Clinically Significant Lesions in Women with Atypical Glandular Cells on Cervical Cytology: A Nine-year Retrospective Study

Ching-Ting TAM MBBS, MRCOG, MHKCOG
Hon-Cheung LEE MBBS, FRCOG (UK), FHKAM (O&G)
Department of Obstetrics and Gynaecology, Tuen Mun Hospital, New Territories West Cluster, Hospital Authority, Hong Kong

Objectives: To determine the incidence of clinically significant lesions in patients with cytologically atypical glandular cells (AGC) in Hong Kong; and to study the association between clinical characteristics and risks of developing clinically significant lesions as well as the long-term impact of cytologically AGC in a patient cohort to make appropriate recommendations for managing these patients.
Methods: A retrospective study in 261 women with cytologically AGC, who were first referred to the colposcopy clinics of the New Territories West Cluster, Hospital Authority, was conducted. Follow-up records, as well as cytological and histological reports, were analysed. Clinically significant lesions were defined as cervical intraepithelial neoplasia 2 or 3, severe glandular dysplasia, atypical endometrial hyperplasia, adenocarcinoma in situ, or invasive carcinoma.
Results: Significant lesions were diagnosed in 77 (30%) patients after referral for cytologically AGC. Twenty-nine (11%) patients had gynaecological cancer. Forty-eight (18%) patients had severe premalignant conditions of the gynaecological tract. Fifty-eight patients (75%) had lesions diagnosed within the first year of referral. Of 229 patients referred for AGC not otherwise specified, 58 (25%) had significant lesions. Of 32 patients referred for AGC-favour neoplasia, 19 (59%) had significant lesions. Presence of concurrent atypical squamous cells of unknown significance (ASCUS) at referral was significantly associated with the diagnosis of genital tract cancer (p=0.02). Concurrent ASCUS at referral was also significantly associated with delayed diagnosis of clinically significant lesions (p=0.01).
Conclusions: Incidence of clinically significant lesions in women with cytologically AGC was high. In particular, concurrent ASCUS at referral conferred an increased risk of clinically significant lesions.
Hong Kong J Gynaecol Obstet Midwifery 2015; 15(1):53-60

Keywords: Neoplasms, squamous cell; Papanicolaou test; Uterine cervical neoplasms

Introduction

Interpreting abnormal cervical smears is one of the most commonly encountered tasks by gynaecologists. Management of smears with glandular abnormalities remains a challenging problem. A significant number of lesions are associated with glandular abnormalities[1]. Atypical glandular cells (AGC) are defined as cells showing either endometrial or endocervical differentiation displaying nuclear atypia that exceeds obvious reactive or reparative changes but without the unequivocal features of invasive adenocarcinoma[1].

In order to improve the clinical relevance of the categories and to further define 'atypical', atypical glandular cells of undetermined significance (AGUS) was reclassified by Bethesda System Workshop in 2001[2]. Atypical glandular cells are now classified into subcategories of 'favour neoplasia' and 'not otherwise specified' (NOS).

A diagnosis of AGC on Pap smear has been shown to have a high correlation with clinically significant histology, ranging from 0% to 83% in various studies[3-5]. Aggressive approach is needed for the evaluation of patients with AGC on Pap smear as many of them have underlying premalignant or malignant changes.

Although algorithms for management vary, the consensus in literature suggests that these patients require colposcopically directed cervical biopsy and endocervical curettage (ECC)[5-7]. Cervical conisation should be done in patients with persistent AGC. Endometrial sampling (ES) is commonly recommended for patients >35 years and in the presence of abnormal uterovaginal bleeding[4,6,7].

Correspondence to: Dr Ching-Ting Tam
Emails: tct248@ha.org.hk; winnietct@yahoo.com.hk

This study aimed to determine the local incidence of clinically significant lesions in patients with cytologically AGC in a local region in Hong Kong. The risk factors for developing clinically significant lesions were also studied. We also examined the long-term impact of cytologically AGC in a patient cohort in order to make appropriate recommendations for management of these women.

Methods

Data were extracted from the electronic endoscopic record systems (ERS) of Tuen Mun Hospital and Pok Oi Hospital. Patients who were referred to the colposcopy clinics of these two hospitals between 1 January 2004 and 31 December 2012 were analysed. The hard copies of the medical records of these patients were traced and reviewed. For the purpose of this study, patient data were examined up to 31 December 2013, allowing for at least 1 year of follow-up for all patients.

Clinically significant lesions were defined by a histological result of high-grade cervical intraepithelial neoplasia (CIN) 2 or 3, severe glandular dysplasia, atypical endometrial hyperplasia, adenocarcinoma in situ (AIS), or invasive carcinoma.

The database (including ERS and hard copies of medical records) was reviewed for patient age, sub-classification of Pap smear, AGC subtypes, the most significant histological result, patient characteristics, follow-up smears, and colposcopy.

Patients were excluded from the study if they had a history of genital tract cancer or hysterectomy. Statistical analysis was performed using IBM SPSS Statistics version 21. Chi-square test, Fisher's exact test, and Mann-Whitney *U* test were employed for statistical analyses, with a value of $p<0.05$ considered statistically significant. Binary logistic regression was used to study the correlation between patient characteristics and presence of clinically significant lesions. Odds ratios with their respective 95% confidence intervals were used to evaluate the magnitude of association.

Results

From the ERS, 287 patients had their first referral to our colposcopy clinics for cytologically AGC in the 9-year study period. Review of the hard copies of the medical records showed that 19 patients who were referred for high-grade squamous intraepithelial lesions (HGSIL) only were wrongly recorded as having AGC cytology in the ERS. In total, 268 patients were truly referred to us for cytological AGC within the study period. Among these 268 patients, seven (3%) who had a history of genital tract cancer were excluded from the subsequent analysis (Table 1).

There were 229 (88%) referrals for AGC NOS and 32 (12%) for AGC-favour neoplasia. The mean age at referral for all patients was 45.4 (range, 22-84) years. The mean age for patients with AGC NOS was 44.9 (range, 22-84) years whereas that for patients with AGC-favour neoplasia was 48.5 (range, 28-79) years. There was no significant difference between the mean age of patients with AGC NOS and that with AGC-favour neoplasia ($p=0.13$, Mann-Whitney *U* test).

The original smear reports were traced to verify the origins of AGC and to examine whether there were concurrent squamous abnormalities. The original smear reports were lost in 16 (6%) patients. These were arbitrarily classified as AGC subtypes not specified and without

Table 1. Patients excluded from the study

Patient No. with previous gynaecological cancer	Previous cancer diagnoses	Previous hysterectomy	Referral smear	Diagnosis after cytological AGC identified
1	Cervical cancer stage 1b1 and vaginal intraepithelial neoplasia 3	Yes	AGC NOS	Vaginal cancer
2	Cancer of corpus uteri	Yes	AGC NOS	No lesion
3	Cancer of corpus uteri	Yes	AGC NOS	Vaginal HPV
4	Cancer of corpus uteri	Yes	AGC NOS	No lesion
5	Cervical cancer stage 1a1	No	AGC NOS	CIN 1, HPV
6	Cancer of corpus uteri	Yes	AGC NOS	No lesion
7	Cancer of corpus uteri	Yes	AGC NOS	Vaginal recurrence

Abbreviations: AGC NOS = atypical glandular cells not otherwise specified; CIN 1 = cervical intraepithelial neoplasia 1; HPV = human papillomavirus

concurrent squamous abnormalities. The subtypes of AGC are shown in Table 2.

The number of patients having concurrent squamous abnormalities was 50 (19%), including 32 (64%), 13 (26%) and five (10%) with atypical squamous cells of unknown significance (ASCUS), low-grade squamous intraepithelial lesions (LGSIL) and HGSIL, respectively.

All 261 patients were followed up in our colposcopy clinics for at least 1 year. They were evaluated by means of colposcopy with or without biopsies, ECC, and ES according to their age and clinical history. One patient had a history of cytologically AGC NOS 3 years before referral to our clinic. Only cervical human papillomavirus (HPV) infection was diagnosed at her first presentation with cytologically AGC. Thirty (12%) patients had repeat AGC smears in the follow-up period. Two (0.8%) patients had repeat AGC diagnosed for more than twice on their follow-up smears.

Endometrial sampling was done in 226 (87%) patients. Significant lesions were detected in 19 (8%) patients. Endometrial cancer was diagnosed in nine (4%) patients. The mean age of patients without ES was 38 years whereas those diagnosed with endometrial cancer on ES was 54 years. For patients with ES done but insufficient quantity of tissue for diagnosis, their mean age was 61 years.

Colposcopy was performed in all 261 patients. The numbers of colposcopic diagnoses made for CIN 2/3, AIS, and cervical cancer were 25, 2, and 7, respectively. Thirty-six (14%) patients had significant lesions detected on colposcopically guided cervical biopsies, by means of punch biopsies or loop electrosurgical excisional procedure. Among them, the numbers with CIN 2/3, AIS, cervical cancer, and severe glandular dysplasia were 19, 3, 8 and 6, respectively. The sensitivity of colposcopy for detecting clinically significant lesions was 94.4%. The mean age of patients diagnosed with cervical cancer on colposcopy was 38 years for squamous carcinoma and 50 years for adenocarcinoma. The mean age of patients with CIN 2/3 was 43 years.

Endocervical curettage was done in 232 (89%) patients. Among them, 10 (4%) patients were diagnosed with significant lesions. The numbers of adenocarcinoma, AIS, glandular dysplasia, and CIN 2/3 were 2, 1, 6 and 1, respectively. The mean age of patients with and without ECC was 46 years and 44 years, respectively. The mean age of patients with malignant lesions on ECC was 51 years.

In all, 77 (30%) patients had significant lesions diagnosed after referral for cytologically AGC. Among them, 29 (38%) patients suffered from gynaecological cancer; 48 (62%) patients suffered from premalignant conditions of the gynaecological tract. Distribution of the significant lesions is shown in Table 3.

Table 2. Subtypes of atypical glandular cells versus final diagnosis

Subtype	Data
Endocervical (n=75; 29%)	
Cancer	6 (8%)
Severe preneoplastic	15 (20%)
Endometrial (n=34; 13%)	
Cancer	2 (6%)
Severe preneoplastic	3 (9%)
Not specified (n=152; 58%)	
Cancer	21 (14%)
Severe preneoplastic	30 (20%)

Table 3. Final histological diagnoses after referral for cytological atypical glandular cells

Diagnosis	No.
Non-cervical significant lesions	
Cancer of fallopian tube	1
Cancer of corpus uteri	12
Atypical endometrial hyperplasia	11
Cervical cancer	
Poorly differentiated carcinoma	1
Adenocarcinoma	9
Squamous cell carcinoma	6
Cervical pre-cancer	
Severe glandular dysplasia	7
Adenocarcinoma in situ	9
Cervical intraepithelial neoplasia 2/3	21
Insignificant lesions	
HPV infection/CIN 1	152
Benign	32

Abbreviations: CIN 1 = cervical intraepithelial neoplasia 1; HPV = human papillomavirus

Among the 77 patients with significant lesions, 53 (69%) suffered from cervical lesions, while 23 (30%) had uterine lesions; one patient suffered from cancer of the fallopian tube. The mean age of patients with cervical lesions was 43 years, and that of patients with non-cervical lesions was 52 years. There was significant difference between the mean ages of these two groups of patients ($p<0.001$, Mann-Whitney *U* test).

Forty-nine (64%) patients had glandular cell lesions while 27 (35%) patients had squamous cell lesions. One patient suffered from poorly differentiated carcinoma of the cervix. The mean age of patients with glandular cell lesions was 48 years, and that of patients with squamous lesions was 42 years. The difference between the mean ages of these two groups of patients was statistically significant ($p=0.02$, Mann-Whitney *U* test).

In all, 58 (75%) patients had lesions diagnosed within the first year of referral; the remaining 19 (25%) patients had lesions diagnosed after more than 1 year of follow-up (Table 4).

At initial evaluation within the first year of follow-up, about one-fifth of women (58/261) with AGC on Pap smear had significant lesions diagnosed. In the remaining women, 9% (19/203) had delayed diagnoses of significant lesions in the 9-year study period. The mean follow-up duration of women with negative initial evaluation in the first year but delayed diagnoses of significant lesions was 3.1 years. Among the 203 women with negative diagnoses in the first year, nine (4%) had CIN 2/3 or AIS diagnosed in the subsequent follow-up. Six patients had cancer diagnosed later, including four patients with cervical cancer and two patients with cancer of the corpus uteri; four patients suffered from atypical endometrial hyperplasia later. The percentage for significant cervical lesions and uterine lesions, diagnosed within second year and after follow-up for 2 years, was 6.4% (13/203) and 3% (6/203), respectively.

The follow-up of each subject (in person-years) was calculated from the date of referral to the date of diagnosis of the most significant lesion, date of death, or date of hysterectomy, whichever came first until 31 December 2013. The total follow-up duration was 1247 person-years and so the respective mean and median duration of follow-up was 4.78 and 4 years (range, 1-10 years). Incidence rates were calculated by dividing the number of cervical or uterine corpus malignancies by the number of person-years of follow-up. The incidence rate of cervical malignancies in these patients with cytologically AGC was 0.013 (16/1247), whereas that of uterine corpus malignancies was 0.010 (12/1247). The crude rate of cervical cancer and uterine cancer was 1283 and 962 per 100,000, respectively. The rates were 123-fold and 52.8-fold of those in the general Hong Kong population (according to the Hong Kong Cancer Registry of Hospital Authority in November 2013, the respective crude rate of cervical cancer and uterine corpus cancer in 2011 was 10.4/100,000 and 18.2/100,000[8]).

Of 229 patients referred for AGC NOS, 58 (25%) had significant lesions. Of 32 patients referred for AGC-favour neoplasia, 19 (59%) had significant lesions. Besides, 21/229 (9%) patients with AGC NOS and 8/32 (25%) patients with AGC-favour neoplasia suffered from genital tract cancer (Table 5).

Table 4. Years of follow-up till diagnosis of clinically significant lesions (n=77)

Follow-up	Data
Within the first year	58 (75%)
Cancer	23
Pre-cancer	35
Within the second year	13 (17%)
Cancer	6
Pre-cancer	7
After follow-up for 2 years	6 (8%)*
Cancer	0
Pre-cancer	6

* No. of patients with lesions diagnosed at the 4th, 5th, 6th, and 8th year of follow-up were 1, 3, 1, and 1, respectively

Table 5. Categories of atypical glandular cells versus distribution of lesions

Category	No. of patients
AGC-favour neoplasia (n=32)	
Clinically significant lesions	19
Genital tract cancer	8
Severe preneoplastic conditions	11
No lesions	13
AGC not otherwise specified (n=229)	
Clinically significant lesions	58
Genital tract cancer	21
Severe preneoplastic conditions	37
No lesions	171

Abbreviation: AGC = atypical glandular cells

Concurrent ASCUS alone was both a significant predictor of cancer (p=0.02, logistic regression) and presence of significant lesions (p=0.001, logistic regression). Concurrent HGSIL alone was not a significant predictor of cancer (p=0.45, Fisher's exact test). Concurrent LGSIL was not a significant predictor of the presence of significant lesions (p=0.47, Chi-square) or cancer (p=0.57, Fisher's exact test).

The distribution of lesions according to the subtypes of AGC is shown in Table 6. There was no significant difference in the presence of significant lesions among patients with AGC NOS or atypical endocervical cells (p=0.40, Mann-Whitney *U* test). There was also no significant difference in the presence of cancer lesions or significant cervical lesions among patients with AGC NOS or atypical endocervical cells (p=0.20 and p=0.87, respectively, Mann-Whitney *U* test). Presence of atypical endometrial cells was not significantly associated with the presence of significant uterine lesions, compared with other AGC subtypes (p=0.20, Fisher's exact test).

Table 6. Subtypes of atypical glandular cells versus lesion sites or cell types

	Not specified	Endocervical	Endometrial
Lesion site			
Non-cervical	16	3	5
Cervical	35	18	0
Lesion cell type			
Others	1	0	0
Squamous	20	7	0
Glandular	30	14	5

The magnitude of association between various factors and disease by binary logistic regression is shown in Table 7. Concurrent ASCUS at referral was associated with the presence of significant lesion (p=0.001), genital tract cancer (p=0.02), or cervical lesions (p=0.003). Diagnosis of AGC-favour neoplasia was associated with the presence of significant lesions (p<0.001), cancer (p=0.02), or cervical lesion (p<0.001). Having multiple sexual partners was associated with the presence of cervical lesions (p=0.02).

The mean number of follow-up smears was 4.77. The mean number of follow-up colposcopies was 0.71 (range, 0-4).

Among patients who did not have any significant lesions detected within the first year of follow-up, repeat AGC on follow-up smear was significantly associated with future disease (p=0.002). Of 25 patients with repeat AGC during follow-up, eight (32%) had significant disease later. Among patients without any significant lesion detected within the first year, AGC-favour neoplasia, as compared with AGC NOS, was not significantly associated with future disease (p=0.59) or cancer (p=0.39). Concurrent ASCUS at referral was significantly associated with future

Table 7. Risk factors associated with clinically significant lesions in women with cytological AGC by binary logistic regression

Factor	Significant lesions		Cancer		Cervical lesions	
	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value
Age	0.98 (0.94-1.03)	0.40	1.04 (0.98-1.10)	0.23	0.95 (0.90-1.00)	0.06
Menopause	2.01 (0.76-5.37)	0.16	1.03 (0.26-4.13)	0.97	1.39 (0.40-4.79)	0.60
Smoker	0.94 (0.35-2.49)	0.90	0.61 (0.13-3.00)	0.55	1.41 (0.52-3.83)	0.50
Multiple sexual partners	1.74 (0.81-3.69)	0.15	2.22 (0.80-6.13)	0.12	2.65 (1.18-5.94)	0.02
History of sexually transmitted diseases	1.53 (0.40-5.80)	0.53	1.08 (0.13-9.29)	0.94	2.22 (0.56-8.77)	0.26
Concurrent ASCUS	3.81 (1.71-8.49)	0.001	3.35 (1.22-9.19)	0.02	3.57 (1.53-8.35)	0.003
Non-barrier contraception	0.80 (0.41-1.58)	0.52	0.80 (0.30-2.17)	0.67	0.97 (0.46-2.03)	0.93
Multi-parity	0.96 (0.72-1.29)	0.81	0.74 (0.14-3.89)	0.73	0.52 (0.13-2.06)	0.35
AGC-favour neoplasia	5.43 (2.41-12.24)	<0.001	3.45 (1.27-9.33)	0.02	6.43 (2.68-15.40)	<0.001

Abbreviations: AGC = atypical glandular cells; ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval

disease (p=0.01). The association between various factors and delayed diagnosis of clinically significant disease is shown in Table 8. Repeat AGC (p=0.001) and concurrent ASCUS at referral (p=0.01) were significantly associated with the presence of cervical lesions after the first year of evaluation.

Discussion

The results of this study strongly suggest that the presence of AGC in a routine cytological specimen is often associated with a pathological condition and warrants investigations and appropriate management.

In our study in predominantly southern Chinese population, 30% of women had significant lesions diagnosed after referral for cytologically AGC, including 11% rate of gynaecological cancer. This is similar to the rate published in the review by Schnatz et al[8], which included 24 studies in predominantly western populations. Their review showed that 29.0% of AGUS Pap tests had findings requiring follow-up or therapeutic intervention, including a 5.2% rate of malignancy.

While the majority of patients may have benign histological follow-up, a significant proportion of patients with precancerous or malignant disease will harbour lesions in difficult-to-sample areas such as the endocervical canal, fallopian tubes, ovaries, or, very rarely, even in extragenital sites. This diversity in follow-up outcomes creates significant challenges for optimal clinical follow-up. One patient in our study suffered from cancer of the fallopian tube, but she was completely asymptomatic and the diagnosis was made only after hysterectomy.

The rate of delayed diagnoses of cervical lesions of CIN 2 or above in this cohort of 203 women was 7.4% (glandular dysplasia in one, CIN 2/3 in five, AIS in four, and cervical cancer in five patients). This was higher than the rate of 4.3% in a cohort of 117 women as reported by Valdini et al[9]. This may be related to the fact that the mean age of women in our cohort was higher (45 years) than that in their study (42 years). Age seems to be a risk factor for delayed diagnoses in patients with AGC, although our study did not demonstrate any statistically significant association.

Among patients with significant lesions, 35% had lesions of squamous cell type only. The possible explanation for the relative absence of glandular pathology might be that the cells were so badly deformed that they appeared to be glandular to the cytopathologists.

Comparing with the 2-year study by Chan et al published in 2003[10] performed in the same regional hospital, the rate of clinically significant lesions on 2 years of follow-up was lower with AGC diagnosis (27%; n=71/261) than with AGUS diagnosis (43%; n=31/72). However, the study by Chan et al[10] regarded patients with CIN 1 (exact number of patients with CIN 1 was not published) and one patient with metastatic tumour from the breast as clinically significant diseases, while our study did not. Also, some patients did not have complete follow-up of 2 years in our study. Judging from these, the rate of significant lesions might well be similar over the years. This was reflected by the fact that the frequency of genital tract cancer in AGC patients in our study in the first 2 years of follow-up was 11% (n=29/261), while the frequency of genital tract malignancy in AGUS patients in the study by Chan et al[10]

Table 8. Risk factors associated with delayed diagnosis of clinically significant lesions in women with normal initial evaluation in the first year by binary logistic regression

Factor	Significant lesions		Cancer		Cervical lesions	
	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value
Age	0.96 (0.89-1.04)	0.31	1.03 (0.92-1.16)	0.59	0.92 (0.83-1.02)	0.11
AGC-favour neoplasia	1.61 (0.29-9.04)	0.59	2.92 (0.25-33.53)	0.39	3.75 (0.56-25.24)	0.18
Repeat AGC	5.91 (1.93-18.07)	0.002	3.31 (0.50-21.84)	0.21	9.62 (2.54-36.47)	0.001
Menopause	1.20 (0.16-9.08)	0.86	0.61 (0.02-19.28)	0.78	1.76 (0.34-8.92)	0.69
Smoker	1.11 (0.25-4.93)	0.90	1.37 (0.14-13.80)	0.79	1.75 (0.34-8.92)	0.50
Multiple sexual partners	1.00 (0.25-4.05)	1.00	3.66 (0.58-23.33)	0.17	1.97 (0.42-9.29)	0.39
Concurrent ASCUS at referral	4.42 (1.36-15.74)	0.01	4.95 (0.74-32.96)	0.01	7.09 (1.64-30.64)	0.01

Abbreviations: AGC = atypical glandular cells; ASCUS = atypical squamous cells of undetermined significance; CI = confidence interval

was 14% (n=10/72).

This was in contrast with the results in previous studies that showed improved sensitivity and specificity in detecting diseases after revision of The Bethesda System (TBS) in 2001. A study in Geneva[11] showed that, when AGUS smears using TBS 1991 were reclassified using AGC subcategories of TBS 2001, the frequency of clinically significant lesions on follow-up was higher with AGC diagnosis (51%; n=21/41) than AGUS diagnosis (36%; n=37/103). In another study by Gurbuz et al[12], when AGUS smears were reclassified according to TBS 2001, a significant difference (p=0.04) between the rates of the malignant pathologies in the AGUS (25%) and in the AGC (43%) was identified. This discrepancy in results between our study and that of the study by Chan et al[10] may be explained by the decreasing cervical cancer incidence rate in the past 10 years (according to the Hong Kong Cancer Registry, the crude rates of cervical cancer in 1998 and 2008 were 14.9 and 9.8 per 100,000, respectively[13]).

In our study, among women with a diagnosis of AGC-favour endometrial cells in origin, 15% (n=5/34) had a significant uterine lesion. This was lower than the rate of 24% of significant uterine lesions (n=11/45) in women with AGUS-favour endometrial origin, as reported by Chhieng et al[14] in 2001. The rate of significant uterine lesions was 33% (n=18/55) in another study on women with AGC-favour endometrial origin in 2006 by Saad et al[15]. The lower rate of significant uterine lesions in our study might be explained by the lower incidence of uterine cancer in Hong Kong (18.2 per 100,000 from the Hong Kong Cancer Registry 2011[13]) than in the western white population (30.9 per 100,000 from Pennsylvania Cancer Incidence and Mortality 2001[16]).

Our study was limited by its retrospective nature. Future study on a greater number of patients may help to identify the risk factors for predicting significant disease, as cytologically AGC is not a common entity. A multicentre prospective study will meet this purpose. A recent literature review[17] suggested that HPV DNA testing may be useful in differentiating between the risk of cervical and endometrial cancer, based on an analysis of 661 women with AGC cytology and HPV DNA testing. In 2006, consensus guidelines for managing AGC released by the American Society for Colposcopy and Cervical Pathology[18] recommended the combined use of colposcopy and endocervical sampling along with high-risk HPV testing for women with AGC-graded Pap test results. Hence, the role of HPV DNA testing will also be the focus of future studies.

The number of significant lesions in the group we studied is big enough to suggest the need for complete evaluation (colposcopy with cervical biopsies, ECC, and diagnostic conisation when needed) of all women with an AGC smear. An endometrial biopsy is warranted in the absence of abnormal cervical findings for persistent AGC. For women with unexplained AGC in the first year of follow-up, the percentage of future uterine lesions was 3% (6/203) in this study. There may be a role for the use of ultrasound or hysteroscopy in helping to exclude uterine lesions, and this needs further studies. The proportion of patients having cancer after negative initial evaluation in the first year was only 3.0% in this study. Hence, aggressive management like hysterectomy is not warranted for these women. If the patient has AGC that favour a neoplastic process, a concurrent ASCUS, or persistent AGC, or a cone biopsy should be performed. In our study, none of the women suffered from cancer outside the genital tract during follow-up. But if all the above-mentioned evaluations are normal, it should be confirmed that the woman has received other age-appropriate screening modalities, including for breast or colon cancer. If all comprehensive evaluations are normal, follow-up Pap tests should be performed because of a high rate of delayed significant diagnoses.

References

1. The 1998 Bethesda System for reporting cervical/vaginal cytological diagnoses. National Cancer Institute Workshop. *JAMA* 1989; 262:931-4.
2. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 2002; 287:2114-9.
3. Cangiarella JF, Chhieng DC. Atypical glandular cells — an update. *Diagn Cytopathol* 2003; 29:271-9.
4. Levine L, Lucci JA 3rd, Dinh TV. Atypical glandular cells: new Bethesda terminology and management guidelines. *Obstet Gynecol Surv* 2003; 58:399-406.
5. Burnett AF. Atypical glandular cells of undetermined significance Pap smears: appropriate evaluation and management. *Curr Opin Obstet Gynecol* 2000; 12:33-7.
6. Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ;

ASCCP-Sponsored Consensus Conference. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002; 287:2120-9.

7. Massad LS, Einstein MH, Huh WK, et al. 2012 Updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *Obstet Gynecol* 2013; 121:829-46.
8. Schnatz PF, Guile M, O'Sullivan DM, Sorosky JI. Clinical significance of atypical glandular cells on cervical cytology. *Obstet Gynecol* 2006; 107:701-8.
9. Valdini AF, Augart CL, Olivieri M. Delayed diagnoses of cervical intraepithelial neoplasia and cancer after negative evaluation for atypical glandular cell pap smear: does age matter? *J Low Genit Tract Dis* 2013; 17:390-6.
10. Chan CW, Cheung KB. Clinical significance and management of cervical atypical glandular cells of undetermined significance. *Hong Kong Med J* 2003; 9:346-51.
11. Kumar N, Bongiovanni M, Molliet MJ, Pelte MF, Egger JF, Pache JC. Reclassification and analysis of clinical significance of atypical glandular cells on ThinPrep using Bethesda 2001: Geneva experience. *Swiss Med Wkly* 2007; 137:635-41.
12. Gurbuz A, Karateke A, Kabaca C, Kir G. Atypical glandular cells: improvement in cytohistologic correlation by the 2001 Bethesda system. *Int J Gynecol Cancer* 2005; 15:903-10.
13. Hospital Authority: Hong Kong Cancer Registry website: www3.ha.org.hk/cancereg/statistics.html. Accessed Mar 2014.
14. Chhieng DC, Elgert P, Cohen JM, Cangiarella JF. Clinical implications of atypical glandular cells of undetermined significance, favor endometrial origin. *Cancer* 2001; 93:351-6.
15. Saad RS, Takei H, Liu YL, Silverman JE, Lipscomb JT, Ruiz B. Clinical significance of a cytologic diagnosis of atypical glandular cells, favor endometrial origin, in Pap smears. *Acta Cytol* 2006; 50:48-54.
16. Pennsylvania cancer incidence and mortality 2001. *Bureau of Health Statistics and Research, Pennsylvania Department of Health*, July 2004.
17. Sharpless KE, O'Sullivan DM, Schnatz PF. The utility of human papillomavirus testing in the management of atypical glandular cells on cytology. *J Low Genit Tract Dis* 2009; 13:72-8.
18. Wright TC Jr, Massad LS, Dunton CJ, Spitzer M, Wilkinson EJ, Solomon D; 2006 American Society for Colposcopy and Cervical Pathology–sponsored Consensus Conference. 2006 Consensus guidelines for the management of women with abnormal cervical cancer screening tests. *Am J Obstet Gynecol* 2007; 197:346-55.