Assessment and Management of Atypical Glandular Cells (AGC) on Cervical Cytology

- a case report and chapter review -

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Abstract

A 54 year old Gravida 4 Para 2, menopausal woman presented to our clinic complaining of spotting. Her PAP smear that was done during her annual checkup at the same time was consistent with AGC. We present the management of her case. The presence of Atypical Glandular Cells (AGC) which is encountered in less than 0.5% of all Pap smears may be associated with premalignant or malignant lesions of the cervix, the endometrium or other organs in rare cases (ovaries, fallopian tubes, vagina, colon). Based on the patient age, gravidity, parity, weight, menopausal status, smoking history, accompanying symptoms (cycle abnormalities) but most importantly on the coexistence or not of squamous cell cervical pathology, we propose a comprehensive algorithm using the Pap smear, colposcopy with/without directed biopsies, HPV-DNA testing, endocervical curettage, endometrial curettage or pipelle biopsy and cervical conization in order to assess, manage and follow-up these patients.

Keywords: *Atypical Glandular Cells (AGC), Atypical Glandular Cells of Undetermined Significance (AGUS), Cervical Glandular Intraepithelial Neoplasia (CGIN), management*

Case presentation

A 54 year old Gravida 4 Para 2, menopausal woman presented to our clinic complaining of spotting. Her PAP smear that was done during her annual checkup at the same time was consistent with AGC. Besides from the diagnosis of hypothyroidism and hypertension, she had an non-significant medical history.

The patient, menopausal since the age of 48, underwent colposcopy and pelvic ultrasound which were both normal and a fractional dilatation and curettage. The pathology report from the endometrial curettage revealed an adenomatous endometrial polyp and atrophic endometrium. The endocervical currettings revealed a low grade dysplasia of the glandular epithelium - Glandular Intraepithelial Neoplasia 1(GIN1) and Low Grade Squamous Intraepithelial Lesion (LGSIL) of the endocervix.

It was decided to proceed with a cold knife cervical conization in order to fully assess the cervical pathology. The cold knife was preferred over Large Loop Excision of the Transformation Zone (LLETZ) in order to avoid the thermal artifact of the surgical border. The procedure was done one month after the fractional curettage and the pathology revealed GIN 1 near the transformation zone. The surgical borders of the specimen were free of any disease.

The patient was followed in 6 months for a new PAP smear with colposcopy and a pipelle curettage of the endocervix. Both the PAP smear and the colposcopy were negative. The pipelle biopsy of the endocervix was consistent with LGSIL. The patient was instructed to follow-up again in 6 months.

Introduction

Based on the broadly accepted revised Bethesda System 2001 Workshop Classification*, AGC is subclassified into:

- AGC (endocervical, endometrial or not otherwise specified [NOS]);
- AGC favor neoplasia (endocervical or NOS).
- Glandular cell abnormalities also include:
- Adenocarcinoma in situ (AIS);
- Adenocarcinoma (invasive).

The management of the last two categories is straightforward and beyond the purpose of this paper.

The new Bethesda System 2001 Workshop Classification does not include cellular changes of benign, reactive, reparative or infectious nature, (findings consistent with the 1991 Bethesda Conference Classification category Atypical Glandular Cells of Undetermined Significance (AGUS) with the modifier "favor reactive").

The challenge of the Gynecologist/Pathologist in the assessment of AGC is difficult due to the rarity of the finding

Table 1 *Bethesda System 2001 Workshop Classification

■ Atypical squamous cells ■ Atypical squamous cells of undetermined significance (ASC-US), cannot exclude HSIL (ASC-H) ■ Atypical endocervical/endometrial/glandular cells: NOS or favor neoplasia
■ Adenocarcinoma in situ (AIS) ■ Adenocarcinoma: endocervical, endometrial, extrauterine, NOS

(0.12-2.5%), the inaccessibility of the colposcope to the endocervix, the small size of the cells and the differential diagnosis consisting of conditions such as microglandular hyperplasia, post radiation atypia, cervical endometriosis, post-operative changes, tubal metaplasia, deciduosis, endometrial glands in the upper cervical canal.

AGC may be associated with cervical dysplasia (Low Grade Squamous Intraepithelial Lesions [LGSIL] 8.5%, High Grade Squamous Intraepithelial Lesions [HGSIL] 11.1%), Adenocarcinoma In Situ (AIS) 2.9%, Endometrial hyperplasia 1.4% and malignancy 5.2%.

The coexistence of Atypical Squamous Cells of Undetermined Significance (ASCUS) may increase the likelihood of LGSIL (21%) and HGSIL (34%) whereas the classification of AGC favor neoplasia may be associated with higher rates of AIS (13%) and malignancy (21%). The malignancies that are encountered are distributed as follows:

- Endometrial adenocarcinoma 57.6%;
- Cervical adenocarcinoma 23.6%;
- Squamous cell cervical cancer 5.4%;
- Ovarian cancer 5.4%;
- Fallopian tube cancer 1.0%;
- Other (vagina, colon) 6.9%.

Assessment modalities

1. Pap smear

The traditional method using the Ayre spatula and the endocervical brush has a false positive rate of 5-10%. The false negative rate varies from 5-50%. The use of the liquid based alternative tests (Thin-Prep, Sure-Path,

Table 2 Comparison of the liquid-based alternatives tests (Thin-Prep, Sure-Path, AutoCyte Prep) compared to the traditional PAP smear technique in regard to the detection of Cervical Cytological Abnormalities

Statistically significant differences	Similar
■ Unsatisfactory rate (↓ 39-97%) ■ Satisfactory but limited-by rate (↓44-67%) ■ LGSIL (↑86%) ■ Cervical cancer (↑300%) ■ ASCUS favor reactive ↑	■ HGSIL ■ ASCUS favor dysplasia ■ AGUS

Table 3 Diagnosis & Management of AGC (endocervical/endometrial/NOS)

■ Women<35			■ Women>35 ■ Women <35 with morbidity factors (obesity, anovulation, DUB)
Initial workup: ■ Colposcopy with/without biopsies ■ HPV-DNA testing ■ Endocervical curettage (ECC) ↓			■ Colposcopy with/without biopsies ■ HPV-DNA testing ■ Endocervical curettage (ECC) ■ Endometrial sampling/pipelle
ECC → normal Colposcopy +/- biopsies → normal		ECC →positive and/ or Coploscopy +/- biopsies →positive	Colposcopy + biopsies → positive and/or ECC → positive and/or endometrial sampling → positive
Low risk HPV	High risk HPV or unavailable HPV status	↓	↓
↓	↓	Cervical conization via LLETZ or cold knife	Treat according to pathology
Repeat cytology + HPV DNA testing in 12 months	Repeat cytology in 6 months until negative x 4		

AutoCyte Prep) offers a statistically significant reduction of unsatisfactory reports by 39-97% and satisfactory but limited-by reports by 44-67%, since there is no loss of specimen from the smear and since the monolayer visualization of atypical and glandular cells allows for a more accurate diagnosis.

There is no statistically significant difference between the detection rate for the atypical diagnostic categories (ASCUS favor dysplasia and AGUS) and also the High Grade Squamous Intraepithelial Lesions (HGSIL), between the conventional and liquid-based smears. On the other hand, the liquid-based tests offer detection rates improved by 31-86% for Low Grade Squamous Intraepithelial Lesions (LGSIL) and cervical cancer by 300% compared to the traditional method.

2. HPV-DNA testing

The isolation of high-risk HPV subtypes (5,8,16,18,31, 33,35,39,45,51,52,56,58) should be seriously taken under consideration in order not only to determine the initial management of the patient but also the frequency of the follow-up appointments after the completion of the initial management. The HPV DNA testing by PCR is a reliable and reproducible technique provided that standardized protocols and validated reagents are used. The addition of HPV mRNA and p16 detection may also play an important role in future screening but only preliminary data are available at present.

3. Colposcopy

As mentioned earlier, the frequent coexistence of AGC and squamous cell abnormalities mandates the use of the colposcope with/without directed biopsies as indicated in the assessment of AGC. In some protocols the absence of colposcopic findings means that the patient should undergo an endocervical or endometrial curettage depending on the menopausal status or accompanying symptomatology such as dysfunctional uterine bleeding.

4. Endocervical/endometrial sampling

Endocervical sampling is a diagnostic modality that should be in the initial workup of all patients with the diagnosis of AGC. In women older than 35 years of age or in women less than 35 years of age with morbidity factors such as the presence of obesity, anovulatory cycles or dysfunctional uterine bleeding, endometrial sampling should be performed as well. Both diagnostic modalities are contraindicated in pregnancy. Alternatively to the use of the typical endometrial curettage, the use of the Cornier Pipelle is a safe and accurate method for diagnosis of endometrial cancer or its precursor, endometrial hyperplasia.

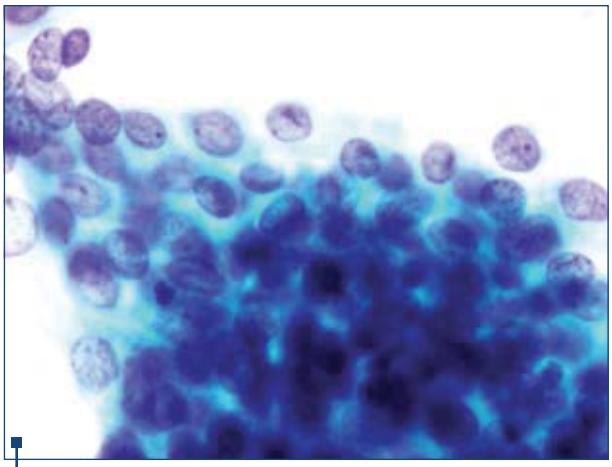

Figure 1. Microscopical aspect of AGUS (original photos)

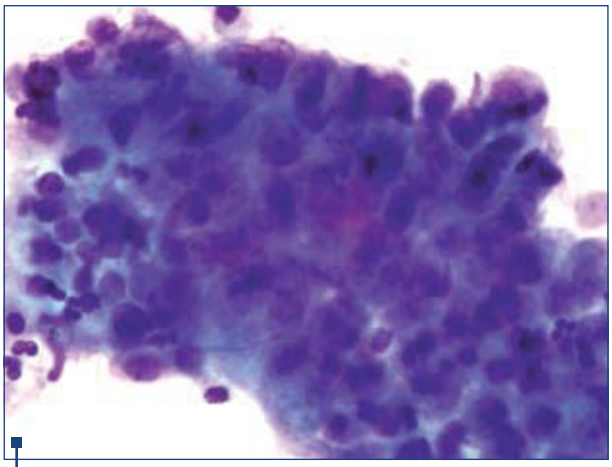

Figure 2. Microscopical aspect of AGUS (original photos)

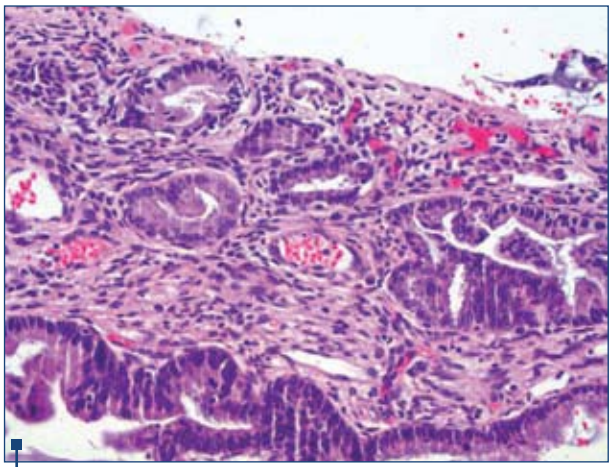

Figure 3. Histological aspect of AGUS x40 H-E (original photos)

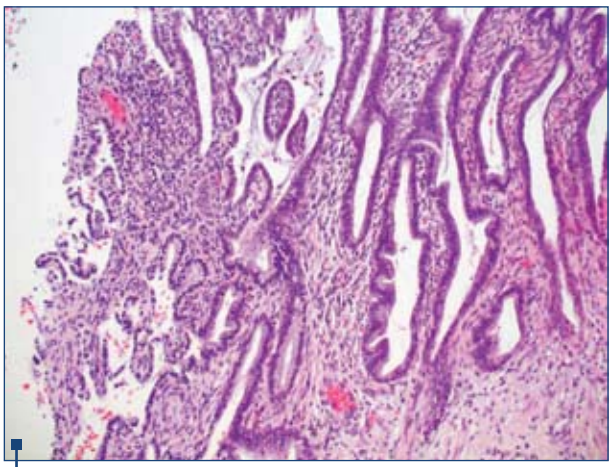

Figure 4. Histological aspect of AGUS x20 H-E (original photos)

Table 4 Diagnosis & Management of AGC (favor neoplasia)

Initial workup negative	Initial workup positive
↓	↓
Cervical conization via LLETZ or cold knife Endocervical curettage Endometrial sampling	Treat according to pathology

5. Cervical conization

Diagnostic and many times therapeutic, cervical conization by cold-knife or the Large Loop Excision of the Transformation Zone (LLETZ)is used when colposcopy is not satisfactory (the transformation zone is not clearly visible), when the cervical biopsy or the endocervical curettage results in High Grade squamous intraepithelial lesions (HGSIL), in non-compliant patients, in patients who have a history of Laser cauterization of the cervix in the past and finally in patients in whom there is a discrepancy between the pathology report of the cervical biopsy and the cytology report (more severe pathology than the biopsy). The pathologists prefer Cold knife conization over LLETZ, because of the avoidance of the thermal artifact in the surgical margins. Some authors prefer the use of a cylindrical rather than a cone shaped specimen especially when the patient desires to retain her fertility. The depth of excision is dependant on the patients' age as younger patients, less than 35, usually have a proximal linear extent of glandular pathology of less than 1cm from the squamocolumnar junction (SCJ). In this case a 1cm length above the SCJ in patients less than 35 is considered adequate. In older women, as the SCJ retreats into the canal, a deeper excision (>1cm) is advised.

Initial work-up

1. Conservative management of AGC

Women up to the age of 35 should undergo immediate colposcopy with /without cervical biopsies (based on the findings) and mandatory endocervical curettage. In women who are >35, or in women <35 with morbidity factors such as obesity, anovulatory cycles or dysfunctional uterine bleeding, endometrial sampling should be performed as well.

HPV-DNA testing should also be done at the time of colposcopy. The presence of High-risk HPV should focus our management on cervical pathology, whereas its absence should elicit a search for endometrial disease especially in women >50.

2. Radical management of AGC

Hysterectomy is an option that could be included in the management of AGC in the following cases:

a. Completed fertility plans;
b. Positive cone margins after conization;
c. Cervical stenosis after conization;
d. Recurrent AGC;
e. Poor patient compliance;
f. Co-existence of other gynecological conditions.

Follow-up

1. Patients with AGC-endocervical/endometrial/NOS: repeat cytology plus HPV testing is recommended at 6 months in the case of HPV positive or unknown, at 12 months if HPV is negative or repeat cytology every 6 months until negative for 4 consecutive follow-ups, if HPV testing is unavailable. If repeat cytology reveals Atypical Squamous cells or HPV positive, colposcopy, endocervical curettage and endometrial biopsy should be repeated. If the diagnosis of AGC-NOS is repeated and the work-up is negative, cold knife conization and fractional dilatation and curettage is recommended. If the work-up is positive, treatment is based on pathology.

2. Patients with AGC-favor neoplasia: if the initial evaluation work-up is negative, cold knife conization with endocervical and endometrial sampling is recommended. If the initial work-up is positive, treatment is based on pathology.

Conclusion

The presence of AGC on the PAP smears should mandate a thorough assessment of the patient based on her age, parity, coexistence of squamous cell abnormalities on the PAP smear and other risk factors such as unopposed estrogen exposure or dysfunctional uterine bleeding. The assessment including the liquid based PAP smears, coploscopy with/without directed biopsies, HPV-DNA testing by PCR, endocervical currettage and endometrial sampling either by curettage or the use of the Cornier Pipelle should direct the physician to a safe diagnosis.

The management and follow-up is tailor-made to the patient based on the individual colposcopy, pathology, cytology reports and HPV-DNA status. ■

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