Clinical significance of atypical glandular cells on cytology: 10 years' experience of a colposcopic referral center

Ermelinda Monti[a], Eugenia Di Loreto[a], Giada Libutti[a], Daniela Alberico[a], Giussy Barbara[a,b], Veronica Boero[a], Giulia Emily Cetera[a], Maria Pasquali Coluzzi[a], Sonia Cipriani[b] and Fabio Parazzini[b]

Introduction **'Atypical glandular cells' (AGC) is an uncommon cytological result of cervical Pap smears which includes a wide of histopathological diagnoses, from benign to premalignant and malignant cervical disorders, endometrial cancer and, occasionally, other genital malignancies. This study aims to provide a comprehensive overview of AGC, assessing risk factors and clinical and histological features in affected patients.**

Materials and methods **A retrospective analysis was conducted on a cohort of 239 women diagnosed with AGC between 2012 and 2022 at the 'Regional Referral Center for Prevention, Diagnosis and Treatment of HPV-related Genital Disorders', Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. Following AGC detection, patients underwent colposcopy with endocervical sampling and endometrial assessment via pelvic ultrasound. Selective cases also received endometrial biopsies.**

Results **Among a total of 190 women who underwent both colposcopy and endometrial assessment, 116 (61%) had negative clinical and histopathological findings. The remainder displayed various abnormalities: 36 women (18.9%) were found to have endometrial or cervical polyps, 23 (12.1%) were diagnosed with preinvasive cervical neoplasia, and 21 (10.9%) with invasive cervical or endometrial disease. Menopause, multiparity, and older age were all significantly associated with endometrial cancer, but none of the abovementioned variables were significantly associated with cervical neoplasia.**

Conclusion **Our data confirm that AGC may reveal the presence of a wide range of histopathological conditions. Patients diagnosed with AGC should undergo a careful evaluation including both colposcopy with endocervical sampling and an endometrial assessment.** ***European Journal of Cancer Prevention*** **XXX: XXXX–XXXX Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.**

European Journal of Cancer Prevention XXX, **XXX**:XXXX–XXXX

Keywords: atypical glandular cells, cervical cancer, colposcopy, diagnosis, endometrial cancer

[a]Dipartimento Materno-Infantile, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico and [b]Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milan, Italy

Correspondence to Eugenia Di Loreto, MD, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda, Ospedale Maggiore Policlinico, Via Commenda, 12, 20122 Milan, Italy
Tel: +39 02 5503 2330; e-mail: eugenia.diloreto@policlinico.mi.it

Received 5 March 2024 **Accepted** 25 June 2024.

Introduction

Glandular cell abnormalities are found in less than 1% of cervical Pap smears, most commonly in women over 40 years of age (Jeng *et al*., 2003; Boyraz *et al*., 2017).

'Atypical glandular cells' (AGC) is a cytologic abnormality in which glandular cells present morphologic changes which exceed reactive or reparative changes but fall short of an interpretation of adenocarcinoma (Arshi and Farci, 2022). AGC can originate both from the endocervical canal or from the endometrium and its cytological diagnosis is burdened by a significant interobserver variability (Kalir *et al*., 2005; Lepe *et al*., 2018).

In the 2014 Bethesda Nomenclature System for Cervical Cytology, glandular epithelial cell abnormalities are subcategorized according to their site of origin and to their potential of malignancy in: (a) atypical glandular cells not otherwise specified (AGC-NOS); (b) atypical glandular endocervical cells (AGC-EC); (c) atypical glandular endometrial cells (AGC-EM); (d) atypical glandular cells favoring neoplasia (AGC-FN) (Nayar and Wilbur, 2015).

More than 50% of AGC cytologies are associated with benign or physiological conditions, such as endocervicitis, microglandular hyperplasia, metaplasia, endometrial o endocervical polyps, pregnancy, use of oral contraceptives, or of intrauterine devices (Arshi and Farci, 2022). Despite this, 17 to 59% of cases are associated with premalignant or malignant conditions (Munro *et al*., 2015). It has been reported that 9 to 38% of cases of cytological AGC are due to cervical intraepithelial neoplasia, including cervical intraepithelial neoplasia 2 or 3 (CIN2-3) and adenocarcinoma in situ (AIS); and to invasive cervical

DOI: 10.1097/CEJ.0000000000000910

carcinomas in 3 to 17% of cases (Marques *et al*., 2011). AGC is also frequently associated with endometrial adenocarcinoma and occasionally with ovarian and fallopian tube malignancies, with a reported rate of 0.6–1% (Schnatz *et al*., 2006; Zhao *et al*., 2009).

Taking into account all of these considerations, the correct interpretation of AGC findings is fundamental for an early detection of female genital tract glandular neoplasias (Pradhan *et al*., 2016).

According to clinical guidelines, all women with glandular abnormalities on cervical cytology should undergo colposcopy with endocervical sampling (Ciavattini *et al*., 2019; Perkins *et al*., 2020). Endometrial evaluation by ultrasound or biopsy is also recommended, while triage by reflex HPV testing is not.

The main purpose of this study is to evaluate clinical and histological features of patients who are diagnosed with AGC on cervical cytology. The secondary purpose is to assess the association between demographic factors and histological findings in this group of patients.

Methods

We conducted a retrospective cross-sectional study on a cohort of women diagnosed with AGC on a Pap smear between 2012 and 2022 at the 'Regional Referral Center for prevention, Diagnosis and Treatment of HPV-related Genital Disorders', Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Milano. Retrospective data were collected from clinical reports. Local institutional review board approval was obtained (#156025, 14 April 2022, Comitato Etico di Milano area 2).

AGC diagnoses were performed according to the 2014 Bethesda System (Nayar and Wilbur, 2015). Cases of AGC with coexisting squamous abnormality such as atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (L-SIL), high-grade squamous intraepithelial lesion (HSIL) were also included in this study. While women with previous preinvasive cervical disease were included, women with previous genital cancer were excluded.

All patients under study underwent colposcopy with endocervical sampling and an endometrial assessment with pelvic ultrasound, as suggested by clinical practice guidelines (Ciavattini *et al*., 2019; Perkins *et al*., 2020). Each patient underwent colposcopy with endocervical sampling, which was obtained through endocervical curettage. Additionally, when relevant, cervical biopsies or cervical excisions were performed. Furthermore, all patients underwent an endometrial assessment with pelvic ultrasound. As per clinical practice guidelines, endometrial biopsies were conducted using vacuum aspiration biopsy random assay (VABRA) or hysteroscopy. This procedure was performed in all postmenopausal women and in premenopausal women with endometrial ultrasound anomalies, risk factors for endometrial carcinoma, or clinic suggestive of endometrial pathology.

Data obtained from consulting medical records were reported in a digital dataset (Microsoft Excel Spreadsheet, version 15.33; Microsoft, Redmond, Washington, USA). Cytological results, colposcopic findings, method of cervical sampling and endometrial assessment, cervical and endometrial histological result, ultrasonographic endometrial appearance, age, menopausal status, parity, tobacco use, hormonal treatment, HPV status, and previous preinvasive cervical disease were recorded for each patient included.

Descriptive statistics were used for demographic and medical data; continuous variables are presented as means and SD, while categorical data are presented as frequencies and percentages. The t-test, Chi-square test, or Fisher's exact test were used as appropriate, setting statistical significance at the usual 5% probability value. Univariate logistic regression analyses were performed to assess menopause, parity, tobacco use, hormonal therapy, and clinically significant cervical histology as potential risk or protective factors for endometrial cancer. Menopause, parity, high risk HPV infection, hormonal therapy, previous preinvasive cervical neoplasia were considered as potential risk or protective factors of cervical neoplasia. Odds ratios (ORs) with relative 95% confidence intervals (CIs) of each model were reported.

All the analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

Results

A total of 244 women were diagnosed with AGC on cervical Pap smear at our center in the study period. Of these, five were excluded from the analysis as we were not able to retrieve data from their colposcopy and/or cervical histology, leaving 239 cases for the analysis. As data from the endometrial assessment were missing in 49/239 women, only 190 cases were complete of data from both cervical and endometrial clinical or histological findings.

The clinical characteristics of the 239 patients included in the study are summarized in Table 1. Mean age was 47.9 years (range 21–87). A total of 81 women (33.9%) were menopausal, 40 (16.7%) were habitual cigarettes smokers, and 34 (12.6%) were under hormonal treatment. Moreover, 31 patients (13%) had a history of preinvasive cervical lesions.

Cytological subcategories of AGC were the following: 177/239 (74.1%) of women were found with AGC-NOS, 25/239 (10.5%) with AGC-EC, 9/239 (3.8%) with AGC-EM, and 9/239 (3.8%) with AGC-FN. In 7/239 (2.9%) individuals, concomitant AGC-NOS and HSIL/

ASCH were detected, while in 11/239 (4.6%) AGC-NOS was concomitant with ASCUS/LSIL.

As what regards cervical histological sampling, 233/239 women underwent endocervical sampling with curettage (a concomitant cervical biopsy was performed in 33 of these patients), while six women underwent a diagnostic cervical excision. A subsequent cervical loop electrosurgical excision procedure (LEEP) was performed in 36 cases according to histological cervical results. Cervical histology revealed the presence of LSIL in five cases (2.1%), HSIL in 24 (10%), HSIL with a concomitant AIS in one (0.4%), AIS in four (1.7%), squamous cervical cancer in six (2.6%), cervical adenocarcinoma in six (2.6%), cervical metastasis of a non-cervical cancer in one (0.4%) and a cervical polyp in seven (3%). In 185 patients (77%) histology was negative.

Among the 190 patients for whom endometrial data were available, 102 had undergone only a transvaginal ultrasound, while 88 had also undergone an endometrial biopsy (reasons for the endometrial biopsy included specific risk factors such as age, abnormal bleeding, and suspicious ultrasound findings). Endometrial samples were retrieved with VABRA in 70 cases and with hysteroscopy in 18.

Table 2 shows clinical and histologic findings according to the cytological subcategories of AGC.

Out of the 190 women who underwent both colposcopy and endometrial assessment, 116 (61%) had a negative clinical or histologic examination.

As many as 36 (18.9%) were diagnosed with benign conditions such as cervical polyps (12.6%) and endometrial polyps (6.3%). A total of 23 women (12.1%) were diagnosed with a preinvasive cervical neoplasia, while the remaining 21 (10.9%) were diagnosed with invasive disease. A total of six women were diagnosed with more than one of the abovementioned comorbidities. The most common types of malignancy were endometrial cancer, which was detected in 10 cases (5.2%), and cervical cancer, which was also detected in 10 cases (5.2%). One patient was found with a cervical metastatic localization of an adenocarcinoma which originated from a distant site.

Table 3 reports cervical and endometrial clinical-histologic findings stratified for patients' age. We found that patients older than 35 years are less likely to be diagnosed with preinvasive cervical disease compared to women aged 35 years or younger. Conversely, patients aged older than 35 years were more likely to be diagnosed with invasive cancer. These findings, however, did not reach statistical significance ($P = 0.07$).

Table 1 Clinical characteristics of patients

	N	%
Tobacco use		
No	193	80.8
Yes	40	16.7
Unknown	6	2.6
Menopause		
No	158	66.1
Yes	81	33.9
HPV test		
Negative	25	10.5
Positive high risk	13	5.4
Unknown	201	84.1
Hormonal treatment		
No	205	85.7
Yes (COC, P, LNG-IUS, HRT, TMX)	34	12.6
Unknown	4	1.7
Parity		
Nulliparous	74	31.0
Multiparous	161	69.0
Previous preinvasive cervical disease		
No	208	87.0
Yes	31	13.0

COC, combined oral contracceptives; HPV, human papilloma virus; HRT, hormonal replacent therapy; LNG-IUS, levonorgestrel intrauterine system; P, progestins; TMX, tamoxifen.

Table 2 Relation between cytological and clinical-histological results

AGC subcategories	Negative	Cervical polyp	Endometrial polyp	LSIL	HSIL	SCC	AIS	CAC	EC	Metastases
AGC-NOS *N* = 141	98 (69.5%)	18 (12.8%)	8 (5.7%)	4 (2.8%)	7 (4.9%)	2 (1.4%)	1 (0.7%)	3 (2.1%)	4 (2.8%)	1 (0.7%)
AGC-EC *N* = 20	10 (50%)	2 (10%)	1 (5%)		3 (15%)	1 (5%)	2 (10%)		1 (10%)	
AGC-EM *N* = 9	5 (55.6%)	1 (11.1%)	2 (22.2%)		1 (11.1%)	1				
AGC-FN *N* = 8	1 (12.5%)				1 (12.5%)	1 (12.5%)		2 (25%)	3 (37.5%)	
AGC-HSIL/ASCH *N* = 6	0				3 (50%)	0	1 (16.7%)	0	2 (33.3%)	
AGC-LSIL/ASCUS *N* = 6	2 (33.3%)	3 (50)	1 (16.7%)							
Total *N* = 190	116 (61%)	24 (12.6%)	12 (6.3%)	4 (2.1%)	15 (7.9%)	5 (2.6%)	4 (2.1%)	5 (2.6%)	10 (5.2%)	1 (0.5%)

% per line.

AGC-EC, atypical glandular cells endocervical; AGC-EM, atypical glandular cells endometrial; AGC-FN, atypical glandular cells favoring neoplasia; AGC-NOS, atypical glandular cells not otherwise specified; AIS, adenocarcinoma in situ; ASCH, atypical squamous cells cannot exclude HSIL; ASCUS, atypical squamous cells of undetermined significance; CAC, cervical adenocarcinoma; EC, endometrial carcinoma; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; SCC, squamous cervical cancer.

We also analyzed the role of risk factors such as age, menopausal status, parity, smoking, hormonal therapy, which may be associated with endometrial malignancy, and cervical neoplasia. Results are shown in Tables 4 and 5. We found that menopause ($P = 0.0101$, OR 6.23, 95% CI 1.297–30.462) and multiparity ($P = 0.0333$) were significantly associated with a diagnosis of endometrial cancer in women with cytological AGC. In addition, as shown in Table 4, patients with endometrial cancer were significantly older than patients without endometrial neoplasia (mean age 63.9 and 49.2, respectively, $P < 0.0001$). Conversely, we found no association between the abovementioned risk factors and cervical neoplasia (Table 5).

The association between cervical histology and colposcopic appearance is reported in Table 6. Colposcopic grade 2 patterns and patterns suspicious for invasion were significantly associated with both squamous and glandular cervical neoplasia ($P < 0.001$ and 0.03, respectively).

Table 3 Association between cervical histology and age (≤35 and >35 years)

		≤35 years	>35 years	*P*-value
		N = 16	*N* = 174	
Cervical histology				**0.0753**[a]
Clinically nonsignificant histology	***N* = 151**	**11 (68.8%)**	**140 (80.4%)**	
Negative		10	106	
Polyps		1	32	
LSIL		0	2	
High grade preinvasive cervical neoplasia	***N* = 18**	**4 (25%)**	**14 (9.8%)**	
HSIL		2	12	
AIS		1	2	
HSIL + AIS		1	0	
Invasive cancer	***N* = 21**	**1 (6.2%)**	**20 (14%)**	
SCC		1	4	
CAC		0	5	
EC		0	10	
Metastasis		0	1	

% per column.
AIS, adenocarcinoma in situ; CAC, cervical adenocarcinoma; EC, endometrial carcinoma; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; SCC, squamous cervical cancer.
[a]Fisher exact test.

Discussion

AGC is an uncommon cytological finding of cervical Pap smears which may be associated with a wide range of histopathological conditions, ranging from benign to premalignant or malignant cervical conditions, as well as endometrial cancer and, occasionally, other genital malignancies (Wang *et al*., 2016; Ciavattini *et al*., 2019; Khan *et al*., 2022). In our series, the majority of patients (78.8%) with AGC was found to have a negative or benign histology. Preinvasive cervical neoplasia was found in 12.1% of cases, while invasive disease (both cervical or endometrial cancer) was found in 10.9% of cases. One patient was diagnosed with a cervical metastatic localization of an adenocarcinoma from a distant site.

Our findings are consistent with the literature. In a large recent series (Jang *et al*.,2019) of about 500 women with cytological AGC who underwent a subsequent cervical and endometrial assessment, a clinically significant histological result was found in 31.5% of women, half of whom (15.9%) were diagnosed with malignant lesions. Similar to our results, most pathological lesions, especially endometrial carcinoma, were found among patients over 50 years of age.

In another study by Wang and coworkers, the author investigated the risk of cervical cancer after a cytological detection of AGC. Among 14 625 women aged 23–59 years, 1.4% had a cervical cancer. The highest proportion of prevalent cervical cancer was found in the age group 30–39 years and the most common type of cancer was cervical adenocarcinoma. The authors also analyzed the cumulative long-term incidence of cancer (up to 15 years of follow-up) and found that the risk of cervical cancer increased steadily over time, reaching 2.6%

Table 4 Association between endometrial cancer and risk factors

	N	Negative or benign	Endometrial carcinoma	OR (95%CI)	*P*-value
Age (mean ± SD)	190	49.2 ± 10.9	63.9 ± 8.5		<0.0001[a]
		N (column %)	*N* (column %)		
Menopause	190				0.0101[b]
No		110 (61.1)	2 (20.0)	1[c]	
Yes		70 (38.9)	8 (80.0)	6.23 (1.30–30.4)	
Parity	187				0.0333[b]
Nulliparous		120 (67.8)	10 (100.0)		
Multiparous		57 (32.2)	0 (0.0)	OR not available	
Tobacco use	186				0.6163[b]
No		148 (84.1)	9 (90.0)	1[c]	
Yes		28 (15.9)	1 (10.0)	0.59 (0.07–4.82)	
Hormonal therapy	187				0.2767[b]
No		155 (87.6)	10 (100.0)		
Yes		22 (12.4)	0 (0.0)	Or not available	
Clinically significant cervical histology	190				0.6098[b]
Negative or LSIL		151 (83.9)	10 (100.0)		
HSIL+ or AIS+		29 (16.1)	0 (0.0)	OR not available	

AIS, adenocarcinoma in situ; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.
[a]t-test.
[b]Fisher exact test.
[c]Reference category.

Table 5 Assotiation between cervical neoplasia and associated factors

	N	Negative or LSIL	HSIL+ or AIS+	OR (95%CI)	*P*-value
Age (mean ± SD)	239	48.3 ± 11.2	46.1 ± 11.9		0.2588[b]
		N (column %)	*N* (column%)		
Menopause	239				0.7225[c]
No		132 (67)	27 (64.3)	1[a]	
Yes		65 (33)	15 (35.7)	1.13 (0.56–2.27)	
Parity	235				0.1302[c]
Nulliparous		57 (29.4)	17(41.5)	1[a]	
Multiparous		137 (70.6)	24 (58.5)	0.59 (0.29–1.18)	
Tobacco use	197				0.3549[c]
No		128 (81.0)	29 (74.4)	1[a]	
Yes		30 (19.0)	10 (25.6)	1.47 (0.65–3.35)	
High risk HPV infection	38				0.1223[c]
No		21 (72.4)	4 (44.4)	1[a]	
Yes		8 (27.6)	5 (55.6)	3.28 (0.69–15.41)	
Hormonal therapy	235				0.4776[c]
No		169 (87.1)	34 (82.9)	1[a]	
Yes		25 812.9)	7 (17.1)	1.39 (0.56–3.48)	
Previous preinvasive cervical neoplasia	239				0.7561[c]
No		175 (88.8)	38 (90.5)	1[a]	
Yes		22 (11.2)	4 (9.5)	0.83 (0.27–2.57)	

AIS, adenocarcinoma in situ; HPV, human papilloma virus; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.
[a]Reference category
[b]t-test.
[c]Fisher exact test.

Table 6 Association between cervical histology and colposcopic appearance

	Total	Negative/LSIL	HSIL/SCC	AIS/CAC	*P*-value[a]
	N = 239	*N* = 197	*N* = 31	*N* = 11	
G0-G1	215	189 (95.9%)	17 (54.8%)	9 (81.8%)	<0.00001
G2 or suspicious for invasion	24	8 (4.1%)	14 (45.1%)	2 (18.1%)	
	N = 228	*N* = 197	*N* = 31		
G0-G1	206	189 (95.9%)	17 (54.8%)		<0.00001
G2 or suspicious for invasion	22	8 (4.1%)	14 (45.1%)		
	N = 208	*N* = 197		*N* = 11	
G0-G1	198	189 (95.9%)		9 (81.8%)	0.033127
G2 or suspicious for invasion	10	8 (4.1%)		2 (18.1%)	

% per column.
[a]Chi-square test.
AIS, adenocarcinoma in situ; CAC, cervical adenocarcinoma; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; SCC, squamous cervical cancer.

at 15.5 years. Contrary to our results, the authors did not find an association between endometrial pathology and glandular abnormalities on cytology (Wang *et al*., 2016).

Toyoda and coworkers investigated the potential risk of both cervical and endometrial neoplasia following a cytological diagnosis of AGC. The authors found a preinvasive cervical neoplasia in 9.7% of patients, while invasive disease (both cervical or endometrial) was found in 39% of cases. The differences with the percentages found in our study (10.9% of invasive disease and 12.1% of preinvasive cervical neoplasia) could be explained by the lower percentage of subcategories of AGC-FN and AGC-EM in our series, which was 3.8% (versus 7.8% in Toyoda's study) and 3.8% (versus 24% in Toyoda's study), respectively (Toyoda *et al*., 2019).

In our study menopause, multiparity and older age were significantly associated with endometrial cancer in women with cytological AGC; however, we failed to find an association between these risk factors and cervical neoplasia. Although parity is a well-known protective factor for endometrial cancer (Lu and Broaddus, 2020), surprisingly, in our series multiparity was rather a major risk factor. This may be due to the fact that age itself is the main risk factor for endometrial cancer and that older patients may have had more pregnancies over time.

Recently, Keles and coworkers analyzed a series of 88 women with AGC and found cervical and endometrial malignancies in about 15% of patients. A multivariate analysis revealed that an age greater than 50 years and menopausal status correlated with neoplasia. Concomitant abnormal squamous lesions and HPV positivity were also significantly associated with the risk of neoplasia (Keles *et al*., 2021). Similarly, Graue and colleagues confirmed that, following atypical glandular cytology, cervical intraepithelial lesions were more common in women under 35 years of age, whereas more than half of the cervical histological findings in women aged 35 years or older were normal or benign. The risk of cervical cancer increased over the

years and the most common type of cancer was adenocarcinoma (Graue *et al*., 2020).

As depicted in Table 2, each subclassification of AGC Pap smears can be linked to different histological outcomes. In our study, 80% of AGC-NOS Pap smears were found to be associated with negative or benign histological findings, while a significantly smaller percentage (12.5%) of AGC-FN Pap smears yielded similar histological results. Moreover, among the 20 AGC-EC Pap smears, only one was associated with endocervical cell anomalies (AIS), while three were associated with squamous cell anomalies and the remainder with benign histology. Likewise, among the nine AGC-EM Pap smears, two were found to be associated with cervical squamous cell anomalies, and none with endometrial anomalies. Therefore, despite the limited numbers of these AGC subclassifications in our series, our results confirm that patients diagnosed with AGC should undergo a careful clinical and histological evaluation of both cervical and endometrial components, regardless of the type of triage AGC pap smears. Finally, given that in our series patients with AGC-FN subclassification were found to be at the highest risk of having preinvasive or invasive lesions of the uterine cervix or endometrium, special attention must be given to the evaluation of these patients.

Our results confirm that colposcopy plays a crucial role in the management of patients with AGC. Indeed, in our series, a G2 colposcopic pattern or a pattern suspicious for invasion significantly correlated with major cervical conditions. Although colposcopy is not equally sensitive for glandular lesions as compared to squamous lesions (Ullal *et al*., 2009), it is still mandatory in patients with AGC, as it allows the diagnosis of associated squamous lesions (Munro *et al*., 2017). Moreover, colposcopy is essential for guiding biopsies, including endocervical sampling, which should always be performed in these cases.

The major strength of our study is the consistent sample size despite the monocentric setting. In fact, AGC findings represent a small percentage of abnormal Pap smear results. Furthermore, all included patients underwent colposcopy in a reference center with a high level of expertise and were subjected to endocervical canal sampling even when colposcopy was negative.

The most important limitation of the current research is that data were collected retrospectively from existing medical records. This methodology carries the typical limitations of recorded patient information, including a high rate of unreported information and possible errors. Moreover, we did not have complete data for all patients and HPV test was not always performed. Lastly, a further limitation is the lack of a long-term follow-up. Such data would be useful to understand the risk of cancer over time, allowing clinicians to carry out the most suitable timing for follow-up.

Conclusion

In conclusion, our data confirm that a wide range of diseases may be diagnosed following the finding of an AGC on a cervical Pap smear. Patients diagnosed with AGC should undergo a careful clinical and histological evaluation given the high risk of malignancy. Women should be referred for colposcopic examination with endocervical sampling. Endometrial assessment is also required, particularly in older and perimenopausal women.

Acknowledgements

We wish to thank all the staff from our unit for making this study possible, and Professor Paolo Vercellini for helping us reviewing this article.

This study was partially supported by the Italian Ministry of Health – Current Research IRCCS.

All named authors contributed to the paper. All the authors provided substantial contributions to the conception of the study. All named authors contributed significantly to data acquisition, analysis, and interpretation. All named authors participated in critically revising the manuscript. All the authors gave their final approval to publish the manuscript. All authors have read and agreed to the published version of the manuscript.

E.M. conducted data analysis and manuscript writing and editing; E.D.L. contributed to data collection, analysis, and manuscript writing; G.L., G.B., V.B., and M.P.C. participated in manuscript editing; D.A. was involved in data collection and manuscript editing; G.E.C. focused on manuscript writing and editing; and S.C. and F.P. concentrated on data analysis and manuscript editing.

Conflicts of interest

There are no conflicts of interest.

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