# Sledenje žensk z atipičnimi žleznimi celicami v brisih maternične vratu

# Follow–up of females with atypical glandular cells on Pap smears

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## Izvleček

**Namen:** *Interpretacija žleznih sprememb v brisih maternične vratu je težka in za citologa še vedno predstavlja velik problem. V raziskavi smo želeli ugotoviti delež atipičnih žleznih celic (AŽC) v brisih maternične vratu (BMV) in pogostnost klinično pomembnih diagnoz.*

**Metode:** *Naredili smo retrospektivno analizo 199.265 BMV v 6–letnem obdobju. Ugotavljali smo delež AŽC med vsemi pregledanimi BMV in analizirali histološke spremembe pri tistih, pri katerih sta bila opravljena kirurška biopsija in histološki pregled. Podatke smo obdelali s statističnim programom SPSS. Statistična značilnost je bila določena z vrednostjo $p < 0,05$.*

**Rezultati:** *V obdobju med 1. 1. 2003 in 31. 12. 2008 je bilo med vsemi pregledanimi BMV 745 bolnic z AŽC (0,4 %). Povprečna starost pacientk*

## Abstract

**Purpose:** *Atypical glandular cells (AGC) are often associated with clinically significant lesions, but the interpretation of AGC and the associated lesions on Pap smears remains challenging, even for experienced cytopathologists. The frequency and histologic follow–up of AGC regardless of gland cell type were investigated.*

**Methods:** *A retrospective review was conducted involving 199,265 cervicovaginal smears which were examined in the Department of Pathology and Cytology of Celje General Hospital between 1 January 2003 and 31 December 2008. We investigated the frequency of AGC on conventional Pap smears and evaluated the follow–up and correlation between cytology results and subsequent biopsy diagnoses over a 6–year*

*je bila 41 let (17–65). S histološkim pregledom smo našli klinično pomembne spremembe pri 79 bolnicah (45,9 %). 63 pacientk je imelo CIN visoke stopnje (2/3), pri 4 je bil ugotovljen adenokarcinom in situ, v 12 primerih pa smo ugotovili invazivni karcinom (5 adenokarcinomov endometrija, 5 ploščatoceličnih karcinomov in dva druga). 26 pacientk je imelo CIN 1, dve žlezne spremembe nizke stopnje, 65 (37,8 %) pacientk pa je imelo normalen histološki izvid.*

**Zaključek:** *AŽC so redka sprememba v BMV, a je zaradi visokega deleža klinično pomembnih diagnoz prognostično in terapevtsko pomembna, zato je potrebno te bolnice skrbno spremljati.*

*period. The data were processed using the statistics program, SPSS. Statistical significance was set at a $p<0.05$.*

**Results:** *Between 1 January 2003 and 31 December 2008, a total of 745 women had AGC, representing 0.4% of all Pap smear results. One hundred seventy–two women (23.1%) with an average age of 41 years (range, 17–65 years) had a subsequent histologic examination. There were 79 patients (45.9%) with a clinically significant diagnosis, including 63 patients with high–grade cervical intraepithelial neoplasia, 4 patients with adenocarcinoma in situ, and 12 patients with invasive carcinoma (5 endometrial adenocarcinomas, 5 cervical squamous carcinomas, and 2 other types). Normal histologic findings were present in 65 patients (37.8%), 26 patients had low–grade cervical intraepithelial neoplasia, and 2 patients had low–grade glandular intraepithelial neoplasia.*

**Conclusion:** *In subsequent biopsy specimens, cytologically AGC are not always glandular or even abnormal. The underlying abnormalities are often so serious that AGC findings require careful clinical and histologic follow–up.*

## INTRODUCTION

Since its introduction by Papanicolaou, cytologic examination of cervical smears has led to the early detection of cervical carcinoma and its precursors (1). Atypical glandular cell (AGC) interpretations remain among the major challenges in gynecologic cytopathology (2, 3). Although interpretation of AGC on Pap smears is of limited reproducibility, a significant subset of AGC cases reflect underlying high–grade intraepithelial squamous, glandular lesions, or even malignant lesions, and should therefore be followed carefully (4–6). The European guidelines for quality assurance in cervical cancer screening recommend that cytology results should be reported using a nationally agreed–upon terminology that is at least translatable into the Bethesda system (7, 8). The Bethesda classification was introduced in Slovenia on 1 October 2011 (8–10). According to the Bethesda system, AGC are not readily classifiable as reactive or neoplastic (5, 10). Although AGC are not commonly encountered in Pap smear reports, AGC are associated with a high proportion of clinically significant lesions (5, 6, 11–13). Annual reviews on the cervical cancer screening program, ZORA, in Slovenia are published regularly and include data about the incidence of AGC; however, the results about the histologic follow–up are insufficient and have not been studied systematically (14, 15). Therefore, we have made an analysis of the incidence and histologic follow–up of patients with AGC in the cytology laboratory of Celje General Hospital.

## MATERIAL AND METHODS

The computerized database in the Department of Pathology and Cytology of Celje General Hospital was searched for all females with a Pap smear and cervical

***Table1.*** *Cervical smears with atypical glandular cells followed by subsequent biopsy between 2003 and 2008*

| Year | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | Total |
|---|---|---|---|---|---|---|---|
| All smears | 12189 | 21118 | 40504 | 39146 | 43728 | 42580 | 199265 |
| AGC smears, N (%) | 186 (1.5) | 183 (0.9) | 179 (0.4) | 129 (0.3) | 32 (0.1) | 36 (0.1) | 745 (0.4) |
| AGC smears with histologic outcome, N (%) | 46 (24.7) | 19 (10.4) | 49 (27.4) | 38 (29.5) | 9 (28.1) | 11 (30.6) | 172 (23.1) |

***Table 2.*** *Smears with atypical glandular cells in the Cytology Laboratory of Celje General Hospital and in Slovenia between 2003 and 2008*

| Year | 2003 | 2004 | 2005 | 2006 | 2007 |
|---|---|---|---|---|---|
| Percent of AGC smears – Celje (%) | 1.5 | 0.9 | 0.4 | 0.3 | 0.1 |
| Percent of AGC smears – Slovenia (%) | 1.6 | 1.1 | 0.9 | 0.6 | 0.5 |

***Table 3.*** *Histopathologic diagnosis in patients with AGC on smears*

| Histopathologic diagnosis | Patients, N | Patients, % |
|---|---|---|
| Normal | 65 | 37.8 |
| CIN I | 26 | 15.1 |
| CGIN NS | 2 | 1.2 |
| CIN II | 23 | 13.4 |
| CIN III | 40 | 23.3 |
| CIN III + AIS | 2 | 1.2 |
| AIS | 2 | 1.2 |
| Squamous cell carcinoma | 5 | 2.9 |
| Endometrial adenocarcinoma | 5 | 2.9 |
| Adenosquamous carcinoma | 1 | 0.6 |
| Mixed mesodermal malignant tumor | 1 | 0.6 |
| Total | 172 | 100.0 |

biopsy which was performed from 0–6 months after the Pap smear in the period between 1 January 2003 and 31 December 2008. A total of 199,265 cervical smears were processed during this period, including screening smears and all others which were obtained for any other reason. Only smears with AGC (cervical, endometrial, or not otherwise specified) were included in the study. In the current study, we compared Pap smear results in patients with AGC with the corresponding diagnosis stated on cervical biopsies. The histopathologic diagnoses in the current study group were as follows: no significant changes (negative); cervical intraepithelial neoplasia (CIN) 1, 2, or 3; low-grade cervical glandular intraepithelial neoplasia (CGIN–LG); adenocarcinoma in situ (AIS); endometrial adenocarcinoma; squamous cell carcinoma; adenosquamous cell carcinoma; and mixed mesodermal malignant tumor.

Statistical analysis was performed using the SPSS system. Descriptive statistics, t-tests, and analysis of variance (ANOVA) were used, as appropriate. A 0.05 significance level was applied for all statistical tests.

The study was approved by the Ethical Committee of Celje General Hospital on 27 January 2011.

## RESULTS

The number of patients with AGC during the study period was 745 (0.4% of all Pap smears). One hundred seventy-two patients (23.1%) had tissue available for follow-up (Table 1).

In comparison to the average frequency of AGC in Slovenia, the frequency of AGC in our hospital was slightly lower (Table 2).

In Table 3, the histopathologic diagnoses in patients with AGC are shown (Table 3). The mean age of these patients was 41.2 years (range, 17–65 years). The distribution of patients in different age groups is shown in Table 4.

Negative histologic diagnoses were statistically more frequent ($p = 0.000$; correlation coefficient = –0.683)

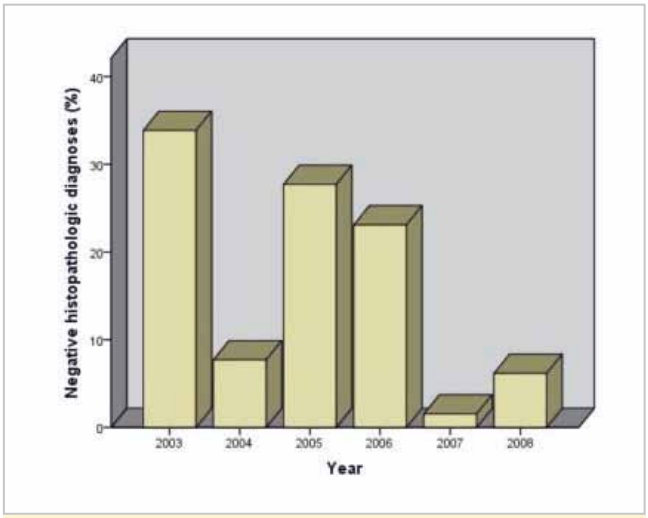


***Figure 1.*** *Negative histopathologic results between 2003 and 2008 (N=172)*

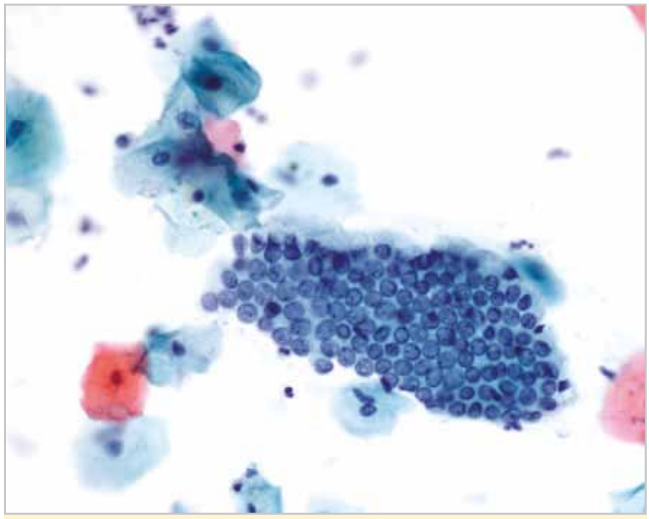

***Figure 2.*** *Smear with normal endocervical cells (PAP, original magnification ×400)*

in the first years of our study interval (Fig. 1). Clinically significant precancerous or malignant histologic outcomes, excluding CIN1 and CGIN–LG, were documented in 79 patients (Table 5).

The results were also analyzed according to age. The mean age in patients with clinically significant histologic diagnoses was 39.9 years, and the mean age of other patients was 42.3 years (p = 0.082). However, patients with CIN 2 or 3 and AIS were significantly

***Table 4.*** *Histopathologic diagnosis vs. patient age (N=172)*

| Histopathologic diagnosis | | Age | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | | < 20 | 21–30 | 31–40 | 41–50 | 51–60 | >60 | |
| Normal | Number | 1 | 3 | 19 | 37 | 4 | 1 | 65 |
| | % | 1.5% | 4.6% | 29.2% | 56.9% | 6.2% | 1.5% | 100.0% |
| CIN I | Number | 0 | 6 | 8 | 9 | 3 | 0 | 26 |
| | % | .0% | 23.1% | 30.8% | 34.6% | 11.5% | .0% | 100.0% |
| CGIN NS | Number | 0 | 0 | 0 | 2 | 0 | 0 | 2 |
| | % | .0% | .0% | .0% | 100.0% | .0% | .0% | 100.0% |
| CIN II | Number | 2 | 3 | 8 | 7 | 2 | 1 | 23 |
| | % | 8.7% | 13.0% | 34.8% | 30.4% | 8.7% | 4.3% | 100.0% |
| CIN III | Number | 0 | 12 | 17 | 9 | 1 | 1 | 40 |
| | % | .0% | 30.0% | 42.5% | 22.5% | 2.5% | 2.5% | 100.0% |
| CIN III + AIS | Number | 0 | 1 | 1 | 0 | 0 | 0 | 2 |
| | % | .0% | 50.0% | 50.0% | .0% | .0% | .0% | 100.0% |
| AIS | Number | 0 | 0 | 0 | 0 | 2 | 0 | 2 |
| | % | .0% | .0% | .0% | .0% | 100.0% | .0% | 100.0% |
| Malignant lesion | Number | 0 | 0 | 2 | 4 | 4 | 2 | 12 |
| | % | .0% | .0% | 16.7% | 33.3% | 33.3% | 16.7% | 100.0% |
| Total | Number | 3 | 25 | 55 | 68 | 16 | 5 | 172 |

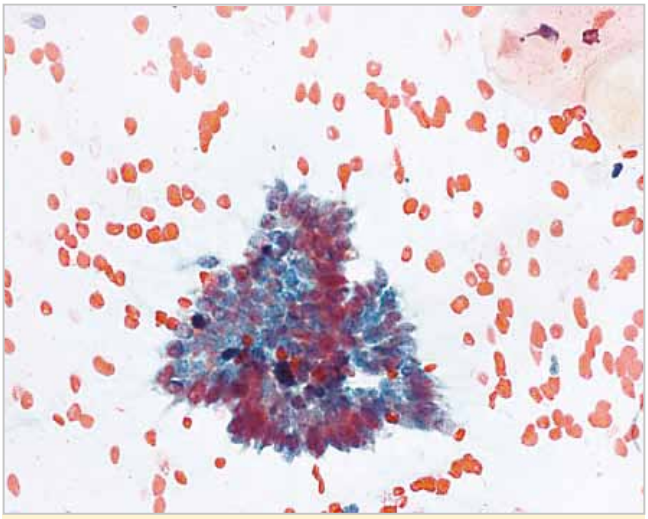

***Figure 3.*** *Smear with adenocarcinoma in situ confirmed by biopsy (PAP, original magnification ×400)*

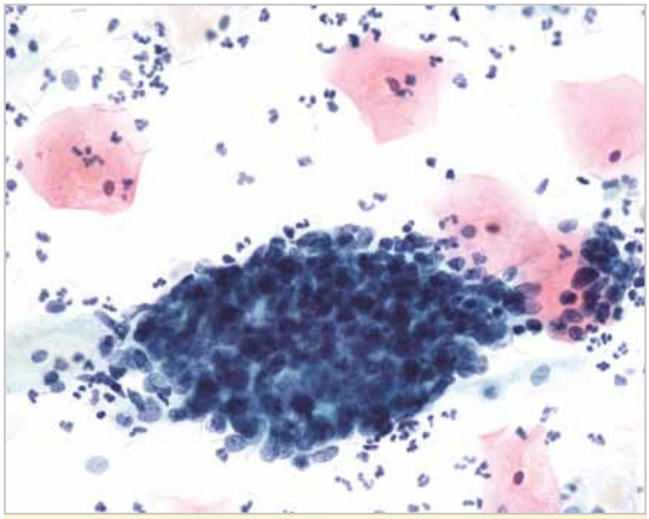

***Figure 4.*** *Smear with H–SIL confirmed by subsequent biopsy as invasive adenocarcinoma (PAP, original magnification ×400 )*

younger (p = 0.01) than patients with invasive disease (Table 6).

There were 94 patients with squamous lesions and 9 patients with glandular lesions, excluding combined changes (Table 7). The average age of patients with histologically–proven glandular lesions was 52.6 years, and 38.9 years in patients with squamous lesions (p = 0.000).

***Table 5.*** *Patients with clinically significant diagnoses (N=172)*

| Histopathologic diagnosis | Patients (N) | Patients (%) |
|---|---|---|
| Clinically significant | 79 | 45.9 |
| Clinically less significant | 93 | 54.1 |
| Total | 172 | 100 |

## DISCUSSION

Interpretation of AGC is one of the most difficult areas in gynecologic cytopathology. It is usually easy to recognize normal endocervical cells (Fig. 2) or severe glandular atypia/AIS (Fig. 3). Nevertheless, in many cases of abnormal cells it is not even possible to distinguish glandular (Fig. 4) from squamous (Fig. 5) lesions by cytologic analysis (5).

AGC are a rare finding on Pap smears. In the current study we found 745 patients (0.4%) with AGC in the 6–year period, which is lower than the reported average in Slovenia (Table 2). Reports about AGC rates in the literature range from 0.1%–2.5% (5, 6, 16). In our cohort, the number of AGC cases with

***Table 6.*** *Age of patients with clinically significant diagnosis*

| Histopathologic diagnosis | Patients (N) | Mean age | Median | Modus | St. dev. |
|---|---|---|---|---|---|
| CIN 2, CIN 3, CIN 3 + AIS, AIS | 67 | 38.1 | 39.0 | 40 | 9.7 |
| Malignant lesions | 12 | 49.6 | 50.5 | 51 | 8.6 |

***Table7.*** *Age of patients with squamous and glandular lesions*

| Histopathologic diagnosis | Patients (N) | Mean age | St. dev. | St. error |
|---|---|---|---|---|
| CIN 1, CIN 2, CIN 3, squamous cell carcinoma | 94 | 38.9 | 9.4 | 1.0 |
| CGIN NS, AIS, endometrial carcinoma | 9 | 52.6 | 4.0 | 1.3 |

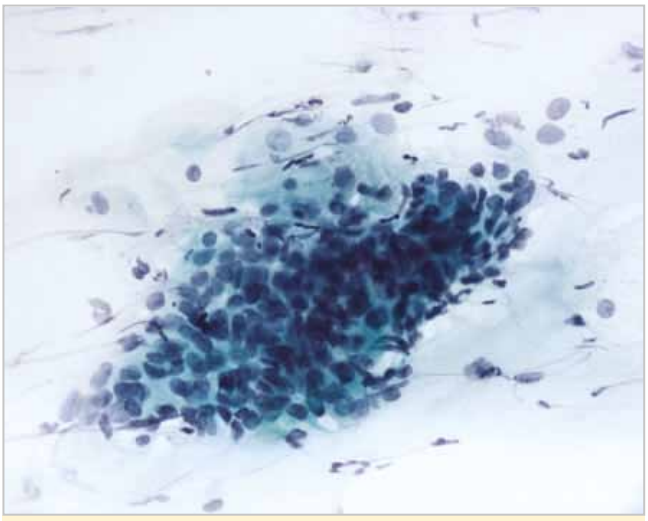

***Figure 5.*** *Smear with AGC confirmed by biopsy as CIN 3 (PAP, original magnification ×400)*

normal histologic results was significantly higher in 2003, 2005, and 2006 (the correlation coefficient = –0.683). The number of AGC is also declining in other Slovenian laboratories (14, 15); the main reasons for the decline in the number of AGC are implementation of quality assurance guidelines and establishment of a school for screeners at the Institute of Oncology in 2006 (15).

The most common pathologic findings were CIN 3 (23.3%), CIN 1 (15.1%), and CIN 2 (13.4%), followed by squamous cell carcinoma and endometrial carcinoma (2.9% each), CIN 3 with AIS and AIS (1.2% each). We also identified 1 case of adenosquamous carcinoma and 1 case of mixed mesodermal malignant tumor (0.6% each). After exclusion of negative cases, combined lesions (squamous and glandular) and mixed mesodermal malignant tumors, we documented a significantly higher number of squamous lesions (94 patients) than glandular lesions (9 patients), which is not unusual (11).

As one would expect, patients with pre–invasive disease were significantly younger (p = 0.01) than patients with invasive disease, which has been documented in a previous report (16). Furthermore, patients with squamous lesions were younger than patients with histologically–confirmed glandular changes (p = 0.000).

For gynecologists, the diagnosis of AGC is important because AGC are often associated with clinically significant lesions (6, 11, 12, 13, 16). Mood et Al. (6) reported clinically significant changes in 52.4% of patients with AGC, and Parellada et al. (11) reported clinically significant changes in 59.5% of patients with AGC. These findings were confirmed in our cohort with clinically significant changes in 45.9% of patients with histologic follow–up.

Among 12 malignant tumors, we diagnosed 5 endometrial adenocarcinomas. We must stress that the purpose of a cervical cancer screening program is not to primarily detecting endometrial carcinomas. However, our results indicate that it is important to follow–up all AGC patients regardless of age. Our patients with endometrial carcinoma were asymptomatic, had stage I disease, and were all younger than typical patients with this disease.

We assume that different gynecologic guidelines for histologic examination and cytologic guidelines for repeat Pap smears before year 2011 were the main reason for the low number of AGC with histologic follow–up (3, 17) in Slovenia. Since 1 October 2011 gynecologists and cytologists have utilized the same guidelines (9, 10, 18), which are consistent with international recommendations (19). We are confident that this unification will lead to more strict indications for subsequent biopsy in patients with AGC.

In conclusion, AGC are a rare finding on Pap smears. However, as females with these changes in cervical smears are associated with a high prevalence of clinically significant disease, they should be carefully followed and treated according to national and international guidelines.

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