

Original Investigation

Clinicopathological importance of atypical glandular cells in cervico-vaginal cytology

Yüksel et al. Atypical glandular cells' importance

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Abstract

Objective: Aim of this observational study is to analyse the histopathological outcomes of patients with atypical glandular cells (AGC) in cervicovaginal cytology examinations.

Material and Methods: Patients with atypical glandular cells in cervicovaginal cytology were included in this study between March 2011 and March 2018 and patient data were collected retrospectively among all cytology results. Atypical glandular cell classification of cervicovaginal cytology were based on Bethesda 2001 classification system.

Results: Total prevalence of cervical epithelial cell abnormality and AGC were found 4.2% and 0.2% respectively in the study cohort. Atypical glandular cells-favor neoplasia (AGC-FN) was the subgroup of AGC with the highest malignancy rate with 62,5 % (p:0.06). Malignancy incidence in the postmenopausal group 33,3% was detected higher than the premenopausal group 8,3% (p:0,07).

Conclusion: Malignancy probability of AGC-FN cytology is more commonly associated with malignancy in the postmenopausal group . Therefore histopathologic examination is strongly recommended in these patients with AGC smears because of the high malignancy risk in this group.

Keywords: Cervical cancer, neoplasms, pap smear

Introduction

Preinvasive lesions of the cervix can be diagnosed with Papanicolaou smear tests and be treated long before overt carcinoma. Routine cervical cancer screening programs in many countries significantly reduced the incidence and mortality rate of cervical cancer.⁽¹⁾ Thorough understanding of cervical cancer pathogenesis and development of effective screening programs both with cervical cytology and Human Papilloma Virus (HPV) typing and vaccine against high risk HPV types significantly altered the distribution of cervical cancer and premalignant lesions of the cervix in countries where screening programs covers majority of the population. Although the incidence of squamous cell cancers of the cervix is decreasing, the rate of adenocarcinomas among cervical cancers is either unchanged or increasing.⁽²⁾ There are many reasons of this relative increase of cervical adenocarcinoma; firstly, location of adenocarcinoma and its preinvasive lesion ; adenocarcinoma in situ (AIS) rather deep and higher localization within cervical crypts which makes these lesions not easily recognizable like squamous counterpart lesions ; secondly , cytological and colposcopic signs of AIS lesions are not easily recognizable like squamous pathologies and thirdly invasive adenocarcinomas may originate from a small foci of adenocarcinoma in situ areas of the cervix.⁽³⁾

Glandular cell anomalies in cervical cytology are relative rare compared with squamous cell anomalies.

Incidence of atypical glandular cell (AGC) was reported 0.17% in a recent large study on cervical cytological screening.⁽⁴⁾ In another study in a tertiary referral center incidence of squamous and glandular abnormality were found 1.5% and 0.4% ,respectively and glandular cytologic abnormalities with different histopathology than squamous counterparts.⁽⁵⁾ Another population-based study including patients with AGC cytology has reported a 1.4% risk for developing invasive cervical carcinoma while this risk was found to be 2.5% and %0,2 in patients with high-grade (HSIL) and low grade squamous intraepithelial lesion (LSIL) cytology, respectively.⁽¹⁾

In the current literature glandular cervicovaginal cytologic abnormality, namely AGC, is questioned to be frequently associated with more severe cervical pathologies and cervical adenocarcinoma and AIS and more frequently associated with cervical squamous lesions than squamous cervicovaginal cytologic abnormalities.

In this study we aimed to analyze the relationship between cervicovaginal cytologic glandular abnormalities with cervical malignant pathologies. For this purpose cervicovaginal cytology reports were examined between March

2011 and March 2018 retrospectively and histopathological surveillance of the patients who were diagnosed with atypical glandular cell were analyzed and resultant cervical malignancies have been traced.

Materials and Method

Liquid based (ThinPrep Pap Test, Hologic) cervicovaginal cytological examinations which were performed between March 2011 and March 2018 within the context of opportunistic cervical screening program were reviewed and the patients reported to have atypical glandular cell were detected. The diagnostic and pathological examinations following cytological examination in these patients were obtained retrospectively by reviewing the patients' medical records. All cytology and pathology specimens were re-evaluated by the department of medical pathology as needed. Bethesda 2001 Classification system was used in classification the atypical glandular cell. Bethesda 2001 system classifies AGC as; atypical glandular cells not otherwise specified (AGC-NOS), atypical glandular cells-endocervical cells (AGC-EC), atypical glandular cells-endometrial cells (AGC-EM) and atypical glandular cells-favor neoplasia (AGC-FN). Only cytologies obtained from cervix uteri included into this study. AGC results of vaginal cuff cytologies excluded. Results of these group explained separately.

This retrospective study was approved by institutional ethical committee with project approval number KA18/230.

Statistical Analysis

SPSS 17.0 (IBM, USA) software were used for statistical analysis. All independent parameters were analyzed by using Chi-Square Test and Mann-Whitney U tests. The value $p < 0.05$ was accepted as statistically significant.

Results

It was determined in the study that totally 30.851 cervicovaginal cytological examinations were performed between March 2011 and March 2018. Epithelial cell abnormality was encountered in 1299 patients (4.2%); while AGC was detected in 69 patients (0.2%) (Figure 1). Cytology obtained from vaginal cuff in seventeen of 69 patients. Fourteen of these 17 patients were diagnosed and operated for endometrial cancer. During surveillance AGC has been detected and further histopathological examinations have been performed, as a result three recurrent cases have been detected. There was one cervical cancer patient and 2 patients were hysterectomized with benign indications. As a result; these 17 patients excluded, since cytological materials were obtained from vaginal cuff, and majority of the patients were already diagnosed with gynecological malignancy.

Median age of the patients who had AGC was 47 years (min: 25 and max: 77 years), 42,3% of patients ($n=22$) were postmenopausal. Sixtyfive percent of AGC cases ($n=34$) were asymptomatic and detected on routine cervicovaginal cytologic examination whereas the complaints of menometrorrhagia, menorrhagia, vaginal itching, urinary incontinence, postmenopausal bleeding and leucorrhoea were reported in 6, 4, 1, 2, 2 and 3 patients, respectively. Further pathologic examination offered to all patients, but among them 19 ($n=10$) were lost to follow up and 80,7 ($n=42$) had histopathological examination which were taken from the cervix, endocervical canal and endometrial cavity as indicated.

The evaluation based on subtypes of AGC revealed that atypical glandular cells not otherwise specified (AGC-NOS), atypical glandular cells-endocervical cells (AGC-EC), atypical glandular cells-endometrial cells (AGC-EM) and atypical glandular cells-favor neoplasia (AGC-FN) in 17 (32,6%), 23 (44,2%), 2 (3,8%) and 10 (19,2%) of patients, respectively (Table 1). Menopausal status has been shown to be associated to subtype distribution of AGC in our study. AGC-EC was predominantly found in premenopausal group (63%) whereas AGC-NOS (50%) was higher in the postmenopausal group and these differences were found statistically significant ($p:0,01$). Human papilloma virus (HPV) genotyping was possible after year 2016 and HPV status was examined in only 10 out of 52 patients and all patients were HPV negative except one patient with low risk HPV positivity.

Twenty eight percent ($n=12$) of the 42 patients with available pathological follow-up data were normal whereas active chronic inflammation, CIN1, CIN3, cervical squamous cell carcinoma, cervical adenocarcinoma, endometrial mixed carcinoma, endometrial polyp, endometrial hyperplasia, metastatic carcinoma and ovarian serous carcinoma were encountered in 10 (23,8%), 6 (14,2%), 2 (4,7%), 3 (7,1%), 2 (4,7%), 1 (2,3%), 3 (7,1%), 1 (2,3%), 1 (2,3%) and 1 (2,3%) patients, respectively.

As far as the patients with a malignant final diagnosis were concerned AGC-FN (62,5%) subgroup has been shown to be by far the most frequent AGC diagnoses ($p:0,06$). The subtypes of AGC in the patient group with malignant lesion according to pathological follow-up examination were found to be 50% of all AGC-FN group (Table 2). On the other hand 66% of all malignant cases' cytology in postmenopausal patients were AGC-FN initially ($p:0,1$) (Table 3). No statistically significant difference was found between the subtypes of AGC in the patients with malignant pathology in the premenopausal group ($p:0,3$) (Table 4).

As menopausal status was concerned malignancy incidence in the postmenopausal group 33,3% was higher than the premenopausal group 8,3% ($p:0,07$).

Discussion

This study confirms that AGC is a rare cervico-vaginal cytologic abnormality with prevalence of 0.2% out of 30.851 cytologic investigation. Similar prevalence rates of AGC have been reported in the literature.^(4,6,7,8) The

prevalence of cervical malignant lesion within AGC cytology was 9.6 % whereas this rate reached 15,3% with addition of all types of gynecologic malignancies and 32,6 % with inclusion of also premalignant lesions . The prevalence rates of the underlying neoplasia ranges between 9- 50% according to AGC cytology reports ; also in the literature.^(6,9) Tam et al. have reported that risk for premalignant-malignant lesion in AGC-NOS cytology was 19% whereas this risk rate was detected 68% in AGC-FN group.^(8,10) In our study, malignancy was encountered in 5 (50%) of the 10 patients with AGC-FN. When premalign lesions encountered also , this rate is nearly 70 % among patients with AGC-FN cytology . Among patients with malign final pathology ; leading prior AGC subtype was also AGC-FN in this cohort , nonetheless difference did not reach statistical significance (p:0,06). AGC cytology may not only be due to cervical pathology, but also can be due to endometrial pathologies. In one study on 41 patients with AGC cytology presented; endometrial cancer was detected in 13 patients and that all these patients were over 40 years old. It has been reported in another study that endometrial pathology is found especially in the patients aged over 45 years .¹¹ It has been suggested after Bethesda 2014 revision that reporting age of the patient with AGC-EM in cervical cytology should be adjusted as 45 years and above. This regulation was attributed to presentation of endometrial pathologies especially in the postmenopausal group.⁽¹²⁾ Endometrial malignant pathology was encountered in 1 patient in this study and this case was endometrial mixed (serous+endometrioid) tumor , age of this patient was 68 years. Benign pathologies of endometrium included endometrial polyp and endometrial hyperplasia in 3 and 1 patients, respectively. In our study showed that menopausal state is an important risk factor for an AGC smear to result with a final diagnoses of malignancy. Only two patients (6,6%) were diagnosed malignant premenopausally both of them which were cervical adenocarcinoma. Age of these patients were 36 and 40 years. On the other hand, postmenopausal patients' pathological follow-up examination were shown that considerably more patients in postmenopausal group were diagnosed malignant (33,3 %) as final diagnoses (p:0,07). Although this difference seem insignificant statistically ; this may result from limited number of patients. Therefore AGC diagnoses in menopause must be evaluated cautiously because of increased risk of a malignant tumor. HPV co-testing with cervical cytology has an important role in triage of the cervical squamous lesions whereas its importance is not clear in the glandular pathologies and cervical adenocancer. In a Swedish population-based study it has been reported that HPV reflex test has a very positive predictive value in prediction of high-grade cervical lesion in the patients with AGC and that planning of follow-up schedule based on HPV status would be reasonable.⁽¹³⁾ A systematic review which analyzed the importance of HPV in AGC cytology has noted that hr-HPV test has a sensitivity of 90% in prediction of CIN-2 and higher lesions in the patients with AGC.⁽¹⁴⁾ In our study only minority of the patients diagnosed with AGC had co-testing with HPV. Since we perform colposcopy to all patients with AGC absence of HPV co-testing were not a concern other than selecting patients who could be followed up less often if they had their HPV detected to be negative. HPV status was analyzed in only 10 patients in our study group and 9 patients were found HPV negative whereas one patient was low risk HPV positivity. Since HPV status is unknown for all 52 AGC patients in our study ; no interpretation could be made about importance of HPV in the triage of AGC. The guideline of American Colposcopy and Cervical Pathology (ASCCP) has recommended colposcopy and endocervical sampling in management of AGC.⁽¹⁵⁾ In accordance with this guideline, we also perform colposcopic examination, cervical and endocervical sampling in the patients. There is more debate on to whom we should make endometrial biopsy. Endometrial sampling can be recommended according to age and symptoms of the patient. Although AGC subtype with endometrial cells (AGC-EM) constitutes only minority of AGC cytology this sub-group carry higher risk for endometrial pathology and malignancies. Absence of enough large number of patients and also retrospective nature of the cohort precludes us from drawing firm conclusions. As a conclusion detection of atypical glandular cells on cervicovaginal cytology carries a potential risk of various malignancies particularly in postmenopausal patients. Among all AGC subtypes it can be stated from our study that AGC-FN cytologies are more commonly correlated with malignancy and this risk was particularly higher for postmenopausal patients. Any result with AGC necessitates further investigation with histopathological examination. Future studies with large series on AGC at cervicovaginal cytology may help to delineate patients at risk for malignancies. There is no conflict interest between the authors of the manuscript.

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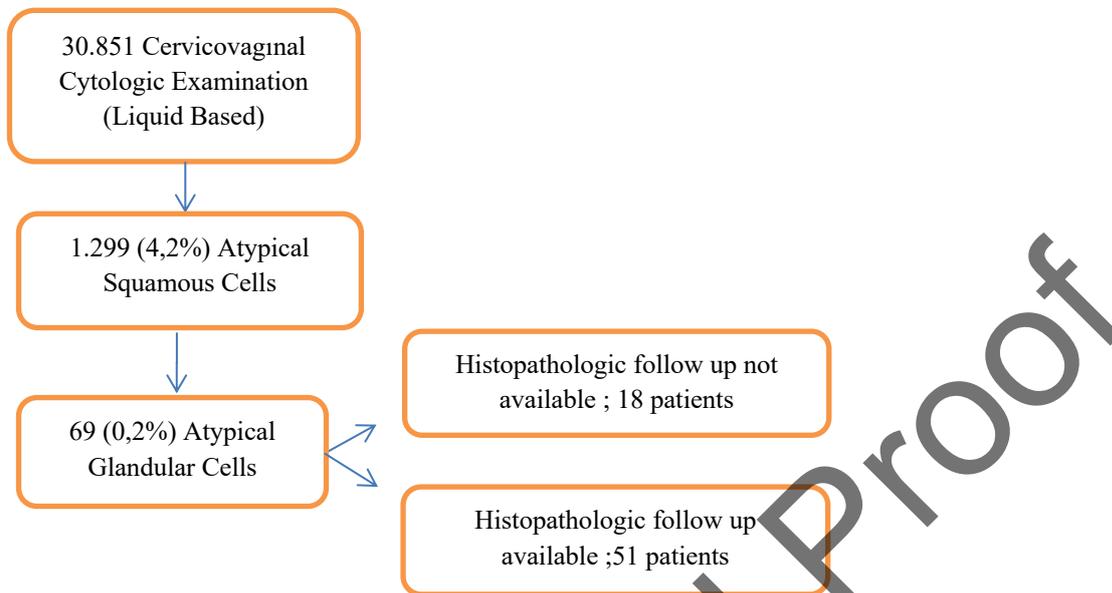


Figure 1. Flowchart

AGC subtypes	Postmenopausal	Premenopausal	Total
AGC-NOS	19 (43%)	6 (20%)	25
AGC-EC	4 (10.3%)	19 (63%)	23
AGC-EM	5 (12.8%)	1 (3.3%)	6
AGC-FN	11 (28.2%)	4 (13.3%)	15
Total	39	30	69

AGC Subtype	Benign	Premalignant	Malignant	Total
AGC-NOS	11 (34%)	3(37.5%)	1(9.1%)	15
AGC-EC	15(46.9%)	3(37.5%)	1(9.1%)	19
AGC-EM	3(9.4%)	0(0%)	2(18.2%)	5
AGC-FN	3(9.4%)	2(25%)	7(63.6%)	12
Total	32	8	11	51

AGC Subtype	Benign	Premalignant	Malignant	Total
AGC-NOS	9(64%)	3(75%)	1(11.1%)	13
AGC-EC	1(7.1%)	1(25%)	0(0%)	2
AGC-EM	2(14.3%)	0(0%)	2(22.2%)	4
AGC-FN	2(14.3%)	0(0%)	6(66.7%)	8
Total	14	4	9	27

AGC subtypes	Benign	Premalign	Malign	Total
AGC-NOS	2(11.1%)	0(0%)	0(0%)	2
AGC-EC	14(78.8%)	2(50%)	1(50%)	17
AGC-EM	1(5.6%)	0(0%)	0(0%)	1
AGC-FN	1(5.6%)	2(50%)	1(50%)	4
Total	18	4	2	24