

The prevalence and spectrum of atypical glandular cells in Dubai hospital: A local experience

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Abstract

Objective: This study was undertaken to analyze the prevalence and spectrum of atypical glandular cells to investigate its clinical significance in our population.

Study design: A 5 year retrospective review of atypical glandular cells diagnosed on ThinPrep pap test was performed. AGC were reported in 40 patients, who underwent colposcopy- directed biopsy, endocervical curettage and endometrial curettage to determine the cytological and histological correlations of AGC.

Results: The prevalence of AGC was 0.2% out of 19836 patients. The patients age ranged from 29 to 81 years (mean age 49.4 years). Significant lesions were defined as Squamous Intraepithelial lesion (SIL), adenocarcinoma in situ (AIS) or invasive carcinoma. This included 2 invasive squamous cell carcinoma of the cervix, 2 high grade squamous intraepithelial lesions, 2 AIS, 5 adenocarcinoma of the cervix, two of which had low grade and high grade squamous intraepithelial lesions one of which was consistent with metastatic colonic carcinoma and 5 endometrial adenocarcinoma, one of which was suspicious of breast carcinoma. The chi-square value was significant at 99% confidence interval.

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Conclusion: AGC were associated with clinically significant lesions in 40% of our cases.. Significant endocervical glandular lesions occurred in younger women whereas the older women had endometrial lesions.. Patients with AGC should be followed up for a substantial period despite initial negative histological findings.

Keywords: The Bethesda system; Atypical glandular cells; ThinPrep Pap test; Adenocarcinoma.

1. INTRODUCTION

The Bethesda System (TBS) in 1988 introduced the term atypical glandular cells of undetermined significance (AGUS) as a diagnostic category for the endocervical or endometrial glandular cells that demonstrate nuclear atypia appearing to exceed reactive or reparative changes but lacking unequivocal features of adenocarcinoma. [1]. In 2001 the classification of glandular abnormalities was significantly revised. The term AGUS has been eliminated and the glandular cell abnormalities are classified into three categories; atypical glandular cells (AGC) either endocervical, endometrial cells or ‘glandular cells’ “not otherwise specified” (AGC-NOS) and favor neoplasia (AGC-FN) and endocervical adenocarcinoma in situ (AIS) [2]. AGC is an uncommon cytological diagnosis occurs in approximately 0.18-0.74% of cervical smears [3]. On further evaluation 50-85 percent of women with AGC will have no histological abnormalities [3]. Some studies have reported that the risk of premalignant and malignant conditions, ranging from 17-59 percent [4] The origin of benign, premalignant or malignant lesions that presents as atypical glandular cells varies with the age of the patient. Cervical pathology is more likely in younger women where as in older women the endometrium is the more likely origin of atypical glandular cells [5]. The AGC represents a wide variety of clinically benign lesions to clinically significant premalignant or malignant lesions. The benign lesions associated with AGC are chronic cervicitis, endometriosis, squamous metaplasia, tubal metaplasia, microglandular hyperplasia, pregnancy, previous cone biopsy, radiation and cervical polyps [6]. The clinically significant premalignant or malignant lesions include squamous cervical intraepithelial neoplasia (CIN), adenocarcinoma in situ (AIS) of the cervix, complex endometrial hyperplasia, malignancy of the lower and upper genital tracts and rarely abdominal or distant non reproductive organs [6] Over the past few decades the incidence of cervical adenocarcinoma in situ (AIS) and adenocarcinoma has been increasing [7]. Although the cervical cytology screening can be used to detect squamous lesions with a low sensitivity for glandular lesions, it offers the potential for the prevention of cervical

adenocarcinoma by detecting the precursor adenocarcinoma in situ (AIS) [8] and also enhances the opportunity to detect endometrial abnormalities in some cases.

The purpose of our retrospective study was to analyze the prevalence and spectrum of atypical glandular cells to investigate its clinical significance in our local population.

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2. MATERIALS AND METHODS

2.1 Study Population

A retrospective computer based search system was carried out to identify all patients with the cytological diagnosis of atypical glandular cells on Thin Prep Pap tests over a period of five years from June 2005 to May 2010 in the Cytology Unit, Pathology and Genetics Department, Dubai Hospital, UAE. A Total of 19,836 Thin Prep pap tests were obtained out of which 60 were diagnosed as atypical glandular cells. Among the 60 patients, 20 patients were excluded due to loss of tissue biopsy follow up. Forty patients had histological follow up with tissue biopsy and these constituted the study.

2.2 Specimen Preparation

Cervical cytology (Thin Prep) specimens were obtained by cervix brush and processed to make Thin Prep slides using an automated processor (Hologic, UK). The Thin Prep slides were fixed in 95% ethyl alcohol and stained by Papanicolaou stain.

2.3 Data Analysis

The demographics and clinical data included the patient age, parity, menopausal status, use of hormone replacement therapy, use of oral contraceptives, symptoms, physical examination findings, history of previous abnormal cervical smears, history of cancer, previous cervical surgery and colposcopic findings and treatment. The method by which tissue was obtained for the histological evaluation varied and included endocervical biopsy, endocervical curettage, endometrial biopsy, endometrial curettage and cervical biopsy. In addition those patients who received other diagnostic or treatment procedures such as cone biopsy, loop electrosurgical excision procedure (LEEP), polypectomy and hysterectomy were also included in the study. We included both pre invasive and invasive gynecologic neoplasms as significant lesions. These included squamous

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intraepithelial lesion, squamous cell carcinoma, adenocarcinoma in situ, cervical adenocarcinoma, endometrial adenocarcinoma and cancer of other sites.

3. CYTOLOGICAL DIAGNOSTIC INTERPRETATIONS

The Thin Prep pap slides of 40 patients initially diagnosed as atypical glandular cells were reviewed by a second blind screening and independently interpreted by two cytopathologists and a cytotechnologist. The cytological diagnosis of AGC were reclassified using TBS terminology as

- 1) Atypical glandular cells (AGC-NOS),
- 2) AGC-endocervical,
- 3) AGC-endometrial
- 4) AGC-favor neoplasm (FN),
- 5) Endocervical adenocarcinoma in situ (AIS)
- 6) Endocervical Adenocarcinoma, and
- 7) Endometrial Adenocarcinoma.

The reviewer's interpretations were tabulated. The cytological results were correlated with histological findings as the gold standard.

3.2 Statistical Analysis

The analysis was performed on SPSS 20 statistical software. A correlation analysis evaluating chi-square and spearman rho was also used to find the histological correlates of the cytological smears reported as atypical glandular cells; which was found to be statistically significant. The overall sensitivity, specificity and the false positive rates were calculated.

4 RESULTS

A total of 19,836 cervical ThinPrep pap tests were obtained over a period of five years. 60 patients were reported as having the diagnosis of atypical glandular cells. Follow up histology was available for 40 patients with a prevalence of 0.2% in our local population. The age of the patients ranged from 25 to 81 years with a mean age of 49.4 years.

From the forty patients thirty eight women (95%) were symptomatic and two women (5%) were asymptomatic. Ten symptomatic women were presented with post-menopausal bleeding, three had perimenopausal bleeding, three had post coital bleeding and intermenstrual bleeding, six had menorrhagia (one

of which had intrauterine contraceptive device), two had prolonged periods, two had lower abdominal pain, five had previous abnormal smears, one had clinically suspicious cervix, one had cervical polyp, one had endometrial polyp, one had bulky cervix, one had uterine fibroid, one had vaginal discharge and one had a previous history of HPV genital infection. The remaining 2 asymptomatic women had routine cervical screening.

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The forty women, who had subsequent histological evaluation, underwent the following clinical procedures with the number of patients in parenthesis: Endometrial biopsy (4), endometrial curettage (8), Endocervical biopsy (3), Endocervical curettage (4), cervical biopsy (5), Cone biopsy (2), Loop electrosurgical excision procedure (LEEP) (1), Polypectomy (7) and Hysterectomy (6). There was no uniform clinical evaluation. Some patients had more than one investigation.

Sixteen women (40%) from the study had histologically significant lesions in the tissue biopsy. Two women had cervical intraepithelial neoplasia (CIN-3) (12.5%), two had invasive squamous cell carcinoma (12.5%), two had adenocarcinoma in situ (AIS) (12.5%), five had endocervical adenocarcinoma (31.25%) one of which showed CIN-3, consistent with metastatic colonic adenocarcinoma and another with HPV changes and CIN-I and five had Endometrial adenocarcinoma (31.25%) one of which was suspicious of breast carcinoma and two were serous papillary. All these lesions were detected at follow up (1-24 months). Twenty four women (60%) had non neoplastic findings (32.5% benign and 27.5% negative) which included seven women with benign cervical & endometrial polyps one of which showed focal complex hyperplasia, two women with cervicitis and squamous metaplasia, two women with simple cystic hyperplasia of the endometrium, one woman with disordered proliferative endometrium, one woman with ectocervical chronic inflammation and granulation tissue and eleven women with no significant pathologic findings.

In our study, significant lesions occurred in 16 patients (40%) who had a mean age of 51.1 years. AGC endocervical origin was reported in 4 women with a mean age of 42.5 years and AGC endometrial origin in 5 women with a mean age of 55.2 years. AIS reported in 2 women with a mean age of 45 years. AGC with low grade and high grade squamous lesions reported in 2 women with a mean age of 55 years and AGC favor neoplasm in 3 women with a mean age of 57.7 years.

The results of follow up histological tissue diagnosis and their relation to menopausal status were also studied. Among the 16 women 10 were premenopausal who had 2 high grade squamous intraepithelial lesions and 1 had squamous cell carcinoma, 2 had adenocarcinoma in situ (AIS) and 4 had endocervical adenocarcinoma and 1 had endometrial carcinoma. The remaining 6 women were post-menopausal and 1 had squamous cell carcinoma, 1 had

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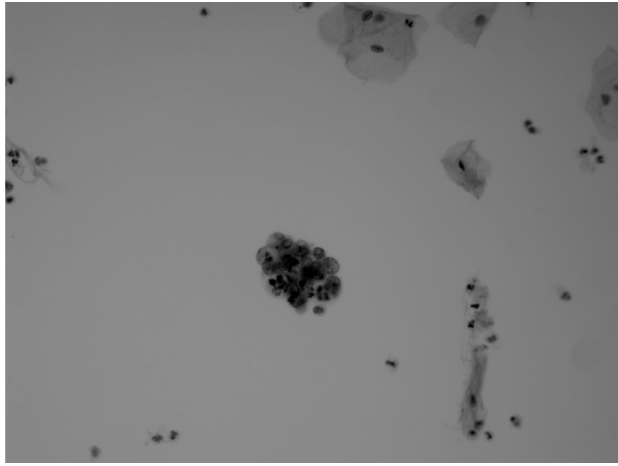


Figure 1: Cytology AGC :Three dimensional cluster of cells with enlarged slightly hyperchromatic nuclei and slight pleomorphism infiltrated by neutrophils. Follow up biopsy showed benign endometrial polyp. (ThinPrep, x 400, Papanicolaou stain).

Table I: Demonstrates the histologic findings and the clinical condition per age group.

Age	Histologic findings						Clinical condition				
	CIN3	SCC	AIS	EC	EM	Total	Pre MB	Post MB	Prev. ABN	Other	Total
35-40	1	0	2	0	0	3	2	0	2	1	5
41-50	1	1	0	4	1	7	0	0	1	2	3
51-60	0	0	0	1	2	3	1	2	0	0	3
>60	0	1	0	0	2	3	2	3	0	0	5
Total	2	2	2	5	5	16	5	5	3	3	16

CIN: cervical intraepithelial neoplasia, SCC: squamous cell carcinoma, AIS: adenocarcinoma in-situ, EC: endocervical carcinoma, EM: endometrial carcinoma; Pre MB: premenopausal bleeding, Post MB: post menopausal bleeding, Prev.ABN: previously abnormal smear, Other: includes polyps and suspicious.

endocervical carcinoma and 4 had endometrial carcinoma as shown by the histological diagnosis. Endometrial lesions occurred in older women (mean age= 61.2 n= 5). Cervical lesions occurred in younger women (mean age=42 n=7). The youngest woman with AIS was 39 years and endometrial carcinoma was found in a 43 year old woman. AGC was diagnosed in almost all the age groups (29-81 years), which is also depicted in Table 1.

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The revised interpretation of the reviewers on the initially diagnosed cases as AGC is shown in Table 2.

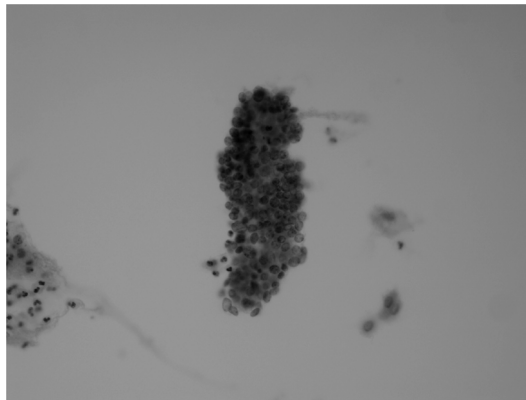


Figure 2 (A): Cytology: Adenocarcinoma, endocervical. Sheet and syncytial group of cells with crowded, overlapped and hyperchromatic nuclei and nucleoli showing high nuclear/ cytoplasmic ratio. (ThinPrep, Papanicolaou stain, x 400).

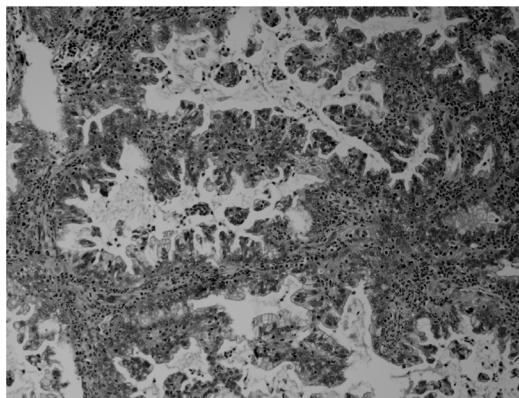


Figure 2(B): Histology: Follow up histology showed invasive adenocarcinoma of the cervix (Haematoxylin and eosin stain, x 200).

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Table II: Summarises the revised interpretation of the reviewers on the initially diagnosed cases as AGC.

Reviewer	AGCs	Negative	HSIL	Favor neoplasm	AIS	SCC	Adeno carcinoma	Total
1	11	14	4	2	3	1	5	40
2	2	14	4	0	4	1	5	40
3	21	8	4	5	2	0	0	40

AGCs: abnormal glandular cells, HSIL: high-grade squamous intraepithelial lesions, AIS: adenocarcinoma in-situ, SCC: squamous cell carcinoma.

Table III: Correlation between Histology and Cytology findings.

		Histology		Total	Chi-square	Spearman's Correlation rho	p-value
		Positive	Negative				
Cytology	Positive	16	0	16	21.818*	0.702*	<0.001
	Negative	12	12	24			
	Total	28	12	40			

(* significant at <0.001)

The 40 Thin Prep Pap slides initially diagnosed as AGC was reviewed by two cytopathologists and a cytotechnologist. From the analysis it is found that the reviewers AGC diagnostic rate was 67.5%, 65% and 80% respectively. AGC interpretation of the three reviewers was retained for only 28 cases and 12 cases were downgraded to reactive/ negative. Of the 28 revised AGC cases 16 (57.14%) had significant histological lesions and the remaining (42.85%) showed benign and normal histological findings. The cytological interpretations of the 16 cases which had significant histological lesion were diagnosed by all the reviewers. No significant lesions were identified in the remaining 12 cases that were downgraded from AGC to reactive / negative and were consistently reported by all the three reviewers. Hence the false positive interpretation was 30%. The study showed 100% sensitivity, with a specificity of 42.85%. The positive predictive value was 57.1%.

The reviewers found difficulty in some cases to differentiate whether the AGC were endometrial or endocervical in origin. A case of endometrial adenocarcinoma was reported as AGC by all the reviewers as they could not sub classify. The initial cytological diagnosis of Suspicious Adeno-squamous carcinoma was

reported as AGC and HSIL by the reviewers and the histology showed Invasive adenocarcinoma with severe dysplasia consistent with metastatic colonic adenocarcinoma. The correlation of cytology and histological results were found by using chi-square analysis and spearman's rho, non-parametric correlation. The correlation rho is found to be significant indicating high association between the results. The cytological diagnosis can be predictive and conclusive.

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DISCUSSION

A typical glandular cells are an uncommon but important cytological diagnosis. The purpose of our retrospective study was to analyze the prevalence and spectrum of atypical glandular cells to investigate its clinical significance in our population on Thin Prep Pap test (liquid based cytology).

The prevalence of AGC was 0.2% during the study period amounting to 40 patients out of 19,836 patients was systematically reviewed over a period of five years. The results were in agreement with the literature occurring in approximately 0.18-0.74% of cervical smears [9]. In this study 66.6% of patients with AGC had histological follow up. The follow-up rate was higher than the reported rate of 22-58% in many studies [10-13]. The rate of clinically significant lesions was 40 % on subsequent histological follow-up. This is in congruence with reported rates of 25-83% [14-15]; the result also stresses the importance of performing subsequent tissue biopsy. Follow up studies on patients with AGC have shown a wide spectrum of benign and clinically significant lesions. Despite the diagnosis of AGC, significant lesions consisted of both glandular and squamous lesions (including adenocarcinoma in situ, invasive endocervical adenocarcinoma and endometrial adenocarcinoma and squamous lesions included invasive squamous cell carcinoma and high grade squamous intraepithelial lesion. Two of our patients were diagnosed as having endocervical adenocarcinoma along with low grade and high grade squamous intraepithelial lesions. This is in keeping with well recognized reports of such coexistence [16]. Benign lesions associated with AGC include polyps, chronic cervicitis, tubal metaplasia, cystic hyperplasia, disordered proliferation and granulation tissue [6].

The study also indicates that the age of the patient appears to be relevant while assessing the AGC smears. The origin of benign, premalignant or malignant lesions varied with the age of the patient [5]. Significant lesions occurred in 16 women who had a mean age of 51.1 years. Cervical glandular lesions occurred in 7 women who had a mean age of 42 years and endometrial lesions occurred in 5 women who had a mean age of 61.2years. This age distribution suggests that younger women are less likely has endometrial disorders [17]. In older women the atypical glandular cells are more likely endometrial in origin [5]. The results of the study concede with other study reports.

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The squamous lesions are diagnosed approximately in 20-100% of AGC, much more than glandular neoplastic lesions [18]. From this study two cases which were interpreted in the initial review and re-concluded by the reviewers as AGC with HSIL turned out to be squamous cell carcinoma in histological follow up. In such cases to distinguish between squamous and glandular lesions, immuno histochemistry stain for P63 can be helpful as it highlights only the squamous lesions [20].

In our study and analysis of the significant lesions, the majority of cases (62.5%) were glandular lesions mostly from the female genital tract. This may be explained by the fact that some cases which were initially under diagnosed as cases of adenocarcinoma and upon secondary review applying strict criteria (adherence to TBS), those cases were revised as adenocarcinoma.

The study showed two cases with histologic findings suggestive of metastatic colonic and breast carcinoma. Histologically proven adenocarcinoma cases, mostly were primary tumors but also included metastatic adenocarcinoma of other sites such as colon and breast [7], which is in accordance with other research findings. Primary and metastatic adenocarcinomas appear to be indistinguishable on cytological material. It appears in the study that post-menopausal condition and abnormal vaginal bleeding are associated with endometrial or glandular disease [19], as is shown in other studies. The study also indicates that an endometrial evaluation is warranted in patients above 35 years and older [20], because the majority of glandular lesions of endometrial origin occurred in post-menopausal women.

The cervical glandular and squamous neoplasia is etiologically linked to human papilloma virus (HPV) [21]. HPV DNA testing was not available during the study period. Testing for high risk HPV with AGC cytology would also prove to be effective. Associated studies have shown that 24-45% of AGC cases test positive for high risk HPV DNA [22].

Patients with AGC diagnosis, in spite of negative tissue biopsy findings may require longer duration of follow up to increase the diagnostic accuracy. Among the significant lesions detected during the follow up in our patients were diagnosed in 1-24 months after the initial diagnosis of AGC. In our study one case cytologically interpreted AIS, revealed cervical polyp in the initial biopsy and AIS in the follow up of 12 months. Another woman had micro invasive adenocarcinoma in the follow up of 24 months. Clinically significant uterine lesions in 13% of women after a mean follow-up of 37 months [23] were also shown in other studies.

AGC with previous abnormal smears totaled five cases which revealed 1 invasive squamous cell carcinoma, 1 micro invasive adenocarcinoma, 1 adenocarcinoma in situ, 1 high grade squamous intraepithelial lesion and

1 was negative for malignancy in the histological follow up. Hence repeat cervical smear testing should be included in the investigation for patients with AGC [24].

Among the 40 cases initially diagnosed as AGC, only 28 cases were retained as AGC by the three reviewers. The remaining 12 cases were interpreted as reactive/negative cytologically and with normal histological findings. The cytological interpretation of atypical glandular cells is poorly reproducible. In a study the poor reproducibility among the expert reviewers was reported by using smears originally classified as AGC[25]. Our high false positive smears were related to reactive atypia in patients with polyps and also in endometrial hyperplasia cases where endometrial cells appeared worrisome on cytological evaluation and may be the reason for overcall. The interpretative pitfalls could also be due to second blind screening without demographic profiling.

This study showed clinically significant glandular lesions in 30% of patients with atypical glandular cells. There was good correlation between cytological and histological results of the significant lesions. The chi-square value also showed that there is significant correlation between the cytological –histological outcome.

There was no National screening program in our population, during the study period; therefore the cases were opportunistic or symptomatic analizations. When compared to other studies this study is very small and may not have significant statistical power.

The patients clinical information is important when interpreting atypical glandular cells. Adherence to interpretation criteria of the atypical glandular cells must be maintained to avoid overuse. A consensus diagnosis may help to improve diagnostic accuracy. While interpreting the Pap smear from a post-menopausal woman a careful search for atypical glandular cells should be made to improve the diagnostic accuracy.

CONCLUSION

The prevalence of AGC in our study was 0.2% and its associated significant pathologic findings found in our population were similar to that of large institution based studies. The presence of atypical glandular cells in cervical smears may exhibit a spectrum of findings from benign or reactive changes to squamous or glandular malignant or pre malignant lesions. This review showed significant endocervical lesions occurred in younger women where as the older women had endometrial lesions. Patients with atypical glandular cells with the clinical presentation of abnormal vaginal bleeding and post menopausal status should be followed up closely. As patients with AGC are

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at risk for clinically significant lesions should be followed up for a substantial period despite initial negative histological findings.

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