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ORIGINAL ARTICLE

# Cytohistological correlation in patients with atypical glandular cells on Papanicolaou test in a Chilean population

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## Abstract

The standard screening test for detecting cervical lesions and cancers is a Papanicolaou (Pap) smear. While squamous cell abnormalities remain the most common positive Pap test result, cytologic findings of glandular cell abnormalities have become more frequent in recent decades. The 2014 Bethesda System for reporting cervical cytology includes the classification "atypical glandular cells" (AGC). AGC have morphological abnormalities that fall outside the range of reactive changes, but are insufficient for a diagnosis of invasive adenocarcinoma. In several histologic follow-up studies, most AGC cases were found to represent a benign condition. In the current study, we evaluate the significance of AGC cytology findings by analyzing the histologic follow-up results of a large number of patients with AGC. Most patients with AGC in this study were found to have a significant lesion on follow-up (63.9%), with negative histologic results in only 36.1% of patients. Among patients with significant lesions, the most common result was low-grade squamous intraepithelial lesion (26.6%), followed by high-grade squamous intraepithelial lesion (23.2%). This provides further evidence to support the Chilean Clinical Guidelines for Cervical Cancer, which recommends diagnostic follow-up studies in all women with AGC to minimize the chance of undetected serious cervical disease.

**KEYWORDS**

atypical glandular cells, cervical cancer, cytohistological correlation, Pap

## 1 | INTRODUCTION

The standard screening test for detecting cervical lesions and cancers is a Papanicolaou (Pap) smear to evaluate cervical cells. Morphologically, squamous carcinoma is the most common type of cervical cancer worldwide. However, adenocarcinoma (ADCa) incidence is rising in several countries.[1-5] Accordingly, while squamous cell abnormalities remain the most common positive Pap test result, cytologic findings of glandular cell abnormalities have become more frequent in recent decades.[6,7]

The 2014 Bethesda System for reporting cervical cytology includes the classification "atypical glandular cells" (AGC). AGC have morphological abnormalities that fall outside the range of reactive changes, but are insufficient for a diagnosis of invasive ADCa.[8] According to the literature, AGC incidence is 0.05% to 2.1%.[6,9-11] In several histologic follow-up studies, most AGC cases were found to represent a benign condition. However, a significant proportion of AGC findings lead to diagnosis of a high-grade squamous or neoplastic glandular lesion of the cervix or endometrium.[9-11]

Identifying AGC is clinically important due to a close association with cervical cancers and premalignant lesions. Prior studies have shown that roughly 9% to 35.5% of women with AGC will be diagnosed with a significant lesion on follow-up.[6,9-13] Significant lesion is a term used to define any lesion ranging from low-grade squamous intraepithelial lesion (LSIL) to invasive carcinoma. Thus, patients diagnosed with ACG should receive comprehensive diagnostic evaluation for malignant or premalignant conditions of the cervix and endometrium.

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Applying AGC findings to early detection of cervical glandular neoplasia remains a major challenge. Some studies have shown limited reproducibility of Pap test AGC interpretations, which makes results less reliable.[14,15] Moreover, the range of follow-up outcomes observed in women with AGC, from benign to malignant, is a barrier to creating efficient and reliable clinical guidelines for AGC management. In the current study, we evaluate the significance of such cytology findings by analyzing the histologic follow-up results of a large number of patients with AGC.

## 2 | MATERIAL AND METHODS

A descriptive retrospective study was performed at the Preventive Oncology Center (University of Chile), over a 11-year period. The clinicopathological data for patients diagnosed with AGC on Pap tests from 1 January 2006 to 31 December 2016 were retrieved from our database. The data retrieved from medical records included the patient's age at the initial AGC diagnosis, the time interval from the Pap test to the colposcopic examination and cervical biopsy, and the histologic findings. AGC interpretations and subcategorizations were based on the 2014 Bethesda System as follows: atypical glandular cells, not otherwise specified (AGC-NOS); or atypical glandular cells, favor neoplastic (AGC-FN). The subcategorizations used in this diagnostic center do not differentiate between atypical endometrial and atypical endocervical cells. As quality control, some of the samples were randomly selected and re-examined to confirm the previous diagnostic.

Documented histologic follow-up studies included cervical biopsy, endocervical curettage, cervical excisional biopsy, endometrial biopsy, and hysterectomy. For cases with two or more procedures and/or more than one diagnosis of a neoplastic lesion during the specified follow-up period, only the most abnormal histologic diagnosis was documented. Only patients with histologic results within 3 years of the AGC finding were considered for this study. All Pap tests included in the analysis were conventional Pap smears. The cases diagnosed with AGC on Pap test during the previously mentioned period were classified into AGC-NOS and AGC-FN, then, subdivided in cases with histologic follow-up and those without histologic follow-up. Next, classification was made according to the histologic finding for each AGC category. The study flowchart is presented in Figure 1. Institutional Ethics Committee approval was not sought, as this study was limited to a retrospective database review.

A Pearson chi-square test was used for statistical analyses, which were performed with RStudio, version 1.2.1335 (©2009-2019 RStudio, Inc.). A *P*-value below .05 was considered statistically significant.

## 3 | RESULTS

Between 1 January 2006 and 31 December 2016, a total of 1 491 697 Pap tests were performed and interpreted at our diagnostic center, of which 533 (0.036%) included an AGC finding. The AGC subtype results are shown in Table 1. AGC-NOS was the most common classification, accounting for 82.6% of all AGC cases. The mean age of the women diagnosed with AGC was 42.8 years (range, 18-79 years; median, 43 years).

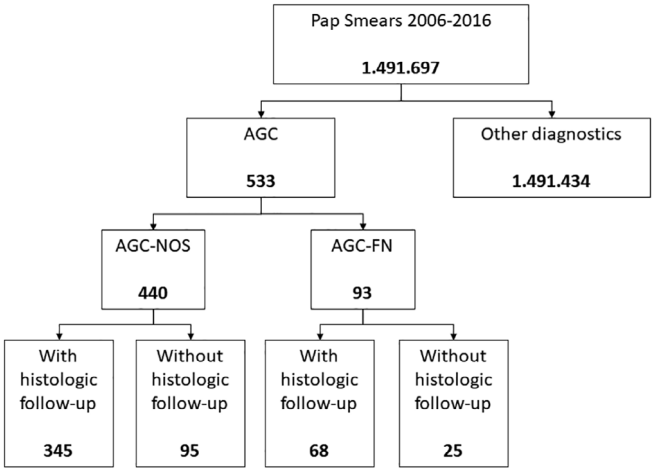


**FIGURE 1** Study flowchart. AGC, atypical glandular cells; AGC-NOS, atypical glandular cells, not otherwise specified; AGC-FN, atypical glandular cells, favor neoplastic

**TABLE 1** Prevalence of AGC subtypes and proportions of cases with histologic follow-up results

| AGC subtype (2001 Bethesda System) | Total cases N (%)[a] | Cases with histologic follow-up results N (%)[b] | Mean age, years (range) |
|---|---|---|---|
| AGC-NOS | 440 (82.6%) | 345 (83.5%) | 42.4 (19-79) |
| AGC-FN | 93 (17.4%) | 68 (16.5%) | 45.4 (18-72) |
| Total | 533 | 413 | 42.8 (18-79) |

Abbreviations: AGC, atypical glandular cells; AGC-FN, atypical glandular cells, favor neoplastic; AGC-NOS, atypical glandular cells, not otherwise specified.
[a]Percentage of cases in each subtype, of all AGC cases.
[b]Percentage of cases with histologic follow-up results.

Histologic follow-up results were available for 413 of the 533 AGC cases (77.5%). Histologic follow-up specimens included cervical biopsy and/or endocervical curettage, endometrial biopsy/curettage, loop electrocautery excision procedure/cone biopsy, and hysterectomy. The cytohistologic correlation results for these 413 cases are shown in Table 2 and Figure 2

Among all AGC cases, normal histologic findings were observed in 149 of 413 patients (36.1%). Significant lesions, including LSIL, HSIL, invasive cervical cancer (ICC), adenocarcinoma in situ (AIS), and ADCa, were found in 264 cases (63.9%), of which 216 (81.8%) were squamous lesions and 48 (18.2%) were cervical glandular lesions, being cervical squamous lesions significantly more frequent than glandular lesions ($P = 2.2e^{-16}$). Among patients with significant lesions, the most common result was LSIL (41.7%), followed by HSIL (34.8%), ADCa (12.9%), ICC (5.3%), AIS (4.2%), and finally HSIL + ADCa (1.1%)

**TABLE 2** Histologic follow-up results for patients diagnosed with AGC on Pap test

| | | Cervical squamous lesions N (%) | | | Cervical glandular lesions N (%) | | | |
|---|---|---|---|---|---|---|---|---|
| AGC subtype | Negative N (%) | LSIL | HSIL | ICC | AIS | ADCa | HSIL + ADCa N (%) | Total N |
| AGC-NOS | 141 (40.8%) | 97 (28.1%) | 72 (20.9%) | 8(2.3%) | 9 (2.6%) | 18 (5.2%) | 0 (0%) | 345 |
| AGC-FN | 8 (11.8%) | 13 (19.1%) | 20 (29.4%) | 6(8.8%) | 2 (2.9%) | 16 (23.5%) | 3 (4.4%) | 68 |
| Total | 149(36.1%) | 110(26.6%) | 92 (22.3%) | 14(3.4%) | 11 (2.7%) | 34 (8.2%) | 3 (0.7%) | 413 |

*Note:* Only the most severe lesion was recorded for each case; however, for cases with HSIL and ADCa, both lesions were recorded.
Abbreviations: ADCa, adenocarcinoma; AGC, atypical glandular cells; AGC-FN, atypical glandular cells, favor neoplastic; AGC-NOS, atypical glandular cells, not otherwise specified; AIS, adenocarcinoma in situ; HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical cancer; LSIL, low-grade squamous intraepithelial lesion in situ.

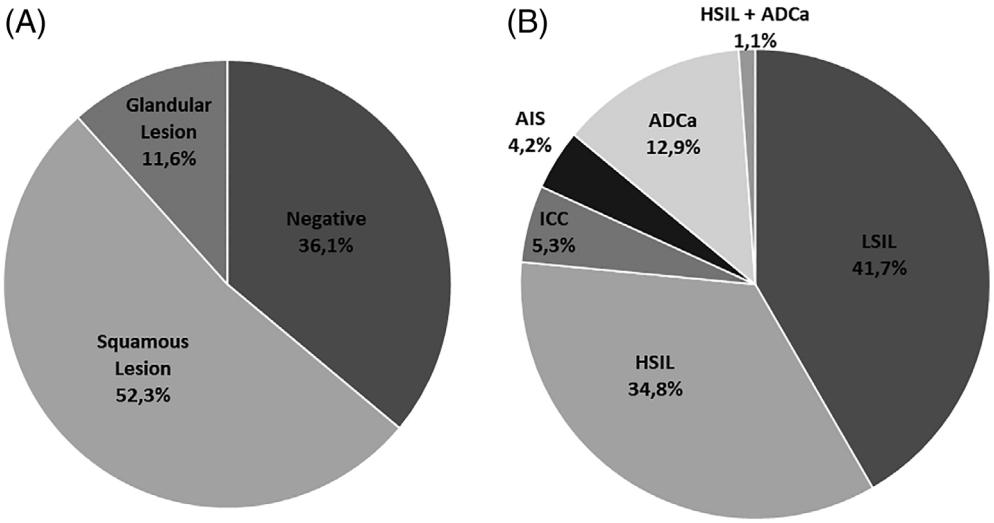


**FIGURE 2** Graphs showing the histologic follow-up results for patients diagnosed with AGC on Pap test. A, Percentage of negative results, squamous lesions and glandular lesions of the total amount of patients diagnosed with AGC on Pap test. B, Percentages of each type of lesion of the total amount of patients diagnosed with a lesion on histologic follow-up. ADCa, adenocarcinoma; AGC, atypical glandular cells; AIS, adenocarcinoma in situ; HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical cancer; LSIL, low-grade squamous intraepithelial lesion in situ

**TABLE 3** Histologic follow-up results for patients diagnosed with AGC on Pap test, by age group

| | | Cervical squamous lesions N (%) | | | Cervical glandular lesions N (%) | | | |
|---|---|---|---|---|---|---|---|---|
| Age | Negative N (%) | LSIL | HSIL | ICC | AIS | ADCa | HSIL + ADCa N (%) | Total N (%) |
| <34 | 29 (34.5%) | 17 (20.2%) | 28 (33.3%) | 2 (2.4%) | 0 (0.0%) | 7 (8.3%) | 1 (1.2%) | 84 |
| 35-49 | 83 (37.7%) | 68 (30.9%) | 38 (17.3%) | 8 (3.6%) | 5 (2.3%) | 18 (8.2%) | 0 (0.0%) | 220 |
| 50-64 | 35 (35.7%) | 23 (23.5%) | 22 (22.5%) | 2 (2.0%) | 6 (6.1%) | 8 (8.2%) | 2 (2.0%) | 98 |
| >65 | 2 (18.2%) | 2 (18.2%) | 4 (36.4%) | 2 (18.2%) | 0 (0.0%) | 1 (9.1%) | 0 (0.0%) | 11 |
| Total | 149 | 110 | 92 | 14 | 11 | 37 | 7 | 413 |

*Note:* For each case, only the most severe lesion was recorded. However, for cases with HSIL and ADCa, both lesions were recorded.
Abbreviations: ADCa, adenocarcinoma; AIS, adenocarcinoma in situ; HSIL, high-grade squamous intraepithelial lesion; ICC, invasive cervical cancer; LSIL, low-grade squamous intraepithelial lesion in situ.

(Figure 2). Among the AGC-FN cases, only 8 of 68 (11.8%) had normal histology, and 60 presented with significant lesions (88.2%), while among AGC-NOS 141 of 345 cases (40.8%) had normal histology and 204 presented significant lesions (59.1%). As expected, patients with a finding of AGC-FN were more likely to have significant lesions on follow-up than those with AGC-NOS ($P$ = .017).

Table 3 shows the AGC cases grouped according to patient age at initial AGC finding. The 35- to 49-year-old age group had the largest

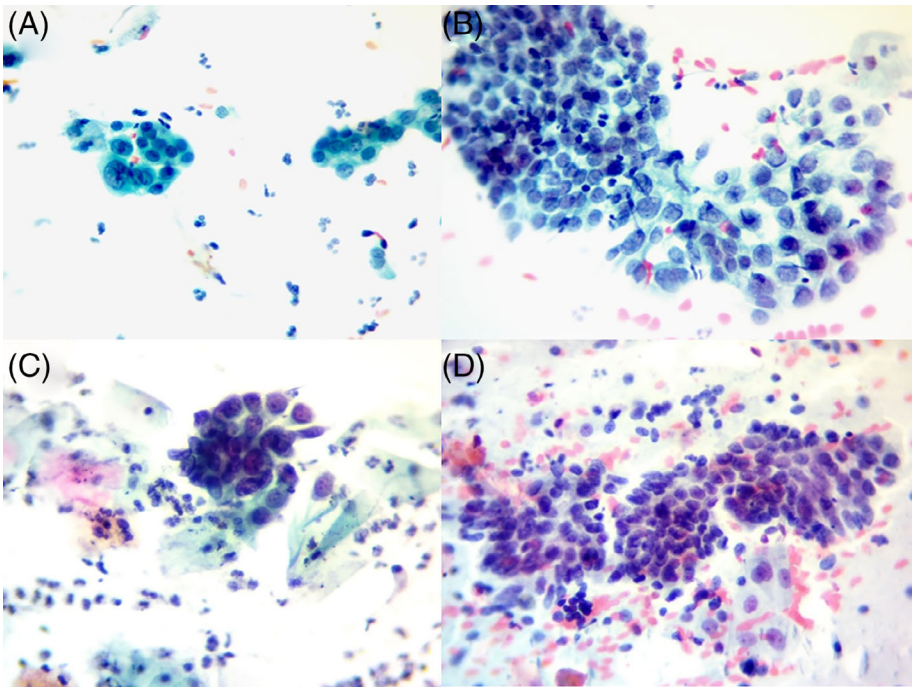


**FIGURE 3** Pap smears diagnosed as AGC. A, ACG case that was negative on follow-up. The image shows nuclear size variability, slightly enlarged with a small nucleolus. B, ACG case diagnosed with LSIL on follow-up. The image shows a group of poorly preserved and much degenerated glandular cells with variation in nuclear size. C, ACG case diagnosed with HSIL on follow-up. The image shows three-dimensional groups of cells with crowded round hyperchromatic nuclei, and the presence of small nucleoli. D, ACG case diagnosed with adenocarcinoma on follow-up. The image shows a large group of glandular cells with edges that display feathering and oval nucleus. The cells lost the typical glandular pattern. There is nuclear hypercromasia and superposition in some areas. AGC, atypical glandular cells; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion

proportion of AGC cases. The most common lesion in this group on follow-up was LSIL (30.9%), followed by HSIL (17.3%). Women 50 to 64 years of age showed similar percentages of LSIL and HSIL (23.5% and 22.5%, respectively). This group also had the highest proportion of glandular lesions, at 16.3%; this diagnosis includes AIS, ADCa, and mixed lesions (ADCa + HSIL). Among women aged 34 years or younger and 65 or older, the most common lesion was HSIL, representing 33.3% and 36.4% of diagnoses, respectively. It is worth noting that women aged 65 years or older had the lowest proportion of negative histologic results.

## 4 | DISCUSSION

The Pap test is a valuable diagnostic tool for identifying premalignant lesions and cervical cancers and has been shown to reduce cancer mortality. Therefore, accurate interpretation of cytologic results is critical, along with comprehensive follow-up after a finding of abnormal cells.

This is the first study to evaluate histologic follow-up results in women diagnosed with AGC in Chile. Our data generally concur with studies on AGC from other countries. Of the total of Pap test analyzed only 0.036% included an AGC finding, similar to values reported by other studies, which typically range from 0.05% to 2.1%.[6,9-11,13] Contrary to previous reports, however, most patients with AGC in this study were found to have a significant lesion on follow-up, with negative histologic results in only 36.1% of patients. These results differ from the literature, where most studies report negative histologic results ranging from 42% to 70.5% of the total cases of AGC,[6,9,10,16] with only two articles reporting a very low percentage of negative histologic results, 20% and 31%.[17,18] It is worth to mention than in those cases the sample size was 44 and 45 cases, respectively.

Of the cases with significant cervical lesions on histologic follow-up, cervical squamous lesions were significantly more frequent than glandular lesions. This result is consistent with previous studies, which have shown squamous lesion to be more frequent, differing only in the fact that HSIL was the most common finding, especially in women under 50 years of age[2,4,7-9] while in our study the most common lesion was LSIL in women between the ages 35 and 64, and HSIL was more frequent in women under 34 years and older than 65 years.

As expected, patients with a finding of AGC-FN were more likely to have significant lesions on follow-up than those with AGC-NOS, which is consistent with the literature. Figure 3 shows four images of Pap smears classified as AGC that were (A) negative for histologic findings or diagnosed histologically as (B) LSIL, (C) HSIL, or (D) ADCa. Potential confounding factors include poor cell preservation, degenerative processes, and reactive changes.

Chilean clinical guidelines for cervical cancer management recommend colposcopic evaluation and endocervical sampling for all patients with AGC on a Pap test.[19] However, only 77% of the patients in our database with AGC had a record of histologic follow-up. As our diagnostic center does not perform or diagnose cervical biopsies, biopsy results are sent to us from the hospital where patients receive treatment. Therefore, it is possible that some results were not delivered despite our requests. Other potential explanations for this low rate of histologic follow-up is that patients failed to attend the recommended colposcopic evaluation or decided to seek further evaluation and treatment in the private health system.

## 5 | CONCLUSION

Our results show that histologic follow-up of patients with AGC findings on Pap test is necessary due to the high possibility of detecting a cervical lesion, providing further evidence to support the Chilean Clinical Guidelines for Cervical Cancer, which recommend diagnostic follow-up studies in all women with AGC to minimize the chance of undetected serious cervical disease.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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