Atypical glandular cells and cervical cancer: systematic review

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Summary

Atypical glandular cells are a common finding in cervical cytology in cervical cancer screening and its occurrence has increased in the last decades. The identification of these cells is clinically very important due to its association with cervical and endometrial dysplasic lesions and cancer. Using a systematic approach, this article reviewed studies investigating cervical lesions that are characteristic in patients previously diagnosed as having atypical glandular cells. Studies in which diagnostic investigation did not include histopathological diagnosis were excluded. A comprehensive search for available material in LILACS, SciELO, PubMed/ Medline and Old Medline databases, dated between 1966 and 2009 was performed. Articles omitted by the electronic database search were also included. Nineteen articles met the inclusion criteria and were selected. This report aims at evaluating whether atypical glandular cells, initially found in cervical cytology and subsequently identified at the histological analysis, are related to the presence of benign, pre-malignant and malignant lesions. Eleven out of 19 selected articles showed the highest correlation between atypical glandular cells with benign diseases and six with squamous pre-malignant lesions.

Keywords: Cervix neoplasm prevention; glandular and epithelial neoplasms; cervical intraepithelial neoplasia; review.

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Introduction

In 1988, when the Bethesda System classification was introduced, the diagnostic category *atypical glandular cells of undetermined significance* (AGUS) was created[1-4]. In 2001, when the second review of the Bethesda System was carried out, the term AGUS was substituted by atypical glandular cells (AGC), mainly due to the fact that it was mistaken for ASCUS (atypical squamous cells of undetermined significance)[1,3]. These glandular atypias, when their location is not specified, are defined as cells with nuclear alterations that exceed the reactive or reparative processes, but which do not exhibit anaplasia characteristic of adenocarcinomas[1-3].

The finding of squamous atypia of the cervix at cytological analysis is ten times more frequent than glandular atypias[1]. The AGC category in cervicovaginal smears is a cytological finding in the routine screening for cervical cancer that has increased in the last decades, although it is still unusual in cytological diagnostics[3,5,6].

In the literature, the report of AGC incidence ranges from 0.1% to 2.1%[4]. The verification of this atypia is clinically important, as the percentage of cases associated with high-degree cervical and endometrial disease and neoplasms is higher than that for ASCUS[3,6]. In fact, 9% to 38% of the women with AGC have significant lesions (CIN2, CIN3 and *in situ* adenocarcinoma) and 3% to 17% have invasive carcinomas[3].

The diagnosis of atypical glandular cells of undetermined significance is an exclusion diagnosis[7]. The lesions must be then classified as that, if they cannot be included in the categories of benign, pre-neoplastic or malignant lesion[7,8]. The histological results of AGC in Pap smears are so broad that they include benign lesions and neoplastic alterations of squamous and glandular cells[9]. The American Society of Colposcopy and Cervical Pathology (ASCCP), as well as the Ministry of Health in Brazil, indicates the immediate colposcopic analysis with endocervical sampling for cases of AGC[1,5,6].

This article aimed to verify the profile of uterine cervical lesions in patients with a previous cytological diagnosis of atypical glandular cells through a systematic review of medical literature, with the objective of identifying its association with other diseases and/or lesions.

Methods

This review included articles selected from journals indexed at the LILACS, SciELO, PubMed/ Medline and Old Medline databases, from 1966 to 2009. The keywords used in the search were based on the MeSH and DeCS lists. The following terms were chosen for the search: atypical glandular cells, uterine cancer and precancerous lesions. Combinations were used for the search in all databases. The references found in the chosen articles were also verified, in order to identify other studies that might have been omitted in the electronic search. The titles and summaries were analyzed for potentially relevant articles. No limitations were considered during the search and the articles were subsequently selected by inclusion and exclusion criteria. The chosen publications were obtained for the reassessment of their results.

Studies that investigated patients with positive cytology for glandular cell atypia and followed histopathological diagnosis were included in the review. The histopathological analysis considered the presence of benign reactive processes and histologically significant lesions, such as squamous and glandular, cervical and endometrial neoplasias, as well as neoplasias from other sites. In this review, patient age was not used as a screening criterion, as well as the morphological criteria used to attain the reported diagnoses. Studies in which diagnosis was not attained through histopathological analysis, the number of biopsies was omitted and review articles were excluded.

Results

The selected articles identified through electronic search comprehended the period from 1992 to 2009, which were recovered in full length for a more detailed analysis. Repeated articles were considered in only one search source. A total of 38 articles were reported by the databases and four were selected for the review.

Through reference analysis, 13 publications initially omitted in the electronic search were identified, and two studies were identified in random searches, totaling 19 articles (Table 1).

The number of cytological analyses with AGC in the reviewed articles varied from 44[10] to 1,117[11], with an incidence of 0.05% to 2.1%. Only one publication showed a higher incidence (6%)[12]. The percentage of histopathological analyses carried out in the patients com atypia ranged from 17%[13] to 100%[10,14,15]. Among the 19 reviewed articles, a predominance of benign lesions was demonstrated in 11 and pre-malignant squamous lesions in 6 articles. In two articles, the percentage of benign and pre-malignant pathologies was the same (43% and 42%)[16,17]. Invasive lesions reported by the reviewed articles showed that the percentage of invasive squamous carcinoma ranged from 0.89%[5] to 4.44%[15] and cervical adenocarcinoma ranged from 1.4%[18] to 18%[5]. Only one report did not describe an association with malignant lesion[10].

Discussion

The Bethesda System classification (1988) included the diagnoses related to atypical glandular cells in the cytological assessment classification of the uterine cervix. Since then, the presence and assessment of endocervical cells has been taken into account in cytological smears[1,2,3]. In 1991, at the first review of the Bethesda System, the abbreviation AGUS was introduced to represent this lesion[3].

Table 1 – AGC study results with histological correlation

Author/year	Incidence	Patients with histopathological diagnosis	SIL	Invasive squamous carcinoma	Cervical adenocarcinoma	Endometrial adenocarcinoma	Benign pathology/ normal	Others
Goff *et al.*, 1992 [10]	100/21.930 (0. 46%)	56/100 (56%)	19/56 (34%)	0	7/56 (12.5%)	0	24/56 (42.85%)	6/56 (10.7%)
Nasu *et al.*, 1993[11]	620/34.384 (1.8%)	279/620 (45%)	140/279 (50.17%)	4/279 (1.43%)	14/279 (5%)	4/279 (1.43%)	114/279 (40.86%)	3/279 (1%)
Bose *et al.*, 1994[12]	44	44 (100%)	35/44 (80%)	0	0	0	9/44 (20%)	0
Lee *et al.*, 1995 [13]	210/79.942 (0.26%)	74/210 (35.2%)	33/74 (44.5%)	0	10/74 (13.5%)	0	31/74 (42%)	0
Jones e Novis, 1996[14]	293/22.439 (1.3%) AGUS	293/293 (100%)	116/293 (40%)	0	13/293 (4.5%)	0	141/293 (48%)	23/293 (7.84%)
Kennedy *et al.*, 1996[15]	136/68.368 (0.2%) AGUS	53/136 (38.97%)	7/53 (13.2%)	0	5/53 (9.4%)	1/53 (1.89%)	37/53 (69.8%)	3/53 (5.66%)
Eddy et al, 1997[16]	1.117/177.715 (0.63%) AGUS	531/1.117 (48%)	143/531 (27%)	0	11/531 (2%)	28/531 (5%)	337/531 (63%)	12/531 (2.25%)
Raab *et al.*, 1997[17]	346 AGUS	116/346 (33.5%)	50/116 (43%)	0	5/116 (4%)	11/116 (9%)	50/116 (43%)	0
Duska *et al.*, 1998 [18]	201/120.338 (0.17%) AGUS	73/201 (36.3%)	19/73 (26%)	0	1/73 (1.4%)	3/73 (4%)	45/73 (61.6%)	5/73 (6.8%)
Veljovich *et al.*, 1998[19]	345/84.442 (0.53%) AGUS	199/345 (57.7%)	45/199 (23%)	0	5/199 (2.5%)	2/199 (1%)	134/199 (67%)	13/199 (6.5%)
Burja *et al.*, 1999[20]	377/ 18.198 (2.1%) AGUS	64/377 (17%)	35/64 (54%)	0	3/64 (5%)	0	26/64 (41%)	0
Ronnett *et al.*, 1999[21]	225/46.009 (0.5%) AGUS	136/225 (60.44%)	23/136 (17%)	0	3/136 (2.20%)	1/136 (0.73%)	109/136 (80.14%)	0
Geier *et al.*, 2001[22]	492/8.221 (6%) AGUS	353/492 (71.74%)	108/353 (31%)	0	9/353 (2.6%)	1/353 (0.2%)	227/353 (64%)	8/353 (2.27%)
Hammoud *et al.*, 2002[4]	207/ 208.041 (0.1%) AGUS	114/207 (60.3%)	28/114 (24%)	0	4/114 (3.5%)	11/114 (10%)	66/114 (57.8%)	5/114 (4.4%)
Verdiani *et al.*, 2003[2]	443/217.245 (0.2%) AGC	102/443 (23.02%)	51/102 (50%)	2/102 (1.96%)	7/102 (6.87%)	1/102 (0.98%)	40/102 (39.21%)	1/102 (0.98%)
Gutman *et al.*, 2004[23]	45 /11.800 (0.38%) AGUS	45/45 (100%)	28/45 (62%)	2/45 (4.44%)	1/45 (2.22)	0	14/45 (31%)	0
Scheiden *et al.*, 2004 [24]	261/566.809 (0.05%) AGC	183/261 (70.2%)	28/183 (15%)	3/183 (1.6%)	13/183 (7.2%)	53/183 (29%)	80/183 (44%)	6/183 (3.27%)
Westin *et al.*, 2008 [25]	155 AGC	126/155 (81.3%)	53/126 (42%)	3/126 (2.4%)	17/126 (13.5%)	0	53/126 (42%)	0
Zhao *et al.*, 2009[5]	525/64.378 (0.8%) AGC	460/525 (87.6%)	32/460 (28.57)	1/460 (0.89%)	19/460 (18%)	30/460 (27%)	348/460 (75.6%)	30/460 (6.5%)

The first publications (1992 to 1995) did not use the abbreviation AGUS, using the terms endocervical glandular atypia[19,20], abnormal endocervical cells[10] and atypical glandular cells[21]. From 1996 onward, the articles used the term AGUS[11-14,16,18,22-24], which was used until the review of the Bethesda System in 2001, when the term AGC started to be used[2,5,17,25]. The publications from 2002[4] and 2004[15] still used the term AGUS.

The results depicted in Table 1 show that there is a small number of publications that correlate the presence of AGC with histopathological alterations. The finding of squamous atypias of the cervix in cytology is ten times more frequent when compared with glandular atypias, resulting in a decreased volume of information available in the literature on cytological alterations[1].

Most studies shown in Table 1 were published between 1992 and 1999. The 1992 publication[19] is noteworthy, as it is the first one to report the findings of atypical endocervical cells in the cytological screening of the cervix. The other studies were published between 2001 and 2009.

The investigations evaluated a total of distinct cervicovaginal smears, resulting in a different amount of AGC diagnoses, which varied from 44[10] to 1,117[11]. The incidence of cases with AGC varied from 0.05%[25] to 2.1%[13] in the 19 articles, showing that there was an increase in incidence in the last decades[13]. The 2001 publication recorded a percentage of glandular atypia diagnosis of 6%[12] (492 patients), being outside the range reported in the literature. Three reports[10,16,17] did not record the percentage of AGC cases, as the total number of smears was not reported. The percentage of histopathological follow-up ranged among the authors from 17%[13] to 100%[10,14,15]. It was observed that in cases that had 100%, the percentage was independent from the number of samples, varying from small[10, 15] to larger samples[14].

The present review evaluated the percentage of intraepithelial squamous cell lesions, invasive squamous carcinoma, cervical and endometrial adenocarcinoma, emphasizing the percentage of benign lesions. In six articles a predominance of intraepithelial squamous cell lesions was evident. The highest percentage of these lesions was of 80%[10], and the lowest, of 13.2%[22]. In the report by Bose *et al.*[10], among the intraepithelial squamous cell lesions, 17 were low-grade and 18 were high-grade. A weak point of this report, which showed this high incidence, was the small sample size (44 patients).

Of the significant histological alterations found in AGC cases, 12% to 46% had glandular origin. However, most of the studies describe the squamous lesions, mainly the high- and low-grade intraepithelial lesions, as the ones found with higher frequencies (9% to 54%)[26]. Invasive squamous carcinoma was diagnosed through a histopathological analysis in patients with AGC in six articles[2,5,15,17,20,25], of which five were published from 2003 to 2009. The incidence ranged from 1.43%[20] to 4.4%[15], being part of the clinically significant diagnoses. The study by Nasu *et al.*[20], carried out with 279 patients, showed the lowest percentage of invasive squamous cell carcinoma of this review. The diagnosis for cervical adenocarcinoma was realized in all articles, with a variable rate of 1.4%[18]-18%[5]. The rates of endometrial adenocarcinoma varied from 0.2%[22] to 29%[25] were observed in 12 articles. Two publications that reported a higher number of adenocarcinomas are worth mentioning. Scheiden *et al.*[25] diagnosed 13 adenocarcinomas of cervix, of which four were adenocarcinomas *in situ* and nine invasive adenocarcinomas. Of the 53 endometrial lesions, three were adenocarcinomas *in situ* and 50 were invasive adenocarcinomas. Zhao *et al.*[5] showed 49 cervical and endometrial adenocarcinomas found in the histopathological analysis of 460 patients with AGC.

According to Table 1 the incidence, at the histopathological analysis, of the findings considered as benign and/or normal lesions varied from 20%[10] to 80.14%[24]. Among the benign lesions, the most frequently reported ones were cervicitis, endocervical and endometrial polyps, tubal metaplasia, microglandular hyperplasia, endometrial hyperplasia and cervical leiomyomas. Some analyses ruled out the presence of other pre-neoplastic and neoplastic lesions. The 2009 study[5] reported 20 cases of atypical complex endometrial hyperplasia, two malignant mixed mullerian tumors, two cases of trophoblastic gestational diseases and six ovarian carcinomas. The other studies revealed, as well as the aforementioned lesions, the presence of teratoma, Brenner tumor and uterine sarcoma, in addition to metastatic neoplasias.

Conclusion

This systematic review showed that the histological follow-up of uterine cervix samples is necessary in all patients that have cytological results of glandular atypia, due to the possibility of their association with pre-malignant and malignant lesions. The diagnosis of glandular atypia is an exclusion diagnosis, attained when it is not possible to define the nature of the lesion, not being possible to be ruled out in the cytological assessment. Its increasing incidence is probably due to a higher degree of observation and training of cytologists, collection improvement, as well as the actual increase in cases of glandular lesions. Based on these results, it can be observed that cervico-vaginal cytology with AGC allows the selection of women that must follow immediately to colposcopy and subsequent histological analysis, so that an adequate therapeutic conduct can be established, aiming at decreasing the rates of cervical cancer.

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