EJGO European Journal of Gynaecological Oncology

Clinical significance of atypical glandular cells in Pap tests: experience of a gynecologic oncology center in 74 patients

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Summary

Purpose of the investigation: To investigate the clinical importance of atypical glandular cells (AGC) on Pap Smear Test (PST). *Materials and Methods:* Clinical records of 74 patients that were detected with AGC were evaluated. *Results:* Of the 55 patients detected with AGC-not otherwise specific (AGC-NOS), 42 (76.3%) had negative histopathologic results, eight (14.5%) patients were detected with cervical squamous intraepithelial lesions, one (1.8%) patient was detected with squamous cell cervical cancer, three (5.4%) patients with endometrial hyperplasia, and one (1.8%) patient with endometrial cancer. Of the 19 patients detected with AGC-favor neoplasia (AGC-fn), seven (36.8%) patients had negative histopathologic results, five (26.3%) patients were presented with squamous intraepithelial lesions, one (5.2%) patient was detected with adenocarcinoma in situ, two (10.5%) patients with squamous cell cervical cancer, one patient had complex atypical endometrial hyperplasia, and one (5.8%) patient with endometrial cancer. The incidence of premalignant lesions in the patients with AGC-NOS and AGC-fn was 20% and 36% and the incidence of malignant lesions in the two groups was 3.6% and 26.3%, respectively. *Conclusion:* Patients detected with AGC on PST should be closely followed up and evaluated by using colposcopy and endocervical and endometrial curettage.

Key words: Atypical glandular cells; Pap smear; Management.

Introduction

Cervical cancer is the second most common gynecological cancer in developing countries after endometrial cancer [1]. With the establishment of screening programs and the improvement of early diagnosis and treatment modalities in the recent period, the incidence of cervical cancer has retreated to the sixth rank in developed countries, even to the tenth rank in some of them [2]. According to the Turkish Health Ministry cancer records, cervical cancer represents the eighth rank in all gynecological cancers in Turkey [3]. Pap smear test (PST) is an inexpensive, widely available, and effective cervical screening method described by Papanicolaou and Taut [4]. To increase the effectivity of PST, the Bethesda System (TBS) was developed at a National Cancer Institute workshop in 1988 and refined in 1991 [4]. TBS, as compared to previous systems, was the first method to classify glandular epithelial cell abnormalities [5]. TBS also introduced two terms including atypical squamous cells of undetermined significance (ASCUS) and atypical glandular cells of undetermined significance (AGUS), which were renamed as atypical squamous cells (ASC) and atypical glandular cell (AGC) in 2001, respectively. In addition, the revision performed in 2001 divided AGC into two subcategories as AGC - not otherwise specific (AGC-NOS) and AGC-favor neoplasia (AGC-fn) [6]. AGC accounts for almost 0.21% of cervical cytology [7]. About 8% of cases AGC are associated with malignant lesions and require extensive investigation [8]. An extensive investigation of patients with AGC-NOS can be performed by using colposcopy with punch biopsy (as needed) and endocervical curettage. Moreover, although routine endometrial sampling is recommended for patients aged over 35 years, endometrial curettage is advised for patients aged below 35 years that are present with endometrial pathology or irregular menstrual bleeding [6-8]. In patients with AGC-fn, due to an increased risk for cervical intraepithelial neoplasia (CIN), routine excisional procedures should be performed after colposcopy, endocervical curettage, and endometrial sampling [7, 8].

In this study, the authors retrospectively evaluated the histopathologic outcomes of the patients that were detected with AGC (AGC-NOS and AGC-fn) on PST and they aimed to investigate the clinical importance of these outcomes.

Revised manuscript accepted for publication December 21, 2017

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXIX, n. 6, 2018
doi: 10.12892/ejgo3977.2018

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Materials and Methods

Clinical records of the patients that were referred to Kanuni Sultan Suleyman Training and Research Hospital Gynecology Department between 2005 and 2016 were retrospectively reviewed. In accordance with the 2013 algorithm of the American Society for Colposcopy and Cervical Pathology (ASCCP), only the patients that underwent cervical cancer screening were included in the study. In total, 80 patients diagnosed with AGC were detected in the database, which also included the patients who were initially diagnosed as having AGUS and were re-evaluated by a pathologist according to the 2001 Bethesda classification. Three patients aged over 35 years, whose endometrial biopsy records were not reachable, were excluded from the study. In addition, three other patients whose smear results were classified as AGUS on 1998 Bethesda classification and were rediagnosed as having AGC-fn on 2001 Bethesda classification, but underwent no diagnostic excision procedure, were also excluded from the study. Of the remaining 74 patients, 55 were classified as AGC-NOS and 19 as AGC-fn.

Diagnostic colposcopy and endocervical curettage were performed in all the patients. During colposcopy, histopathologic sampling was performed on the sites where an abnormal endometrial appearance was detected. Endometrial curettage was performed for all the patients aged over 35 years. In patients aged below 35 years, endometrial curettage was performed when abnormal uterine bleeding or endometrial irregularity was noted. Depending on histopathologic evaluation, the lesions were classified into three groups as benign, preneoplastic, and neoplastic. Benign lesions included endocervical polyp, atypical squamous metaplasia, koilocytosis, endometritis, endometriosis, endometrial polyp, and endometrial proliferations. Preneoplastic lesions included CIN, CIN I, CIN II, CIN III, carcinoma in situ, and adenocarcinoma in situ. All the invasive cancers were classified as neoplastic lesions. Preneoplastic and neoplastic lesions were further classified as clinically important lesions, whereas benign lesions were classified as clinically unimportant lesions. Data were analyzed using SPSS 10.0.

Results

A total of 74 patients were detected with AGC on PST and were further categorized as AGC-NOS (n=55) and AGC-fn (n=19). In the patients with AGC, mean age was 45.8 ± 10.044 (range, 22-78) years, mean gravida was 3.53 ± 2.665 (range, 0-17), and mean parity was 2.62 ± 1.773 (range, 0-9) (Table 1).

Of the 55 patients detected with AGC-NOS, 42 (76.3%) had negative histopathologic results (Table 1). Eight (14.5%) out of 55 patients were detected with cervical squamous intraepithelial lesions, of which six patients were present with LSIL (CIN I) and 2 patients with HSIL. Of the patients detected with HSIL, one patient was present with CIN II and the other patient with carcinoma in situ (Table 2). In the patients with AGC-NOS (n=55), no patient was detected with adenocarcinoma in situ, one (1.8%) patient was detected with squamous cell cervical cancer, and one (1.8%) patient was detected with endometrial cancer (Table 2). Endometrial hyperplasia was detected in three (5.4%) patients, of which one (1.8%) patient was present with simple non-atypical endometrial hyperplasia, one (1.8%) patient with simple atypical endometrial hyperplasia, and one (1.8%) patient with complex atypical endometrial hyperplasia (Table 2). In the patients with AGC-NOS, the incidence of premalignant lesions including LSIL, HSIL, adenocarcinoma in situ, and endometrial hyperplasia was found in 11/55 (20%), and the incidence of malignant lesions including cervical and endometrial cancers was 2/55 (3.6%) (Table 1).

Of the 19 patients detected with AGC-fn on PST, seven (36.8%) patients had negative histopathologic results (Table 1). Five (26.3%) out of 19 patients were present with squamous intraepithelial lesions, of which three patients were detected with LSIL (CIN I) and two patients with HSIL. Of the patients with HSIL, one patient had CIN III and the other patient had carcinoma in situ (Table 2). Of all the patients with AGC-fn (n=19), one (5.2%) patient was detected with adenocarcinoma in situ, two (10.5%) patients with squamous cell cervical cancer, one patient with complex atypical endometrial hyperplasia, and one (5.8%) patient with endometrial cancer (Table 2). In the patients with AGC-fn, the incidence of premalignant lesions including LSIL, HSIL, adenocarcinoma in situ, and endometrial hyperplasia was 7/19 (36%) and the incidence of malignant lesions including cervical and endometrial cancers was 5/19 (26.3%). (Table 1)

Overall, of all the 74 patients with AGC (AGC-NOS and

Table 1. — *Clinical characteristics of the women and incidence of benign, pre-neoplastic, and neoplastic lesions.*

		Min-max	Mean ± SD
Age (years)		22-78	45.8 ± 10.044
Gravidity		0-17	3.53 ± 2.665
Parity		0-9	2.62 ± 1.773
	Benign n (%)	Pre-neoplastic n (%)	Neoplastic n (%)
AGC-NOS (n=55)	42 (76.3)	11 (20.1)	2 (3.6)
AGC-fn (n=19)	7 (36.8)	9 (47.3)	3 (15.7)
AGC (n=74)	49 (66.2)	20 (27.02)	5 (6.75)

Table 2. — *Incidence of pre-neoplastic and neoplastic lesions.*

	AGC-NOS (n=55)		AGC-fn (n=19)		AGC (n=74)	
	(n)	(%)	(n)	(%)	(n)	(%)
LSIL (CIN I)	6	10.9	3	15.7	9	12.1
HSIL (CIN II-III)	2	3.7	2	10.5	4	5.4
CIN II	1	1.85	0	0	1	1.3
CIN III	1	1.85	1	5.2	2	2.7
Carcinoma in situ	0	0	1	5.2	1	1.3
Adenocarcinoma in situ	0	0	1	5.2	1	1.3
Endometrial hyperplasia	3	5.55	1	5.2	4	5.4
Cervical cancer	1	1.85	2	10.5	3	4.0
Endometrial cancer	1	1.85	1	5.2	2	2.7

AGC-fn), 18 (24.3%) patients were detected with premalignant lesions, and seven (9.4%) patients with malignant lesions (Table 1).

Discussion

AGC is term that refers to atypical glandular cells of undetermined significance and has been shown to cause increased risk of preinvasive and invasive lesions in women. It is diagnosed in 0.08% to 5.96% of all the smear test results evaluated by TBS [8]. This rate has been reported to be 0.53% by Veljovich *et al.* [9] 0.053% by Daniel *et al.* [10], 0.4% by Chan *et al.* [11], and 0.51% by Chhieng *et al.* [12]. However, the rate of AGC found in the present study was 1.05%, and similar with the reference range reported in the literature. Mean age of the cases with AGC has been reported to be 43.7 (range, 17-85) years by Veljovich *et al.* [9] and as 48.9 ± 14.8 (range, 21-79) years by Parellada *et al.* [12]. In the present study, in line with the literature, mean age of the patients with AGC was 45.8 ± 10.044 (range, 22-78) years and the incidence of AGC was found to increase in the perimenopausal period.

Literature reviews indicate that the studies reporting on AGC are scarce and these studies have reported cytological and histopathological results with marked differences. Chan *et al.* [11] conducted a retrospective study and reported the incidence of malignancy in the patients with AGUS as 13.8%. Chhieng *et al.* [13] retrospectively reported the incidence of malignancy in 30,036 postmenopausal women as 15%, whereas Seok *et al.* [14] reported the incidence of invasive cancers to be 57%. In another study, Sun-suk-kim *et al.* [15] analyzed 83 patients detected with AGC on PST and found malignancy in 24 (28.9%) patients with breast, ovarian, and gastric cancers. The same study also found endometrial and cervical cancers in 16.8% of the patients. In patients detected with AGC, the most common histopathologic indication was squamous cell carcinoma, which has a reported incidence of 8-83%. Of these, high-grade squamous cell dysplasia is the most common type, with an incidence ranging between 40% and 68% [10, 16-18]. In a study conducted by the Collage of American Pathologists (CAP), 52% of the patients diagnosed with AGC were found to be present with clinically important lesions, of which 40% of the patients were present with squamous cell lesions and 5.8% of them with glandular cell lesions [16-18]. In the present study, of the 74 patients detected with AGC (AGC-NOS and AGC-fn), 18 (24.3%) of them were detected with premalignant lesions and seven (9.4%) of them with malignant lesions. Overall, in line with the literature, a total of 25 patients were detected with premalignant-malignant lesions, of which 16 (64%) were present with squamous cell lesions and seven (43.7%) with high-grade squamous cell lesions. Moreover, of the 16 patients with squamous cell lesions, three patients were detected with squamous cell cervical cancer, two patients with carcinoma in situ, two patients with CIN III, and the remaining nine patients with CIN I.

The 2001 Bethesda System defined the term AGC as a different term from AGC-NOS and AGC-fn and introduced the term AGC-fn to define lesions with higher risk of malignancy. However, the 2012 American Society of Colposcopy and Cervical Pathology guidelines [19] recommended that the patients with AGC-NOS that are detected with benign lesions after colposcopy and endocervical and endometrial sampling should be followed up, whereas the patients detected with AGC-fn should undergo routine excisional procedures due to the increased risk of malignancy even if negative results are obtained after colposcopy endocervical and endometrial sampling. In a similar study, Sawangsang *et al.* [20] found that the incidence of CIN II-CIN III, adenocarcinoma in situ, endometrial hyperplasia, and cancer-like lesions in patients detected with AGC-fn was significantly higher than in patients detected with AGC-NOS (41.2% *vs.* 15.2%; $p = 0.02$). Moreover, Westin *et al.* [21] found a significant correlation between CIN II and higher-grade lesions and AGC-NOS, AGC-fn, and adenocarcinoma in situ and reported that higher-grade lesions had a stronger correlation with AGC-fn and adenocarcinoma in situ compared to AGC-NOS. In the present study, the incidence of malignancy was significantly higher in patients with AGC-fn compared to patients with AGC-NOS (26.3% *vs.* 3.6%; $p < 0.01$). It is commonly known that the routine use of PST in Turkey has become more widespread in the recent periods. It is also known that in the previous periods, women presented to clinics at the symptomatic stage since PST was not routinely performed in all the patients. As a result, a great number of women with premalignant and malignant lesions might have directly undergone biopsy, although most of them could have been diagnosed with AGC if they had promptly undergone cytological testing. The present authors consider that this fact could explain the lower rate of malignant lesions found in the present patients.

Conclusion

AGC is a cytological abnormality which should be definitely evaluated for premalignant and malignant lesions. As noted in the ASCCP algorithm, the patients detected with AGC should undergo a thorough clinical examination including colposcopy and endocervical and endometrial curettage. Previous studies have also indicated that high-risk patients, even if their cervical and endometrial examinations are normal, should undergo a thorough examination for other organs. The present authors consider that once routine smear test becomes available for all the women in Turkey, the effect of AGC in the prediction of malignancy will be better revealed in further studies.

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