

Evaluation of Clinicopathologic Features of Patients Diagnosed with Atypical Glandular Cells in Cervical Cytology

Servikal Sitolojide Atipik Glandüler Hücre Tanısı Konan Hastaların Klinikopatolojik Özelliklerinin Değerlendirilmesi

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ABSTRACT

Objective: In our study we aimed to evaluate the clinicopathologic features of patients diagnosed with atypical glandular cells on cervical cytology.

Method: The records of 9375 patients who were examined in the gynecology outpatient clinic between 2010 and 2018 and underwent cervicovaginal smear were retrospectively reviewed. Seventy-three (0.8%) patients were diagnosed as atypical glandular cells. Colposcopic examination, cervical biopsy, endocervical and endometrial curettage were performed in patients diagnosed with atypical glandular cells. Age, gravida, parity, systemic diseases and clinicopathologic features of the patients were examined and recorded

Results: Cervical and endometrial abnormal histological findings were detected in 26 (35.6%) of 73 patients with atypical glandular cells. Of these 26 patients, 14 (19.1%) had cervical intraepithelial lesions, 3 (4.1%) had endometrial hyperplasia and 9 (12.3%) had invasive cancer. Five (6.8%) of the 9 patients with the diagnosis of invasive cancer had adenocarcinoma (endocervical and endometrial), in 3 (4.1%) patients cervical squamous carcinoma, and in 1 patient endocervical lymphoma was observed. The majority of cancers detected in our study were in the age group of 50 years and older.

Conclusion: Invasive cancer is seen in 12.3% of the patients diagnosed with atypical glandular cells, and most of these patients are 50 years or older. Therefore patients diagnosed with atypical glandular cell in cervicovaginal smear should be carefully evaluated with all clinical features.

Keywords: Atypical glandular cell, cervical cytology, cervical premalignant lesion

ÖZ

Amaç: Çalışmamızda servikovajinal smear sonrası atipik glandüler hücre tanısı konan hastaların klinikopatolojik özelliklerini değerlendirmeyi amaçladık.

Yöntem: Kadın hastalıkları polikliniğinde 2010-2018 yılları arasında muayene edilen ve servikovajinal smear yapılan 9375 hastanın kayıtları retrospektif olarak incelendi. Yetmiş üç (% 0,8) hastaya atipik glandüler hücreler tanısı kondu. Atipik glandüler hücreler tanısı konulan hastalarda kolposkopik muayene, servikal biyopsi, endoservikal ve endometriyal küretaj yapıldı. Hastaların yaş, gravida, parite, sistemik hastalıklar ve klinikopatolojik özellikleri incelendi ve kaydedildi

Bulgular: Atipik glandüler hücreli 73 hastanın 26'sında (%35,6) servikal ve endometrial anormal histolojik bulgular saptandı. Bu 26 hastanın 14'ünde (%19,1) servikal intraepitelyal lezyon, 3'ünde (%4,1) endometrial hiperplazi, 9'unda (%12,3) invaziv kanser mevcuttu. İnvaziv kanser tanısı alan 9 hastanın beşinde (%6,8) adenokarsinom (endoservikal ve endometrial), 3'ünde (%4,1) servikal skuamöz karsinom gözlemlendi. Bir hastada endoservikal lenfoma izlendi. Çalışmamızda tespit edilen kanserlerin büyük çoğunluğu 50 yaş ve üstü yaş grubundaydı.

Sonuç: Atipik glandüler hücre tanısı konan hastaların %12.3 de invaziv kanser görülmektedir ve bu hastaların çoğunun yaşı 50 yaş ve üzeridir. Bu nedenle servikovajinal smear nedeniyle atipik glandüler hücre tanısı konan hastalar tüm klinik özelliklerle dikkatlice değerlendirilmelidir.

Anahtar kelimeler: Atipik glandüler hücre, servikal sitoloji, servikal premalign lezyon

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INTRODUCTION

Cervical cancer is the second most common gynecological cancer in developing countries^{1,2}. Presence of a screening test and human papillomavirus (HPV) vaccine effects the incidence of cervical cancer. Screening programs can detect precancerous lesions which are treatable early stage cancers. Cervical cancer screening began with the development of the Papanicolaou (Pap) test which is routinely applied in many countries. The Bethesda System standardized the cervical cytology terms in 1988³. This system has been revised several times and the last review was made in 2014⁴⁻⁶. Atypical glandular cells (AGC) exhibit reactive and restorative nuclear changes, but they have not fully features of invasive carcinoma. AGC were divided into four groups. These groups are AGC, AGC favor neoplastic, endocervical adenocarcinoma in situ (AIS) and adenocarcinoma. Atypical glandular cell endocervical, endometrial, or not otherwise specified (NOS) is noted as a subcategory. AGC replaces the previous term "atypical glandular cells of undetermined significance (AGUS).

Based on cervical cytology findings, AGC usually originate from the glandular epithelium of the endocervix or endometrium. AGC is found less commonly than abnormal squamous cells. Glandular abnormalities are found in approximately 0.1 to 2.1 percent of cervical cytology samples⁷. Women with atypical glandular cells require further evaluation for premalignant conditions of the cervix, uterus, and rarely, ovary.

AGC's histologic evaluation may identify normal findings or squamous or glandular lesions. Approximately 30 % of AGC seems to be associated with premalignant and malignant lesions. Mostly squamous rather than glandular cells are detected upon histologic evaluation¹⁰⁻¹⁸. There are many risk factors for the development of premalignant and malignant diseases. These risk factors include high-risk HPV subtypes, age, gynecological history, immunodeficiency and socioeconomic sta-

tus. Especially age is an important risk factor for the development of premalignant and malignant diseases¹⁴.

The initial evaluation of AGC should include colposcopic examination, cervical biopsy, endocervical and endometrial sampling for women over 35 years of age. Endometrial sampling is recommended in patients under 35 years of age who have complaints of abnormal menstrual bleeding¹⁹. All these diagnostic procedures pose a risk to the health of the patient and an economic burden. Therefore, in this study, we aimed to evaluate the clinicopathologic features of patients diagnosed with AGC in cervical cytology.

MATERIAL and METHODS

This study approved by the Eskişehir Osmangazi University Ethics Committee for Clinical Studies (5 December 2018, 2018-14).

The records of 9375 patients who were examined in the gynecology outpatient clinic between 2010 and 2018 and underwent cervicovaginal smear examination were retrospectively reviewed. Two hundred and fifty-one patients were excluded due to missing medical data records. A total of 9124 cervicovaginal smears were evaluated. Seventy-three (0.8%) patients were diagnosed as AGC. Files of patients diagnosed with AGC were retrospectively reviewed. Conventional Pap smear test method was used for cervical cytology. The patients were taken to the gynecologic table in the lithotomy position and the vulva, vagina and cervix were evaluated. In the smear procedure, endocervical brush was used and samples from squamocolumnar junction and endocervical canal were obtained. The cells on the brush were spread on the slide and fixed with 95% ethyl alcohol and examined by a pathologist specialized in gynecology. After cervicovaginal smears of patients with AGC were evaluated according to the Bethesda classification system, they were referred for colposcopic examination. Colposcopy device

with WelchAllyn brand number 13153 was used for colposcopic examination of patients. Three percent acetic acid and lugol solutions were used during the examination. During the procedure, paracervical block was applied with local injection of 5 ml 2% lidocaine solution. Cervical biopsy, endocervical and endometrial curettage were performed in adherence to the colposcopy guide. One patient underwent conization, whereas the remaining patients underwent total abdominal hysterectomy (n=14) or radical hysterectomy (n=2). Specimens obtained were evaluated by the same gynecological pathologist. Patients whose medical file could not be accessed or missing and patients who did not consent to diagnostic procedures were excluded from the study.

Age, gravida, parity, systemic diseases and clinicopathological features of the patients were examined and recorded. The ages of the patients with AGC were grouped in 10-year intervals starting from the age of 20. Distributions of the patients according to age groups were evaluated. Ethics committee approval was obtained for our study with the decision number 2018-294.

Data were analysed using IBM SPSS 21 package program. Summary values of quantitative data were shown as mean standard deviation (SD) or median (Q1-Q3). Summary values of qualitative

variables are shown as frequency and percentage. The normal distribution of quantitative variables was investigated by Shapiro-Wilk test. Quantitative comparisons of two groups were performed by Mann-Whitney U test. Results with $p < 0.05$ were considered significant.

RESULTS

AGCs were detected in 73 (0.8%) patients when cervicovaginal smear results were examined. The mean age (42.64 ± 10.2 years), gravida (3.25 ± 1.7), and the parity (2.4 ± 1.1) of the patients diagnosed as AGC were also estimated. Sixty-two (84.9%) patients with AGC were in the premenopausal and 11 (15%) in the postmenopausal period. It was observed that 18 (24.6%) patients had postcoital bleeding, 23 (31.5%) had abnormal discharge and 44 (60.2%) patients did not use contraceptive methods. Twenty-nine patients were using birth control methods. The patients were using intrauterine device (IUD) (n=14: 48.2%), condoms (n=10: 34.4%) Mirena (52 mg levonorgestrel releasing IUD) (n=1: 3%) and 4 (13.7%) patients had their tubes ligated. The mean age of patients who had multiple births was 38 and they mostly preferred IUD Clinicopathologic features of patients are shown in Table 1.

When the patients diagnosed with atypical glan-

Table 1. Characteristic features (mean value) all patients (n:73).

Gravidy (n±standart deviation)	3.25±1.7	Not using contraception n (%)	44 (60.2%)
Parity (n±standart deviation)	2.45±1.1	KT-RT story n (%)	9 (9.5%)
Abortus(n±standart deviation)	0.84±1.1	DM n (%)	6 (8.2%)
Age (years±standart deviation)	42.6±10.2	HT n (%)	3 (4.1%)
Marriage duration(years±standart deviation) mean	21.06±9.9	Hypothyroidism n (%)	3 (4.1%)
Postcoital bleeding n (%)	18 (24.6%)	Premenopausal n (%)	62 (84.9%)
Abnormal cervical discharge n (%)	23 (31.5%)	Postmenopausal n (%)	11 (15%)

DM: diabetes mellitus, HT: hypertansion

Table 2. Distribution of AGC patients according to age groups.

Age groups	20-29	30-39	40-49	50-59	60-69	70-79
AGC n (%)	6 (8.2%)	22 (30%)	26 (35.6%)	14 (19.1%)	4 (5.4%)	1 (1.3%)

AGC: Atypical glandular cell

Table 3. Distribution of abnormal results according to age groups.

Age groups	20-29	30-39	40-49	50-59	60-69	Total
CIN 1	1	5	5			11 (15%)
CIN 2		1	1			2 (2.73%)
CIN 3			1			1 (1.36%)
Endometrial hyperplasia				1	2	3 (4.1%)
Endometrial adenocarcinoma				3	1	4 (5.4%)
Cervical squamous carcinoma		1		2		3 (4.1%)
Endocervical adenocarcinoma				1		1 (1.36%)
lymphoma			1			1 (1.36%)
total	1 (1.36%)	7 (9.5%)	8 (10.9%)	7 (9.5%)	3 (4.1%)	26 (35.6%)

CIN: Cervical intraepithelial neoplasia

Table 4. Clinical features of tumour patients.

No	Origin	Diagnosis	Colposcopy	First diagnosis	Age	Menopause	Stage ^{&}
1	Endometrium	Adenocarcinoma	Abnormal*	AGC	50	no	1ag1
2	Endometrium	Adenocarcinoma	Insufficient	AGC	52	yes	1ag1
3	Endometrium	Adenocarcinoma	Normal	AGC	56	yes	3ag2
4	Endometrium	Adenocarcinoma	Abnormal*	AGC	52	yes	1ag2
5	Cervical	Squamous	Abnormal*	AGC+HSIL	34	no	1b1
6	Cervical	Squamous	Abnormal*	AGC	50	no	1a1
7	Cervical	Squamous	Abnormal*	AGC+ASC-H	57	yes	2b
8	Endocervical	Adenocarcinoma	Normal	AGC	56	yes	1b
9	Endocervical	Lymphoma	Abnormal*	AGC	44	no	4

*Atypical vascularization, Asetowhite epithelium, Punctuation, Locoplaci, Mosaic; AGC: Atypical glandular cell, &: Figo TNM Classification, HSIL: High grade squamous intraepithelial neoplasia, ASC-H: Atypical squamous cell–high grade squamous intraepithelial lesions cannot excluded.

dular cell were separated according to age range of 10 years, 26 (35.6%) patients were in the age bracket of 40-49 and 22 (30%) of them in the age bracket of 30-39 years. The distribution of patients according to age groups is shown in Table 2.

Cervical and endometrial abnormal histological findings were detected in 26 (35.6%) of 73 patients with AGC. Of these 26 patients, 14 (19.1%) had cervical intraepithelial lesions, 3 (4.1%) endometrial hyperplasia and 9 (12.3%) invasive cancer. In 5 (6.8%) of 9 patients with the diagnosis of invasive cancer, adenocarcinoma (endocervical and endometrial), and in 3 (4.1%) patients cervical squamous carcinoma was observed. The incidence rates of these lesions according to age groups are shown in Table 3.

Four of the invasive cancers detected in patients with AGC were endometrial origin, four were

originated from cervix, and one was detected as metastasis to cervix. All patients diagnosed with endometrial adenocarcinoma were 50 years and older. Of the 4 cancers caused by cervix, only 1 patient is 34 years old and other patients are 50 years and older. One cervical lymphoma was also 44 years old.

In the patients with AGC, 1 patient was diagnosed as high grade squamous intraepithelial lesion (HSIL) and in 1 patient diagnosed as cervical squamous cell carcinoma, atypical squamous cell-high grade squamous intraepithelial lesion cannot be excluded (ASC-H). Five (55%) patients with invasive cancer were in postmenopausal period. Clinicopathologic features of patients with invasive cancer are shown in Table 4.

Colposcopic examination of patients with AGC was normal in 37 patients and pathological findings (acetowhite epithelium, punctuation, mosaic

structure, etc.) were detected in 36 patients. No invasive cervical cancer was found in the group with normal findings. The histological biopsy results of the patients with normal colposcopic examination were reported as cervical intraepithelial neoplasia (CIN) 1 in 5, CIN 2 in 1, endocervical adenocarcinoma in 1, and endometrial cancer in 1 patient.

DISCUSSION

AGC is a less common lesion in cervicovaginal smears than squamous cell anomalies, but it should be evaluated carefully because of its relationship with precancerous and cancerous lesions. In our study, as a result of histopathological evaluation of patients diagnosed with AGC, cellular abnormalities were detected in 26 (35.6%) patients. Nine (12.3%) of these abnormal results were invasive cancer. Seven patients with invasive cancer consisted of patients aged 50 years and over.

In our study, 73 patients (0.8%) were diagnosed with AGC. This ratio is consistent with the rates between 0.05% and 6% indicated in the literature review study of Marques JP et al⁷ in which 19 studies were examined in 2011²³. In another literature study, the reported rate of AGC in cervical smears ranged from 0.08% to 2.5%. When the patients were examined according to age groups of 10 years, it was observed that patients with AGC were most frequently seen in the age group of 40-49 years in accordance with the literature²¹. In the study of insignia RP et al²⁰, squamous cell-derived lesions were found to be higher in the 30-39 age group. The subsequent occurrence of cervical squamous lesions in our study may be related to differences in risk factors such as age at the onset of sexual intercourse, multipartner sexual intercourse and socioeconomic status.

Histological examination of AGC patients revealed premalignant and malignant lesions in 26 (35.6%) patients. In the literature, this rate varies in a very wide range as 17-100%^{8-20,23,24}. In the study of

Marques JP et al²⁰ the average detection rate of abnormal lesion was 58%⁷. In the study in which 622 AGC patients were evaluated, Zhao C et al¹⁴ abnormal lesion rate was found to be 15.3%. In a study by Philip Castle et al¹, detected abnormal lesions (excl. CIN1 lesion) in 18.1% of their patients. When the literature is reviewed, the extreme difference between the number of patients participating in the studies is remarkable. The risk factors for cervical and endometrial cancers vary among the centers. Therefore, the detection rate of abnormal lesion (35.6%) in our study was consistent with the literature findings. In our study, 11 (15%) patients with AGC had cervical CIN1 lesions and 3 (4.1%) had CIN2-3 lesions. Cervical intraepithelial neoplasia occurs in 20-28% of the patients with AGC in the literature. In the literature, the detection rate of CIN2-3 lesion of is higher when compared with our study^{7,15,21}. The difference in these rates may be related to the prevalence of risk factors for cervical intraepithelial lesions. Another reason for the differences between studies may be that the reproducibility rate in AGC and other diagnoses is different between observers²⁵.

In our study, invasive cancer was found in 12.3% of our patients. Adenocarcinomas, and squamous carcinoma accounted for 6.8%, and 4.1% of the cases with invasive cancers, respectively. In contrast to preinvasive lesions, the rate of cancer with glandular origin is higher in invasive cancers in accordance with the literature^{23,24}. The majority of cancers detected in our study were in the age group of 50 years and older^{22,2}. In addition, squamous cell lesions were detected in cervical cytology in patients with cervical cancer.

There are some limitations of our study. Retrospective design of our study, its small sample size, lack of HPV vaccine history, and information about patients in subcategories of AGC were the weaknesses of the study. However, our sample size still gives some information about the clinical characteristics of patients diagnosed as AGC.

CONCLUSION

Patients diagnosed with AGC based on histopathological examination of cervicovaginal smear samples should be carefully evaluated with all clinical features. Some (35.6%) of these patients had precancerous and cancerous lesions and 12.3% of them had invasive cancer. Most cancer cases have been detected in patients 50 years and older.

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