Analyses of atypical glandular cells re-defined by the 2006 Bethesda System: histologic outcomes and clinical implication of follow-up management.

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Summary

Background: To evaluate the histopathology and the long-term follow-up outcome of women who had atypical glandular cells on Pap smears. *Materials and Methods:* All women with atypical glandular cells (AGC) who underwent colposcopic and histopathologic evaluation between January 2005 and October 2010 were reviewed. Patient data were examined up to October 2012, allowing for at least two years of follow-up for all patients. *Results:* Forty-four women with AGC Pap test underwent histologic follow-up during the study period. Overall, upon reclassification of smears, 35 (79.5%) cases were diagnosed with AGC ''not otherwise specified'' (NOS) and nine (20.5%) with AGC ''favour neoplasia''. Seven out of nine patients (77.7%) with AGC ''favour neoplasia'' had significant pathology. On the other hand, only 11 out of 35 cases (31.4%) with AGC ''NOS'' had significant pathology. Significant correlation was found between AGC ''favour neoplasia'' smears and a significant pathology (*p*: 0.01). Of the 44 patients, 18 (40.9%) had significant pathology. Eight patients (18.2%) had low grade cervical intraepithelial neoplasia (CIN 1), four (9%) had high-grade cervical intraepithelial neoplasia (CIN 2 / 3), one (2.2%) had microinvasive squamous cell carcinoma of uterine cervix, one (2.2%) had cervical adenocarcinoma in situ, one (2.2%) had cervical adenocarcinoma, one (2.2%) had endometrial adenocarcinoma, and two (4.5%) had endometrial hyperplasia. *Conclusion:* Reporting AGC in the population is clinically significant due to the high prevalence of underlying preinvasive and invasive diseases (40.9%). The subtypes of the AGC category are significant predictor of such lesions.

Key words: Atypical glandular cells; AGC; AGUS; Favour neoplasia; Not otherwise specified; NOS.

Introduction

The diagnostic category of atypical glandular cells of undetermined significance (AGUS) was introduced by the Bethesda System in 1988 [1]. In 2001, the category was renamed 'atypical glandular cells' (AGC) to avoid confusion with atypical squamous cells of undetermined significance (ASCUS) [2]. The Bethesda system classifies AGC as glandular cells that demonstrate changes beyond those typical of benign reactive processes but that lack unequivocal features of adenocarcinoma. These abnormal glandular cells may be endocervical or endometrial in origin. The Bethesda definition (2001) further divides the glandular cell abnormalities less severe than adenocarcinoma in situ (AIS) and invasive adenocarcinoma into two categories; AGC ''not otherwise specified'' (NOS) and atypical glandular cells (AGC) ''favor neoplasia'' because the risk of neoplasia associated with the latter is substantially higher [3].

The diagnosis of AGC occurs relatively infrequently (0.05-0.74%) compared with other cytological abnormalities [4,5]. Besides its low frequency, the rate of biopsy-proven clinically significant lesions ranges from 9% to 38%, including high-grade squamous cervical intraepithelial neoplasia (CIN2/ 3) and endocervical AIS and 3% - 17% of women with AGC have invasive cervical carcinoma or non-cervical uterine / adnexal carcinoma [6]. Because of the spectrum of neoplasia linked to AGC, initial evaluation must include multiple testing modalities. The 2006 consensus guidelines of American Society of Colposcopy and Cervical Pathology (ASCCP), as well as National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology-V.2.2012, indicates the immediate colposcopic evaluation with endocervical sampling for all women with AGC. Endometrial biopsy is recommended for all women 35 years or older and on younger women with risk factors for endometrial neoplasia (unexplained uterine bleeding or chronic anovulation). As well, testing for high-risk human papillomavirus (HPV) is especially useful as an adjunctive screen in patients with AGC-NOS cytology [6,7].

The objective of this study was to determine the association between atypical glandular cells on Pap smear and clinically significant histology. In this research, the authors also evaluated the long-term (minimum of two years) follow-up outcome of women with an AGC diagnosis in a referral colposcopy-gynecological oncology clinic at a tertiary-care health center.

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Materials and Methods

This retrospective study was approved by the Institutional Review Board at the Kanuni Sultan Süleyman Training and Research Hospital (KSS-TRH). The computerized cytopathology archives and tumor registry databases of KSS-TRH were searched from January 2005 to October 2010 for patients with AGC or AGUS Pap results. The interpretations of AGC were made by staff cytopathologists, based on categories defined by the 2001/2006 Bethesda System. In this study, the authors reviewed the archival smears reported as AGUS and these smears were reclassified by a cytopathologist experienced in cervical cytology, according to the Bethesda 2001/2006 System, reporting the AGC as NOS or ''favor neoplasia''. The patients' clinical information and final diagnoses were not known to the cytopathologist during the review process. For the purpose of this study, patient data were examined up to October 2012, allowing for at least two years of follow-up for all patients.

Women with AGC results were managed according to the American Society for Colposcopy and Cervical Pathology (ASCCP) recommendations [6]. The colposcopic examination, postcolposcopy management including surgical procedures, and pathologic interpretation were performed by gynecologic oncologists and pathologists, respectively. The pathologic results were obtained from one or more of the following sources: tissue biopsy of suspected lesions under colposcopy, endocervical and/or endometrial curettage, loop electrosurgical excision procedure (LEEP) or cold knife conization, and surgical specimens (cervix and uterus). For patients undergoing two or more procedures during the initial evaluation, only the most abnormal histologic diagnoses were recorded. Significant histopathologic findings included CIN 1, CIN2, 3, AIS, endometrial hyperplasia, and cancer of any primary site. In this report CIN terminology is used exclusively for histologic diagnoses. Benign lesions, including endometrial polyp, chronic endocervicitis, endocervical polyp, endocervical tubal metaplasia, and unintentional sampling of the lower uterine segment were also recorded. The postcolposcopy follow-up of women with AGC NOS who do not have CIN or glandular neoplasia histologically identified was to repeat cytological testing at six-month intervals. After four consecutive ''negative for intraepithelial lesion or malignancy'' results were obtained, the patients were advised to return routine cytological testing. In all patients with AGC favour neoplasia, if the initial biopsies were nondiagnostic or negative, then diagnostic excision procedure was performed because of the high risk for underlying premalignant or malignant conditions. Since HPV status has only been investigated in a limited number of patients, the results of this test were not taken into consideration. Cases with cytological interpretations of suspicious for AIS or adenocarcinoma were excluded from the study as well as women with a history of gynecologic malignancy or endometrial hyperplasia. During the study period, approximately 61% of Pap tests were obtained using liquid-based cytology (LBC).

Statistical analyses were performed using the Statistical Package for the Social Sciences software version 13.0 (SPSS). Pearson's chi-square or Fisher's exact tests were used to analyze the categorical variables. The results were considered statistically significant if the p-value was < 0.05.

Results

Over the six-year study period, 42,027 Pap tests were reported. The number of records with AGC / AGUS abnormalities during this period was 49 (0.11%), of which five records were excluded from the study for the following reasons: one record because the further analysis of Pap smears with an initial cytological diagnosis classified as AGUS were considered compatible with benign reactive changes; one record owing to a previous history of endometrial hyperplasia; and one record because further investigations after the AGC result were lost. In addition, two records were excluded owing to management that was against the ASCCP recommendations or because there were no histologic reports although guidelines had been followed. As a result, 44 records were included for analyses. Among the 44 smears from patients with follow-up data, 27 were done by LBC and 17 were conventional smears.

The mean age of the study population was 39.2 ± 7.5 years (range 23 to 51) with a median of 40 years. The average follow-up period was 40.7 months (range 26 to 60). In addition to cervical biopsies and endocervical / endometrial sampling, tissue follow-up specimens included 14 LEEP / cold knife cone biopsies, five hysterectomies, and one radical hysterectomy. Of the 44 patients, 18 (40.9%) had significant pathology. Eight patients (18.2%) had low grade CIN 1, 4 (9%) had high-grade CIN 2 / 3, one (2.2%) had microinvasive squamous cell carcinoma of uterine cervix, one (2.2%) had cervical AIS, one (2.2%) had adenocarcinoma of cervix, one (2.2%) had endometrial adenocarcinoma, and two (4.5%) had endometrial hyperplasia. Both of the AIS and invasive cervical adenocarcinoma patients had concurrent CIN 1, while one microinvasive squamous cell carcinoma patient had synchronous simple hyperplasia. Additionally, two patients (4.5%) with AGC ''NOS'' had vulvar condyloma. Diagnoses of cervical squamous neoplasia after AGC Pap results were significantly more likely than diagnoses of endometrial neoplasia (P: 0.005). The distribution of clinically significant lesions is shown in Table 1. Overall, upon reclassification of smears, 35 (79.5%) cases were diagnosed AGC ''NOS'' and nine (20.5%) were diagnosed AGC ''favour neoplasia''. Seven of the nine patients (77.7%) who had AGC ''favour neoplasia'' had significant pathology. On the other hand, only 11 of the 35 cases with AGC ''NOS'' had significant pathology (31.4%). Significant correlation was found between AGC ''favour neoplasia'' smears and a significant pathology (P: 0.01). Results were analyzed with respect to the initial Pap smear subclassification (Table 2). Of the 18 patients who had significant pathologies, 16 had the diagnoses made during their initial investigations. The remaining two patients had diagnoses made during follow-up visits. Both of them had AGC ''NOS'' smears. One of them had colposcopic examination with endocervical curettage only as the initial investigation. Endometrial sampling was performed after they had abnormally thickened endometrium on pelvic sonography during her infertility work-up. They were finally diagnosed as having simple endometrial hyperplasia. The remaining patient had cervical biopsy with endocervical curettage as the initial investigation and no abnormality had been detected.

Table 1. — *Histological correlation of initial Pap tests with AGC ''NOS" and AGC "favour neoplasia".*

	AGC "NOS" no. (%)	AGC "favour neoplasia" no. (%)
Low-grade CIN	6 (13.6%)	2 (4.5%)
High-grade CIN	2 (4.5%)	2 (4.5%)
Squamous carcinoma of the cervix	-	1 (2.2%)
AIS	1 (2.2%)	-
Adenocarcinoma of the cervix	-	1 (2.2%)
Endometrial hyperplasia (simple/atypical)	1 (2.2%)	1 (2.2%)
Endometrial adenocarcinoma	1 (2.2%)	-

AGC: atypical glandular cell; NOS: not otherwise specified; CIN: cervical intraepithelial neoplasia; AIS: adenocarcinoma in situ

Table 2. — *Analysis of histological diagnosis with respect to the initial Pap smear subclassification.*

	AGC "NOS"	AGC "favour neoplasia"	*p*-value
Significant lesion no. (%)	11/ 35 (31.4%)	7/9 (77.7%)	0.01

Table 3. — *Histological follow-up results according to patient age.*

	< 40 y (n: 23)	≥ 40 y (n:21)	*p*-value
Significant pathology	12/23 (52.1%)	6/21 (28.5%)	0.06
Squamous vs. glandular lesions	11/1	2/4	0.009

Cervical smear was repeated six months later and it was suggestive of presence of high-grade CIN. Colposcopy with endocervical curettage was repeated and the diagnosis of CIN 2 was made. Of those 26 patients who did not have any significant pathology, two had hysterectomies for non-neoplastic gynecological conditions and defaulted on follow-up after the postoperative histopathologic examination. The remaining 24 patients and the other 18 patients who had significant pathology were followed-up with Pap smears with or without colposcopy or endometrial biopsy for a mean of 40.7 months.

Significant benign biopsy diagnoses from 26 women with AGC Pap test results who had non-neoplastic histologic outcomes were also documented. Non-specific chronic cervicitis and reactive squamous metaplasia were the most common benign histologic findings reported. Endocervical polyps, endocervical tubal metaplasia, and endometrial polyps were the first, second, and third most common benign histologic outcomes (15.3%, 11.5%, and 7.6%, respectively).

Results were also analyzed with respect to patient age. When stratified according to age, it was found that AGC results in patients younger than the age of 40 were more significantly associated with CIN 2/3/CxSqCa histologic outcomes than with either tissue findings of endocervical or endometrial glandular neoplasia (*p*: 0.009). Five women over the age 40 years or older, adenocarcinoma / glandular hyperplasia were the most common significant histologic outcomes, including two cases of adenocarcinoma of the uterine cervix and one case of atypical endometrial hyperplasia. On the other hand, a clinically significant lesion was noted in 52.1% of women younger than 40 years and in 28.5% of women aged 40 years or more (*p:* 0.06) (Table 3).

Discussion

Cervical cancer screening has proved to be a valuable method that reduces both the incidence of and mortality from cervical cancer. In contrast to the decreased incidence of squamous cell carcinoma, the prevalence of glandular cell neoplasia of the cervix has increased in countries with screening. Although many studies have addressed AGC cytology, few were based on LBC or carried out the analysis under the subclassification of AGC cytology [8]. In addition, a significant number of patients with AGC in previous study did not receive appropriate investigations and histologic follow-up.

The incidence of AGCs in the present study (0.11%) is relatively low compared with that found in previous studies in other countries (0.2% - 0.8%) [9-11]. The differences between the results from the Western series and the present experiences may be attributed to the fact of the low prevalence of cervical cancer in Turkey. The prevalence of preinvasive cervical neoplasia and invasive cervical neoplasia in Turkey has been reported as 1.7% and 0.06%, respectively, by a Turkish cervical cancer and cervical cytology research group [12]. The prevalence of abnormal cervical cytology based on the data from 33 healthcare centers in this study was two to five times lower than in Europe and North America. Therefore, authors concluded that, this might be due to socio-cultural differences and lower HPV prevalence rate in Turkey.

The finding of AGCs is important clinically because the percentage of cases associated with underlying high-grade disease is higher than for ASC-US. Various studies have found that 9% to 54% of women with AGCs have biopsy-confirmed CIN, 0% to 8% have biopsy confirmed AIS, and less than 1% to 9% have invasive carcinoma [13]. The present experience with AGC patients is very similar to that reported in the literature and the incidence of clinically significant uterine lesions for AGC patients with a histologic follow-up was 40.9%. According to results of the present study, the subtypes of AGC reflected the incidence of significant pathology. Among the cases of AGC ''favour neoplasia'' and AGC ''NOS'', significant disease was found 77.7% and 31.4% of women, respectively. These findings support the Bethesda 2001 subclassification of AGC cytology and ASCCP 2006 recommendations, although interpretation of AGC is poorly reproducible among cytologists primarily due to subjective interpretation and subcategorization. Thus, women with AGCs should undergo extensive examination by colposcopy, endocervical curettage, endometrial sampling, and further investigation may include hysteroscopy with strong consideration given the likelihood of the involvement of organ sites.

Several factors contribute to the difficulty in studying the natural history and progression of glandular atypia's in gynecologic cytology. First is the relatively rare occurrence of AGCs. There are also no well-defined preneoplastic endocervical lesions compared with squamous counterparts. The next factor is that AGC is a heterogeneous entity caused by a wide variety of squamous, endocervical, and endometrial lesions. Finally, the frequency of clinically significant lesions found on subsequent follow-up varies not only with the population's risk of development of cervical cancer, but also with the age distribution among different patents populations [14,15]. In the present study, the mean age of the women with AGCs was 39.2 ± 7.5 years (range 23 to 51) with a median of 40 years. It is interesting to note that although younger patients (< 40 years) were more likely to have a clinically significant uterine lesion (54.5%) on follow-up compared with older patients (> 40 years) (27.2%), the proportion of high-grade squamous or glandular lesions was higher in older than in younger patients. In the present analysis, all glandular neoplasms including; two case of adenocarcinoma of the uterine cervix, one case of endometrial adenocarcinoma, and one case of atypical endometrial hyperplasia occurred in women older than 40 years of age. In one retrospective study, the rate of malignancy was highest in women 50 years or older (15% including: endometrial 12.7%; ovarian cancer 1.4%; cervical adenocarcinoma 0.9%) compared with those ages 40 to 49 years (2.8%) or less than 40 years (2.0%) [16].

The present study confirms that squamous lesions are very common diagnoses (29.5%) in women with a Pap smear result suggesting AGC [4]. Among these women, 18.2% had low grade CIN, 9% had high-grade CIN, and 2.2% had squamous cell carcinoma. On the other hand, adenocarcinomas (6.8%) were the most common malignancies identified in women with AGC (75% of all diagnosed malignancy); 2.27% had endometrial adenocarcinoma, 2.27% had cervical AIS, and 2.27% had adenocarcinoma of the cervix. Based on data from largest published meta-analysis [17], endometrial adenocarcinoma is still the most commonly diagnosed malignancy in women with AGC (57.6%), followed by cervical adenocarcinoma (23.6%), and cervical squamous cell carcinoma (5.4%). The present authors found approximately a 2.27% incidence of endometrial adenocarcinoma among patients with AGCs in Pap smears. This is consistent with reports in two previous publications [18,19], and is lower than the 6% reported by Zweizig et al [20]. In addition, AGC has been associated with ovarian, fallopian tube, or vaginal cancer, and some cases of colon or breast cancer have also been reported [17,21]. Ovarian cancer has been reported in 0.1% to 0.6% of women with AGC [16,22].

It is noteworthy that in the present series, two patients with previously undiagnosed squamous and endometrial premalignant lesions were found during follow-up visits by repeat cytological testing at six-month intervals. One patient had a simple endometrial hyperplasia, while the other one had a high grade squamous intraepithelial lesion. Some data suggest that women with persistent AGC-NOS (two or more cytology results) are at especially high risk of significant glandular disease (three of five women had endometrial adenocarcinoma in one study) [15]. Women with negative findings on initial evaluation require further assessment, including repeat assessment of the cervix or endometrium. Further evaluation may consist of repeat cervical cytology, colposcopy, HPV testing, endometrial biopsy, or cervical conization.

It has been established that neither HPV-DNA testing nor repeat cervical cytology is sensitive enough to be used alone as an initial screening test for women with AGC. Studies have shown that only 24% to 45% of AGC cytology test positive for high-risk HPV-DNA [23,24]. However, patients with AGC cytology who also test positive for high-risk HPV-DNA have an increased risk for cervical pathology. One study demonstrated that 96% of women with biopsy-confirmed CIN 2-3 and 85% with AIS or invasive cervical adenocarcinoma had AGC cytology and were positive for high-risk HPV-DNA [23]. As well, Zeferino et al. reported that the probability of detecting a significant cervical lesion, either squamous or glandular, in women with AGC ''NOS'' and negative HPV-DNA test is low [3]. HPV testing has also limitations although it was considered to have high sensitivity for the detection of cervical lesions. Of 251 women with AGC and a negative HPV test, Chen and Yang [25] found one case of CIN 2, and three cases of adenocarcinoma in situ. On the other hand, HPV-DNA testing does not appear to add any significant clinical information in cases of AGC ''favour neo-

plasia'', since the likelihood of a glandular lesion, especially of glandular origin, is higher in these cases, and is not dependent on the result of the HPV-DNA test [3].

As a consequence, the incidence of AGC on Pap smear in a large population is low, but the risk associated with such a diagnosis necessitates follow-up and investigation. On the basis of the present results, for women with AGC ''favour neoplasia'', the risk is substantial and a thorough evaluation is indicated. In addition, in a small proportion of patients, these clinically significant lesions were diagnosed during follow-up visits within at least one year of the initial cytological diagnosis of AGCs. Until a better understanding of the natural history of AGCs and the relationship of this finding to high-grade squamous or glandular lesions are obtained, patients with AGCs should be followed-up for a substantial period despite initial negative findings.

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