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Clinical Implication of Atypical Glandular Cells; a Five Years Experience of a Single Institution in Portugal

Vânia Costa Ribeiro*, Lúcia Correia , Sofia Aguilar, Tereza Paula and Jorge Borrego

Maternity Dr. Alfredo da Costa, Department of cervical-vulvovaginal pathology, Lisbon, Portugal

Abstract

Objective: The study aimed to evaluate the clinical significance of atypical glandular cells (AGC) in cervical cytological reports and its correspondent subtypes.

Material and methods: Retrospective study of AGC cervical cytological diagnoses, from January 2009 to December 2013, at a tertiary centre. A global analysis of AGC and its correspondent subtypes was performed, according to age, onset of sexual life, Human Papilloma Virus deoxyribonucleic acid (HPV-DNA) status, diagnostic procedures and follow-up histological outcomes.

Results: Cervical AGC cytology had a prevalence of 0.3% among women with an average age of 46.8 ± 14.5 years. The distribution showed 81% of AGC-not otherwise specified (AGC-NOS) and 10.7% of AGC-favor neoplastic (AGC-FN). AGC-NOS had a higher prevalence of benign pathology. AGC-FN showed an association to *in situ* adenocarcinoma, a superior incidence of endometrial carcinoma and a tendency towards a higher prevalence of squamous cervical intraepithelial neoplasia. Glandular and squamous coexisting cytological abnormalities accounted for 8.3% and were mostly associated with squamous lesion. HPV-DNA testing demonstrated a sensitivity of 50% with a specificity of 100% for detection of cervical lesions.

Discussion: Close follow-up of AGC is required once pre-malignancy and malignant disease was identified in 20.8% of patients. A precise study of cervix and endometrium assumes equal importance, significant pathology was found in both locations.

Keywords: Atypical glandular cells; Atypical glandular cells-not otherwise specified; Atypical glandular cells-favor neoplastic; Human papilloma virus; Cervical cytology; Glandular cervical lesions

Introduction

In 1988 the National Cancer Institute established «The Bethesda System», a standardized terminology to report cervical cytology. Over the years several reviews to «The Bethesda System» have been made. In 2001 the terminology of atypical glandular cells of undetermined significance (AGUS) was updated to atypical glandular cells (AGC) which was meant to describe morphologic changes in glandular cells that were felt to be beyond normal changes, but not sufficient to be diagnostic of *in situ* adenocarcinoma (AIS). Since then AGUS was re-named AGC and subdivided into atypical glandular cells-not otherwise specified (AGC-NOS) and atypical glandular cells-favor neoplastic (AGC-FN). This terminology chance in AGUS was motivated by the substantial risk of high grade lesions associated with AGC which for so current guidelines recommend an extensive initial evaluation of women with AGC, in cervical Pap tests, based on age and AGC subtype [1].

Since the introduction of cytological screening in the 20th century there has been a decreasing incidence of squamous cell carcinoma but an increased relative rate of adenocarcinoma is being perceived throughout European countries, especially among younger women [2,3]. Whereas these used to account for less than 5% of all cervical cancers, they now comprise 20% to 25% [4]. One of the main reasons for the increasing relative rate of adenocarcinomas seems to be the lower Pap sensitivity in diagnosing glandular lesions and a high false negative rate [5,6].

Glandular abnormalities are found in 0.1 to 2.1% of Pap tests being more frequent in women over 40 [7,8]. The most common source of glandular cells on a Pap test is the endocervical canal followed by the endometrium, in most cases by flaking [6,9]. Cells from another location like the tube, ovary and other intraperitoneal sources can also migrated and be reported [6,9].

Following a cytological diagnose of AGC, most women, on the colposcopy-guided biopsies, show no significant pathology [5,10]. The association to premalignant and malignant disease is seen is approximately 30% of the cases [5,11-13].

Once AGC prevalence is low, a review through literature shows few data regarding the histological outcome of AGC-NOS in comparison to AGC-FN and no studies on AGC subtypes histological outcomes, among Portuguese women, were found. For so our retrospective study aimed to investigate the clinical significance of AGC and its correspondent subtypes in a group of Portuguese patients.

Material and Methods

From January 2009 to December 2013 a total of 26662 liquid-based Pap tests (ThinPrep®; Hologic 1996) collected with cytobrush were interpreted at the Pathology Department of our hospital, a tertiary centre in the capital of Portugal. All Pap test were classified according to the 2001 revision of Bethesda classification system.

A total of 84 from 26662 patients had AGC in the cytological

***Corresponding author:** Vânia Costa Ribeiro, Maternity Dr. Alfredo da Costa, Department of cervical-vulvovaginal pathology, Lisbon, Portugal, Tel: 00351910212287; E-mail: dokvcr@gmail.com

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interpretation. Medical records of those patients were retrospectively analysed and data was collected in what regards age, onset of sexual life, Human Papilloma Virus (HPV)-polymerase chain reaction (PCR) and histological results from cervical punch biopsy, endometrial hysteroscopy biopsy or curettage, endocervical curettage, excisional procedures of transformation zone or hysterectomy.

The HPV-PCR was preformed according to the guidelines from Portuguese Gynaecology Society which are based on the American Society of Colposcopy and Cervical Pathology guidelines [14]. Samples for HPV-PCR were collected with cytobrush and sent to virology analyses in a ThinPrep® (Hologic 1996).

In what concerns histological results it was considered the higher grade lesion for each patient. Classification of histologic specimens from cervical biopsies was performed according to the 2001 Bethesda System: CIN1-mild dysplasia, CIN2-moderate dysplasia, CIN3-severe dysplasia/*in situ* carcinoma) [1].

Statistical analysis was performed using SPSS version 20.0 (IBM, New York, USA). Data were analysed as a whole and by AGC subgroups; results were determined via Pearson chi-square for categorical variables and Student´s t-test for continuous ones. Two-tailed p-value inferior to 0,05 was considered to be statistically significant.

Results

Prevalence and characterization of AGC

Abnormalities of glandular cells had a prevalence of 0.3% (84/26662). The study group had an average age of 46.8 ± 14.5 with a range from 22 to 86 years old, 64.9% more than forty years.

The distribution within different sub-types of AGC is shown in Table 1.

AGC-NOS and AGC-FN groups

Clinical and histological outcomes: Characterization of AGC subgroups is presented in Table 2.

Patients with AGC-NOS were diagnosed at younger ages although the onset of sexual life was identical between groups.

The prevalence of benign cervical pathology was higher in AGC-NOS, being endocervical polyps the most common histological finding (63.4%). AGC-NOS and AGC-FN relate to a disease ratio of 75% and 100%.

The subgroup AGC-FN showed an association with AIS and a higher correlation with endometrial carcinoma. Although there was no statistical significant difference between groups in what concerns squamous cervical intraepithelial neoplasia (CIN), the study evidences a tendency towards a higher prevalence of CIN in AGC-FN group. There was no evidence of cervical squamous cell carcinoma.

Correlation of HPV with histological findings: Twenty-eight HPV type-specific testing were performed in AGC-NOS pap tests and HPV-deoxyribonucleic acid (DNA) was identified in 8 cases (28.8%). Table 3 describes HPV-DNA positive finding in AGC-NOS.

Between the 8 patients that tested positive for HPV-DNA, 4/8 (50%) showed CIN pathology in the follow-up (one case of CIN1 and three cases of CIN 3). All the AGC cytology that tested negative for HPV-DNA (n=20) had benign histological findings during follow-up study.

Cytological diagnosis	N	%
AGC-NOS	68	81.0
AGC-FN	9	10.7
Glandular and squamous coexisting abnormalities	7	8.3

Table 1: Prevalence of AGC sub-groups.

Characteristics	AGC-NOS (n=68)		AGC-FN (n=9)		p value
	n	%	N	%	
Age (mean ± standard deviation) (years)	45.7 ± 14.6		57.0 ± 14.6		0.032
>40 years (mean ± standard deviation) (years)	41	60.3	9	100	0.031
Onset of sexual life	18.0 ± 2.5		18.8 ± 0.8		0.314
Cervical disease:	**47**	**69.1**	**6**	**66.7**	**0.882**
Benign pathology	41	60.3	3	33.3	0.001
CIN1	3	4.4	1	11.1	
CIN2	0	0	0	0	0.219
CIN3	3	4.4	1	11.1	
AIS	0	0	1	11.1	0.006
ADC	0	0	0	0	0
Endometrial disease:	**4**	**5.9**	**3**	**33.3**	**0.001**
Endometrial hyperplasia	1	1.5	0	0	0.716
Endometrial cancer	3	4.4	3	33.3	0.003

ADC: Adenocarcinoma; AIS: *in situ* adenocarcinoma; CIN: squamous cervical intraepithelial neoplasia

Table 2: Clinical and histological outcomes of AGC-NOS and AGC-FN.

Case	HPV type	Patients tested positive for HPV-DNA
1	11	Benign histological findings
2	16*	CIN3
3	16*,58*	Benign histological findings
4	35*, 53*, 59*	CIN1
5	53*	CIN3
6	56*,61*	CIN3
7	69	Benign histological findings
8	82	Benign histological findings

CIN: squamous cervical intraepithelial neoplasia *high risk HPV

Table 3: Type-specific HPV detected in AGC-NOS.

Coexisting squamous and glandular abnormalities

From the total of 84 AGC interpreted Pap tests, seven patients (8.3%) had dual squamous and glandular abnormalities.

The patient mean age was 44.1±9.7 years old. Follow-up histological results of these patients, presented in Table 4, evidenced lesions predominantly of squamous origin (57.1%) with three reported cases of CIN 3 and one case of squamous cell carcinoma. Glandular lesions, with AIS were detected in two cases (28.6%). There was one identified case of benign pathology and no coexisting cases of squamous and glandular pathology.

Discussion

The AGC (including the subgroups: AGC-NOS and AGC-FN) in our population study had a low prevalence of 0.3%, being more commonly found in women over 40. In our 5 years retrospective analyse AGC are predominately associated with benign pathology (57.1%).

Our study also emphasizes the knowledge that although glandular cells originate from a variety of locations and the majority of abnormal cells derives from benign lesions (endocervical and endometrial polyp,

Pap tests dual results	AGC-NOS	Histological Outcome
	n	
ASC-US	3	Benign histological findings
		CIN3
		AIS
ASC-H	1	AIS
HSIL	2	Invasive squamous cell carcinoma
		CIN3
	AGC-FN	
	n	
HSIL	1	CIN3

AIS: *in situ* adenocarcinoma; CIN: squamous cervical intraepithelial neoplasia

Table 4: Outcomes in coexisting squamous and glandular abnormalities.

endocervicitis, endometriosis, microglandular hyperplasia, tubal metaplasia, endosalpingiosis and Arias-Stella chances of pregnancy cervix) [6,9], the identification of this cells on cervical cytology must be vigorously investigated, to identify other significant pathology, given the fact that low grade lesions, pre-malignancy and malignancy accounted for 20.8% of all clinical reports. The histological follow-up evidenced that most of the pre-malignant cervical pathology found were squamous lesions (5.2% of CIN3 versus 1.3% of AIS). In what concerns malignancy, endometrial adenocarcinoma was the most prevalent (7.8%).

The literature shows that only 41% to 71% of AIS are diagnosed histologically through a cytological AGC report [15-18]. The neoplastic glandular cells can proliferate hidden under normal metaplastic and dysplastic squamous epithelium in 60% of the cases which makes these cells not accessible to cytological sampling [19]. Although cytological screening has a high false negative rate for adenocarcinoma for now there is not a better available screening test.

In the present study, histological examination of AGC found a total of 7.8% of malignancy which agrees with Chhieng et al. that showed a prevalence of 13.3% of malignant disease among 45 diagnosed AGUS [20]. The subgroup of AGC-FN has older women, being all above forty years old (AGC-NOS: 45.7 ± 14.6 versus AGC-FN: 57.0 ± 14.6 years, p-value=0.032) with a higher prevalence of AIS (AGC-NOS: 0% versus AGC-FN: 11.1%, p-value=0.006) and endometrial adenocarcinoma (AGC-NOS: 4.4% versus AGC-FN=33.3%, p-value=0.003). Our reported results highlight the importance of cervical study and pelvic sonography in AGC evaluation, and for so, close follow-up is recommended [14].

The relationship between cervical cancer and HPV is well known particularly in what concerns HPV type 16 and 18 which are identified in about two thirds of cervical cancer cases worldwide [21]. Current guidelines have suggested a role for HPV testing in the management of Pap test that report AGC [14]. In this study we tested 28 AGC liquid-based cytology for HPV DNA with posterior identification of 10 types of HPV DNA, 7 being high risk HPV DNA. The HPV associated disease ratio in our study was 50% which is in agreement with existing literature that reports rates which range from 11 to 53% (average 21%) [11].

In our study the sensitivity of HPV-DNA in detecting cervical lesions was 50% with a specificity of 100%, a positive predictive value (PPV) of 50% and a negative predictive value (NPV) equivalent to 100%. From the sample tested for HPV-DNA, in our study, no conclusion can be taken about the most commonly isolated HPV types. Although there are limitations, due to the retrospective design and the small sample analyses, our results confirm that HPV DNA testing has an important role in the management of AGC Pap results follow-up once HPV-DNA presence is associated with cervical disease, with a PPV of 50% in our study. Based on the evidence of HPV-DNA PPV for cervical pathology, current guidelines recommend, in the absence of significant pathology in the initial evaluation, a re-evaluation of AGC-NOS patients, in 6 months if HPV DNA is positive and 12 months if HPV DNA is negative [14].

In the majority of abnormal Pap tests, only a single epithelial cell abnormality is observed and reported. The incidence and relevance of coexisting squamous and glandular epithelial is unknown. Our study shows an 8.3% prevalence of dual cell abnormality being the squamous abnormalities more prevalent (57.1%) in relation to glandular abnormalities (28.6%). Although we report these results, the sample is too small in size and consequently we cannot predict the final histological findings based only in the evidence of dual interpretation.

Our study emphasises the importance of close follow-up when AGC cytology is reported since pre-malignancy and malignant disease was identified in 20.8%. Along this review it becomes evident that AGC-FN subgroup has higher prevalence of malignant pathology. It is clear the importance of cervical and endometrial evaluation when in the presence of AGC cytological diagnosis. In our study group similar rates of cervical and endometrial pathology (Cervix: 11.7%; Endometrium 9.1%; p-value=0.599) were found possibly owing to the fact that the average age of AGC study group is above 40.

Although our HPV-DNA testing sample was small in size we found a ratio of HPV associated cervical disease of 50% which indicates that the concomitant use of HPV-DNA can be very useful on AGC follow-up when no significant pathology is found on cervix or endometrium since studies report a false negative rate of 4.7% in AGC follow-up [6].

Beyond the retrospective design there are other limitations to this study that should be noted. Mostly because of the low prevalence of AGC cytology, our study sample is small in size, which has implications when it comes to subgroup analyses. In the particular case of AGC-FN, although women are older, and the presence of non-benign pathology is more prevalent we cannot exclude a possible bias effect as a result of the small number of patients. When it comes to coexisting squamous and glandular abnormalities we are not able to predict histological outcomes based on the small sample of dual interpretation.

Although showing some limitations our study compares histological findings between AGC subgroups highlighting the importance of HPV-PCR co-test in AGC-NOS follow-up and the concomitant evaluation of the endometrium especially in women with AGC over 35 years old.

References

1. Solomon D, Davey D, Kurman R, Moriarty A, O'Connor D, et al. (2002) The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 287: 2114-2119.
2. Bray F, Carstensen B, Møller H, Zappa M, Zakelj MP, et al. (2005) Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev 14: 2191-2199.
3. Gien LT, Beauchemin MC, Thomas G (2010) Adenocarcinoma: a unique cervical cancer. Gynecol Oncol 116: 140-146.
4. Smith HO, Tiffany MF, Qualls CR, Key CR (2000) The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States--a 24-year population-based study. Gynecol Oncol 78: 97-105.
5. Zhao C, Florea A, Onisko A, Austin RM (2009) Histologic follow-up results in 662 patients with Pap test findings of atypical glandular cells: results from a large academic womens hospital laboratory employing sensitive screening methods. Gynecol Oncol 114: 383.
6. Schnatz PF, Guile M, O'Sullivan DM, Sorosky JI (2006) Clinical significance of atypical glandular cells on cervical cytology. Obstet Gynecol 107: 701-708.

7. Marques JP, Costa LB, Pinto AP, Lima AF, Duarte ME, et al. (2011) Atypical glandular cells and cervical cancer: systematic review. Rev Assoc Med Bras 57: 234-238.

8. Insinga RP, Glass AG, Rush BB (2004) Diagnoses and outcomes in cervical cancer screening: a population-based study. Am J Obstet Gynecol 191: 105.

9. Van Dinh T, Haque M, Lucci JA 3rd, Smith ER, Hannigan EV (2003) Management of atypical glandular cells of undetermined significance pap smears: a reappraisal. J Low Genit Tract Dis 7: 11-15.

10. Wood MD, Horst JA, Bibbo M (2007) Weeding atypical glandular cell look-alikes from the true atypical lesions in liquid-based Pap tests: a review. Diagn Cytopathol 35: 12-17.

11. Sharpless KE, Schnatz PF, Mandavilli S, Greene JF, Sorosky JI (2005) Dysplasia associated with atypical glandular cells on cervical cytology. Obstet Gynecol 105: 494-500.

12. DeSimone CP, Day ME, Tovar MM, Dietrich CS 3rd, Eastham ML, et al. (2006) Rate of pathology from atypical glandular cell Pap tests classified by the Bethesda 2001 nomenclature. Obstet Gynecol 107: 1285-1291.

13. Scheiden R, Wagener C, Knolle U, Dippel W, Capesius C (2004) Atypical glandular cells in conventional cervical smears: incidence and follow-up. BMC Cancer 4: 37.

14. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, et al. (2007) Consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol 197: 346-355.

15. Laverty CR, Farnsworth A, Thurloe J, Bowditch R (1988) The reliability of a cytological prediction of cervical adenocarcinoma in situ. Aust N Z J Obstet Gynaecol 28: 307-312.

16. Cullimore JE, Luesley DM, Rollason TP, Byrne P, Buckley CH, et al. (1992) A prospective study of conization of the cervix in the management of cervical intraepithelial glandular neoplasia (CIGN)--a preliminary report. Br J Obstet Gynaecol 99: 314-318.

17. Schooland M, Segal A, Allpress S (2002) Adenocarcinoma in situ of the cervix. Cancer 96: 319-323.

18. Ayer B, Pacey F, Greenberg M, Bousfield L (1987) The cytologic diagnosis of adenocarcinoma in situ of the cervix uteri and related lesions. I. Adenocarcinoma in situ. Acta Cytol 31: 397-411.

19. Colgan TJ, Lickrish GM (1990) The topography and invasive potential of cervical adenocarcinoma in situ, with and without associated squamous dysplasia. Gynecol Oncol 36: 246-249.

20. Chhieng DC, Elgert P, Cohen JM, Cangiarella JF (2001) Clinical significance of atypical glandular cells of undetermined significance in postmenopausal women. Cancer 93: 1.

21. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, et al. (1999) Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol 189: 12-19.