5%), and stomach cancer (3/24 patients, 12.5%).[14] Krane *et al.* detected malignant or premalignant lesions in 34.3% of 108 patients with AGC. In their study, 24 patients had cervical neoplasia, while 13 had other neoplasia consisting of five EM adenocarcinoma, 4 EM hyperplasia, 2 ovarian carcinoma, and 2 fallopian tube adenocarcinoma.[15] Mood *et al.* reported that neoplastic or preneoplastic diseases were detected in

Table 1: Histopathologic results in patients with AGC

Histopathologic results	*n* (%)
Nonsignificant genital lesion	53 (66.25%)
Significant pathology	27 (33.75%)
Endometrial adenocarcinoma	10 (12.5%)
Cervix squamous cell carcinoma	4 (5.0%)
Cervix adenocarcinoma	4 (5.0%)
CIN 3	2 (2.5%)
CIN 2	1 (1.25%)
Endometrial carcinosarcoma	1 (1.25%)
Endometrial serous carcinoma	1 (1.25%)
Ovarian serous carcinoma	1 (1.25%)
Ovarian mucinous carcinoma	1 (1.25%)
Krukenberg tumor	2 (2.5%)
Total	80 (100%)

AGC: Atypical glandular cell, CIN: Cervical intraepithelial neoplasia

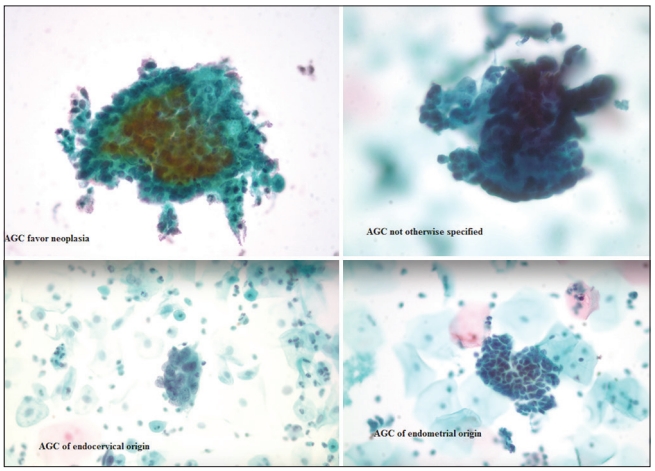

Figure 2: Glandular cell abnormalities

Table 2: Significant pathological diagnoses according to AGC subgroups

	AGC-NOS (*n*=39)	AGC-EC (*n*=18)	AGC-EM (*n*=14)	AGC-FN (*n*=4)	AGC-EX (*n*=3)	AGC and ASC-US (*n*=2)	Total (*n*=80)
Endometrial lesion	7 (18.0%)	1 (5.5%)	2 (14.3%)	1 (25.0%)	1 (33.3%)	-	12 (15.0%)
Endometrioid adenocarcinoma	5 (12.8%)	1 (5.5%)	2 (14.3%)	1 (25.0%)	1 (33.3%)	-	10 (12.5%)
Serous adenocarcinoma	1 (2.6%)	-	-	-	-	-	1 (1.25%)
Carcinosarcoma	1 (2.6%)	-	-	-	-	-	1 (1.25%)
Cervical squamous lesion	3 (7.7%)	2 (11.1%)	-	1 (25.0%)	-	1 (50.0%)	7 (8.8%)
Squamous cell carcinoma	2 (%5.2)	-	-	1 (25.0%)	-	1 (50.0%)	4 (5.0%)
CIN II/III	1 (2.6%)	2 (11.1%)	-	-	-	-	3 (3.7%)
Cervical glandular lesion	2 (5.2%)	-	-	2 (50.0%)	-	-	4 (5.0%)
Cervical adenocarcinoma	2 (5.2%)	-	-	2 (50.0%)	-	-	4 (5.0%)
Ovarian lesion	2 (5.2%)	-	-	-	-	-	2 (2.5%)
Serous adenocarcinoma	1 (2.6%)	-	-	-	-	-	1 (1.2%)
Mucinous adenocarcinoma	1 (2.6%)	-	-	-	-	-	1 (1.2%)
Metastatic tumor	1 (2.6%)	-	-	-	1 (33.3%)	-	2 (2.5%)
Krukenberg tumor	1 (2.6%)	-	-	-	1 (33.3%)	-	2 (2.5%)
Total	15 (38.5%)	3 (16.6%)	2 (14.3%)	4 (100.0%)	2 (66.7%)	1 (50.0%)	27 (33.7%)

AGC: Atypical glandular cells, AGC-NOS: AGC not otherwise specified, AGC-EC: AGC of endocervical origin, AGC-EM: AGC of endometrial origin, AGC-FN: AGC favor neoplasia, AGC-EX: AGC of extragenitalial origin, AGC and ASCUS: AGC and atypical squamous cells of undetermined significance

Table 3: Risk factors for significant pathology in patients with AGC

	Significant pathologic results *n* (%)	Nonsignificant pathologic results *n* (%)	*P*
Menopausal status			
Postmenopausal	20 (62.5%)	12 (37.5%)	<0.001
Premenopausal	7 (14.6%)	41 (85.4%)	
Symptoms			
Any	23 (41.1%)	33 (58.9%)	0.04
None	4 (16.7%)	20 (83.3%)	
Age			
≥50	20 (66.7%)	10 (33.3%)	<0.001
<50	7 (14.0%)	43 (86.0%)	
Cytology			
AGC-FN	4 (100%)	0	0.04
Others	23 (30.2%)	53 (69.8%)	
Total	27 (33.7%)	53 (66.3%)	

AGC-FN: Atypical glandular cells favor neoplastic

22 of 44 patients (55.3%). Of those, 15 (68.1%) had cervical premalignant disease and 2 (9%) had cervical adenocarcinoma. Other diseases included EM adenocarcinoma, metastatic lobular breast carcinoma, vaginal adenocarcinoma, simple EM hyperplasia, and nonvillous trophoblastic tissue in that series.[16] In the study from Zhao *et al.*, clinically significant pathology was reported to be 22.8% in women with AGC, which mostly consisted of EM lesions (in 51%) followed by cervical squamous and glandular lesions (in 43%).[17]

In the present study, 27 of 80 patients (33.8%) were diagnosed to have either malignant or premalignant disease. The most common origin of significant pathology was endometrium followed by cervix and ovary. Of patients in our study group, 10 (12.5%) had endometrioid type EM adenocarcinoma, which was the most common invasive pathology. In addition, serous adenocarcinoma was detected in one patient and carcinosarcoma of the endometrium was seen in another. Cervical pathologies included invasive squamous cell carcinoma in four patients, invasive adenocarcinoma of cervix in four, and preinvasive cervical disease in three women. Although the most commonly reported pathologies in patients with AGC are preinvasive and invasive cervical lesions and EM diseases are less likely according to the literature,[9,16] the highest incidence of EM malignancies in the current series may be attributed to the relatively low incidence cervical neoplasms in Turkey compared to EM neoplasia.[18]

On rare occasions, ovarian cancer may also be diagnosed during the further evaluation of women with AGC cytology. The ovarian cancers in this patient population may be primary or metastatic and the metastases mostly originate from the gastrointestinal system.[8] The rates of ovarian pathology in patients with AGC were reported to be <1%.[7,9] However, Tam *et al.* reported that five (3.6%) had ovarian cancer and two (1.4%) had extragenital malignancies among 138 women with AGC.[19] In the present study, ovarian cancer was detected in two patients (2.5%) and extragenital malignancies metastatic to the ovaries were detected in two (2.5%). This high rate of ovarian origin in this series could be a result of relatively small sample size. Nevertheless, in cases without any malignancy detected by pathological evaluation of the cervix and endometrium, abdominal and pelvic imaging modalities as well as serum tumor markers should be used to reveal the ovarian or abdominal origin of malignant glandular cells.

It is apparent that patients with AGC result on cervical cytology carry a significant risk for having a diagnosis of genital or less commonly extragenital invasive or preinvasive neoplasia. The question is whether some women with AGC have more risk of having these neoplasia than others. Several predictive factors were reported on this issue. Tam *et al.*[19] reported that while 67.6% of the 34 patients with AGC-FN had significant pathology, only 19.2% of patients with AGC-NOS had significant pathology. Similarly, Sawangsang *et al.*[20] found that the rate of significant lesions in women with AGC-FN was significantly higher than in women with AGC-NOS. In accordance with the literature, while 38.5% of patients with AGC-NOS had significant pathology, all patients with AGC-FN had significant pathology in our study. In addition, among patients with AGC cytology, age was reported to be a predictor for significant pathology in several studies.[7,9,16,21] Cheng *et al.*[7] showed that women who are aged over 60 years have a higher possibility of having gynecological cancer. The role of age was mentioned by another study where no EM cancers were detected if patients with AGC were younger than 35 years of age.[22] Current study also confirmed the importance of age because the rate of significant pathology was higher if the patient with AGC was aged 50 years or older. The other risk factors for significant pathology in the current series were being in the postmenopausal state and having gynecological complaints during initial presentation.

In conclusion, AGC result on cervical cytology is associated with significant pathology in a considerable proportion of patients. Therefore, such a result should trigger the clinician to thoroughly evaluate the patient with special attention on endometrium and cervix. Ovaries, tubes, and abdominal structures should also be investigated in detail when endometrium and cervix are free of malignancy. It should also be kept in mind that especially older and postmenopausal patients with AGC may carry a higher risk for having premalignant and malignant disease, which may warrant a more aggressive diagnostic workup in those women.

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Conflicts of interest

There are no conflicts of interest.

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