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Prevalence of Clinical Significant Lesions in Atypical Glandular Cell of Undetermined Significance (AGUS) From Cervical Pap Smear

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ABSTRACT

Objective: To determine the prevalence of clinical significant lesions from the underlying pathology of women with atypical glandular cell of undetermined significance (AGUS) from cervical Pap smear.

Materials and Methods: Women with cytologic diagnosis of AGUS from cervicovaginal Pap smears in our institution from January 2000 to June 2008 were identified. Clinical data and their subsequent tissue histologic diagnoses were reviewed.

Results: The prevalence of AGUS in 100,648 Pap smears was 0.26% (266 smears); 151 of them had further investigations and were included in the study. The histology/histopathology turned out to be normal and cervicitis in 35 cases (23.2%) and 28 cases (18.6%), respectively, cervical intraepithelial neoplasia (CIN) I in 51 cases (33.9%), CIN II in 18 cases (11.9%), CIN III in 4 cases (2.7%) adenocarcinoma in situ (AIS) in 4 cases (2.7%), invasive adenocarcinoma of cervix in 4 cases(2.7%), complex hyperplasia with atypia in 2 cases (1.3%) and endometrial adenocarcinoma in 5 cases (3.3%).

Conclusion: The clinical significant lesions were found in 37 cases (24.5%) of AGUS cervical cytology, with 6% prevalence of invasive cancers.

Keywords: atypical glandular cell of undetermined significance, AGUS, AGC, cervical pap smear, histopathology

Introduction

Cervical cancer was the second most common gynecologic cancer worldwide, accounting for 15% of all female cancers in developing countries.[1] In Thailand, cervical cancer was the most common gynecologic cancer and the most common cause of death with the incidence rate of 20.9 in 100,000 women.[2] One effective mean to reduce mortality

from cancer of the cervix is early detection and treatment of pre-invasive cervical lesions. This can be achieved by cervical cytologic screening programs.

The first system to report cervical cytology is the Papanicolaou system,[3] which was developed in 1943 and has been used for many years. However, due to several limitations of Pap smear reports in correlation with the clinical data as well as emerging knowledge about the etiology and clinical course of cervical cancer, the new system was introduced by the National Cancer Institute in Bethesda, Maryland, in 1988,[4] and was modified in the Bethesda Workshop 2001.[5] This Bethesda System is widely used nowadays for exfoliative cytology of the female genital tract. In the Bethesda system, one specific category of cells displaying nuclear atypia that exceed reactive or reparative changes but lack the features of dysplastic cells or invasive carcinoma has been adopted, so called "atypical cells of undetermined significance". In Bethesda 1988, these atypical cells were classified into ASCUS (atypical squamous cells of undetermined significance) and AGUS (atypical glandular cells of undetermined significance). Because the term "undetermined significance" usually misleads clinicians to regard it as unimportant and neglect the underlying problems, the term "ASCUS" and "AGUS" were dropped out in the Bethesda 2001. Focusing to AGUS, the term was replaced by a more definite classification of atypical glandular cells (AGC): "atypical glandular cells" and "atypical glandular cells favor neoplastic".

Unlike ASCUS wherein the squamous cells are almost invariably come from cervix, the glandular cells in AGUS may derive from endometrium, endocervix, or other glandular tissues. Aside from various sites of origin, AGUS could be associated with a wide varieties of squamous and glandular diseases, including benign, premalignant, and malignant diseases. These possibilities certainly bring about a clinical diagnostic challenge to a clinician to reach for a correct diagnosis especially in the clinical significant lesions that require a further investigations and management, such as, cervical intraepithelial neoplasia (CIN) II-III, adenocarcinoma in situ (AIS), endometrial hyperplasia with atypia, or invasive cancers. Previous reports demonstrated a high proportion of clinical significant lesions related to AGUS ranging from 8.4% to 53.3%.[6-15]

Our study aimed to determine the prevalence of histolopathologic diagnoses which had clinical significance, in women who had cytologic diagnosis of AGUS from cervical Pap smear.

Materials and Methods

This study was conducted after an approval from the Ethics Committees involving Human Subjects of Bangkok Metropolitan Administration. Women with the cervical cytologic diagnosis of AGUS between January 2000 and June 2008 were identified from the annual records of gynaecologic and family planning out-patient clinics of the Department of Obstetrics and Gynecology. Inclusion criteria were women who had AGUS or AGC cytology from conventional Pap smear performed in our institution and who underwent further investigation, such as cervical biopsy with or without colposcopic examination, endocervical curettage, cervical conization including loop electrosurgical excision procedure (LEEP), endometrial biopsy, fractional curettage (F&C), or hysterectomy. Exclusion criteria were women who had history of cervical cancer or pre-invasive cervical lesions, had prior hysterectomy, had incomplete medical records, or were lost to follow up before any investigations. The term of AGUS was used in this study instead of AGC because our study was a retrospective study when AGUS has been generally used for a long time before changing to the newer terminology.

Clinical and pathological data were retrieved from the in-patient and out-patient records and the Archive of the Anatomical Pathology Department. Histopathologic diagnosis referred to the most severe pathological finding as revealed from biopsy, curettage, conization, LEEP, or hysterectomy. Clinical significant lesions that were determined from subsequent histopathology included cervical intraepithelial neoplasia (CIN) II-III, adenocarcinoma

in situ (AIS), endometrial hyperplasia with atypia, or invasive cancers either of the cervix, endometrium or other genital organs. Data were analyzed using SPSS statistical software version 11.5 (SPSS, Chicago, IL, USA). Descriptive statistics were used for demographic data and summarized as frequency with percentage, mean with standard deviation (SD).

Results

Out of 100,648 Pap smears which were performed in our institution during the study period, 266 (0.26%) were diagnosed as AGUS or AGC. Among these 266 women, 115 were excluded due to the following reasons: prior history of cervical carcinoma or pre-invasive cervical lesions (21 women), no available or incomplete medical records (52 women), or loss to follow up or self referred to other hospitals due to reimbursement reason before any investigations could be carried out (42 women). The remaining 151 women met inclusion criteria and were included for analysis. The specific subtypes of AGUS were denoted as: reactive in 11 cases (7.3%), favor for neoplastic lesions in 34 cases (22.5%), and not otherwise specified in 106 cases (70.2%).

Mean age of the 151 women was 44 years (range, 20-90 years). Mean gravidity and parity were 1.8 (range, 0-9 pregnancies) and 1.5 pregnancies (range 0-9 pregnancies) respectively. Approximately 1/5 was postmenopausal (27 women or 17.9%).

Over 2/3 of the women (105 women or 69.5%) who had AGUS in this study were asymptomatic and had Pap test as a general health screening (98 women) or postpartum check up (seven women). Among women who had symptoms and sought for medical consultation, abnormal vaginal bleeding was more common than abnormal vaginal discharge: 31 women (20.5%) and 15 (9.9%), respectively. The vaginal bleeding was specifically noted as postmenopausal in 12 women.

Histopathology was obtained by various means. Nine women did not have colposcopic examination due to the following reasons: gross cervical lesions leading to a direct cervical biopsy after cytologic smears (two women); postmenopausal bleeding in women with endometrial thickness $\geq$ 4 mm (4, 9.3, 17, and 19 mm), in whom fractional curettage was done (four women); co-incidental pathology of myoma uteri and adenomyosis when hysterectomy was performed prior to the scheduled colposcopy (two women); and no obvious lesions at ectocervix with minimal uterine bleeding in whom endocervical curettage and endometrial biopsy were immediately done after cytologic smear in the out-patient clinic (one woman).

Colposcopy was performed in 142 women (94.0%): 91 were assessed as satisfactory while 51 as unsatisfactory. Colposcopic directed biopsy were done in 76 women whose lesions were evidenced over the ectocervix. LEEP was subsequently performed in 27 women who had biopsy results of high grade lesions (CIN II-III). In 103 women who had no lesion over ectocervix or the colposcopy was unsatisfiactory, endocervical curettage was done as a single mean or together with cervical biopsy. Base on the age, menstrual history, and degree of suspicion for endometrial lesion, fractional curettage or endometrial biopsy was performed in 25 and 8 women, respectively.

From the 151 AGUS cervical cytology, the histology/histopathology turned out to be normal cervix or cervicitis in 63 cases (41.7%): 35 cases (23.2%) and 28 cases (18.6%), respectively. Among 88 cases with abnormal epithelial lesions, 81 cases had primary lesions of the cervix while the other seven had endometrial pathology. CIN I was diagnosed in 51 cases (33.9%). Clinically significant lesions were evidenced from the histopathology in 37 cases (24.5%, excluding normal/ cervicitis and CIN I) including CIN II in 18 cases (11.9%), CIN III or cervical AIS in four of each (2.7% each), invasive adenocarcinoma of cervix in the other four (2.7%), endometrial complex hyperplasia with atypia in two cases (1.3%) and endometrial adenocarcinoma in five (3.3%). A summary of the established histologic/ histopathologic diagnoses in 151 women is presented in Table 1.

Focusing on the clinically significant lesions, invasive cancers comprised 24.3% of the cases

(9/37): all were adenocarcinoma (four from cervix and five from endometrium). Almost all women (3/4) who had adenocarcinoma of cervix were asymptomatic while the only woman with symptoms had problem of abnormal vaginal bleeding. Two cases underwent cervical biopsy of the gross lesions evidenced during pelvic examination while the other two had biopsy under colposcopic examination or endocervical curettage followed by LEEP. Three of them finally had a diagnosis of clinical stage I cervical cancer, underwent radical hysterectomy with lymph node dissection while another one had clinical stage IIb and had concurrent chemoradiation.

All of the five women with endometrial adenocarcinoma were postmenopausal and presented with abnormal bleeding. The diagnoses in 4 out of 5 cases were achieved by transvaginal ultrasonography, which revealed endometrial thickening (thickness 9-19 mm), followed by fractional curettage. Diagnosis in another woman, who did not have transvaginal ultrasonography, was made from colposcopic directed biopsy and endocervical curettage in which small pieces of malignant endometrial tissues were also obtained. All women with endometrial adenocarcinoma eventually had complete surgical staging as a definite treatment.

Considering the subtypes of AGUS, the prevalences of clinically significant lesions were not significantly different among those being reported as favor reactive (3/11 cases, 27.3%), favor neoplastics (9/34 cases, 26.5%) and not otherwise specified group (25/106 cases, 23.6%). However, no one of AGUS favor reactive were found to have CIN III, AIS or invasive cancer while 6/34 (17.6 %) of AGUS favor neoplastic lesions and 11/106 (10.4%) of those not otherwise specified were revealed to have CIN III, AIS, or invasive carcinomas.

Discussion

Since the Bethesda system was first adopted in 1988, the cytotechnologists and the pathologists in our institution have incorporated this new system into their cytopathological reports.

Being retrospective in nature, one limitation of our study was well recognized that a considerable number of women with AGUS could not be included in the analysis (115/266 women). The majority of them (94 women) were due to administrative problems: loss to follow up or referred to other hospitals for reimbursement reason or no available or incomplete medical records due to the demolition system of the institution to manage with the long uncontacted medical records. Nevertheless, the 0.26% prevalence rate of AGUS in our study was in the range as had been reported from other studies, 0.08- 0.46%.[6-15] The study which reported lowest prevalence among others was by Kim, et al[12] who found AGUS in only 0.08% of total Pap smears. This might be because the majority of patients in their hospital were low-risk populations and the overall lower incidence of uterine adenocarcinoma in Korean women than in western women.[12]

Regarding the histology/ histopathology associated with the AGC, similar to ASCUS from which the cervical tissue could turn out to be normal or have various underlying histopathologies from dysplastic lesions to cancers such as; high and low-grade squamous lesions, AIS and adenocarcinoma. Other possible benign findings include squamous or tubular metaplasia, endometriosis, Arias-Stella reaction, microglandular hyperplasia, endocervical polyps and etc.[16] However, in contrast to ASC when the squamous cells are almost invariably derived from cervix, the glandular cells of AGC may have origin from the cervix itself or the endometrium or rarely fallopian tubes or ovaries. Schnatz, et al[17] found 0.6% of AGC in their study having diseases of ovaries and Fallopian tube. Another study even reported that one of their AGC patients had primary colonic cancer which metastasized to endometrium which consequently yielded the atypical glandular cells from the cervical Pap smear.[10] This fact certainly leads to broader spectrum of final histopathology of AGC than the ASC. We also found in our study that the women with AGC had histology/ histopathology ranging from normal to invasive cancers.

Our primary objective was to evaluate the prevalence of clinical significant lesions associated with AGC because they would certainly affect the lines or options of treatment. In our study, 24.5% of cytology diagnoses of AGC were histologically proven to be of clinical significance. Other reports demonstrated the prevalence of clinical significant lesions related to AGUS ranging from 8.4% to 53.3%.[6-15] The prevalences of AGUS and their associated clinical significant lesions of other studies in comparison to our study are shown in Table 2. Gutman, et al[15] found prevalence of clinical significance lesion higher than our study (53.3%). This may be due to their AGUS cases had high prevalence of coexisting ASCUS (31/45 cases or 68.9%) which were subsequent revealed from histopathological findings to be high grade squamous interaepthelial lesions in up to 46.6% (21 cases). They reported three cases of invasive cancers (6.7%) from AGUS which 2/3 cases were AGUS coexisting ASCUS, and found that no difference between pre- and post menopausal women in terms of pathology.[15] Our study performed only in cases of AGUS and found most cases 6/9 of invasive cancer (66.7%) occurred in postmenopausal women.

In our study, carcinoma of endometrium was more common in women who presented with postmenopausal abnormal vaginal bleeding and all of them had endometrial thickness more than 4 mm. These clinical presentations were similar to other studies. Chan, et al[18] found that women with endometrial adenocarcinoma had clinical presentation of abnormal vaginal bleeding in both premenopausal and postmenopausal group. Thus, any abnormal vaginal bleeding in a woman especially in postmenopause should be regarded as important.

When we classified AGUS into subtype, we found that the prevalences of clinically significant lesions were not significantly different among those being reported as favor reactive, favor neoplastics and not otherwise specified group. Nevertheless, no cases of AGUS favor reactive were found to have lesions > CIN II while approximately 18% of AGUS favoring neoplastic lesions and 10.0% of those not otherwise specified subtype were revealed to have CIN III, AIS, or invasive carcinomas. These findings were similar to the study of Chan, et al[18] who also found higher association of clinical significant lesions with subtypes of neoplastics (40.0%) and not otherwise specified subgroups (43%) than those favoring reactive (8%).

AGUS or AGC finding should alert the physician to proceed with further investigations and to choose appropriate diagnostic tools for evaluation, especially when the diagnosis is in favor of neoplastics and not otherwise specified group. Concerning that the lesions might be from either cervix or endometrium, clinical evaluations with colposcopy and endocervical curettage, supplemented with endometrial thickness measurement by transvaginal sonography followed by endometrial sampling or fractional curettage if indicated in women with postmenopausal bleeding.

Conclusion

This study showed 0.26% prevalence of AGUS while the prevalences of clinical significant lesions and invasive cancer were 24.5% and 6.0%, respectively.

Table 1. Histology/ histopathology from 151 women with cervical cytologic diagnosis of AGUS.

Histology/ histopathology	Subtypes of AGUS (N, %)			
	Favor reactive	Favor neoplastics	NOS	Total
Normal	2 (18.2)	8 (23.5)	25 (23.6)	35 (23.2)
Cervical lesions				
Cervicitis	2 (18.2)	9 (26.6)	17 (16.0)	28 (18.6)
CIN I/ HPV	4 (36.4)	8 (23.5)	39 (36.8)	51 (33.8)
CIN II/ HPV	2 (18.2)	3 (8.8)	13 (12.3)	18 (12.0)
CIN III	0 (0)	0 (0)	4 (3.8)	4 (2.6)
AIS	0 (0)	2 (5.9)	2 (1.9)	4 (2.6)
Adenocarcinoma	0 (0)	3 (8.8)	1 (0.9)	4 (2.6)
Endometrial lesions				
CH with atypia	1 (9.0)	0 (0)	1 (0.9)	2 (1.3)
Adenocarcinoma	0 (0)	1 (2.9)	4 (3.8)	5 (3.3)
Total	11	34	106	151 (100)

Abbreviations: AIS, adenocarcinoma in situ; CH, complex endometrial hyperplasia; CIN, cervical intraepithelial neoplasia; HPV, Human Papilloma virus infection; NOS, not otherwise specified

Table 2. Prevalence and histologic diagnosis of AGUS Pap tests on follow up from different studies.

Study	Total Pap smears (N)	AGUS		Women with follow up data (n)	Histology/ histopathology outcomes		
		(n)	(%)		Normal/ Cervicitis (%)	Clinical significant lesions (%)	Malignancy (%)
Goff[14]	21,930	100	0.46	56	23.8	41.1	3.6
Gutman[15]	11,800	45	0.38	45	31.1	53.3	6.7
Hammoud[6]	280,041	207	0.10	114	51.8	37.7	10.5
Jeng[11]	51,452	49	0.10	49	73.4	20.4	4.1
Kim[12]	407,451	326	0.08	268	23.9	21.3	7.5
Manetta[10]	76,018	141	0.19	80	55.0	17.5	5.0
Nasuti[9]	86,234	187	0.22	112	NA	8.9	5.4
Sharpless[8]	241,224	648	0.27	477	NA	8.4	2.7
Zweizig[7]	46,804	127	0.27	85	11.8	30.6	10.6
Our study	100,648	266	0.26	151	41.7	24.5	6.0

Abbreviations: AGUS, atypical glandular cells of undetermined significance; NA, not applicable

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การศึกษาความชุกของการเกิดรอยโรคที่มีความสำคัญทางคลินิกในสตรีที่มีผลการตรวจ แปปสเมียร์ของปากมดลูกเป็นชนิด Atypical Glandular Cell of Undetermined Significance (AGUS)

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วัตถุประสงค์ *: เพื่อศึกษาความชุกของการเกิดรอยโรคที่มีความสำคัญทางคลินิกในสตรีที่มีผลการตรวจแปปสเมียร์ของปากมดลูกเป็นชนิด Atypical Glandular Cell of Undetermined Significance (AGUS)*

วัสดุและวิธีการ *: ศึกษาย้อนหลังโดยรวบรวมประวัติผู้ป่วย ประวัติส่วนตัว และผลทางพยาธิวิทยาของสตรีที่มาตรวจ Pap smear และมีผลเป็น AGUS ที่วิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาลตั้งแต่เดือนมกราคม 2543 ถึงเดือน มิถุนายน 2551*

ผลการศึกษา *: พบความชุกของ AGUS ร้อยละ 0.26 จาก 100,648 pap smears ผู้ป่วย 151 รายได้รับการตรวจสืบค้นเพิ่มเติม ผลปกติ 35 ราย (ร้อยละ 23.2), ปากมดลูกอักเสบ 28 ราย (ร้อยละ 18.6), cervical intraepithelial neoplasia (CIN) I 51 ราย (ร้อยละ 33.9), CIN II 18 ราย (ร้อยละ 11.9), CIN III 4 ราย (ร้อยละ 2.7), adenocarcinoma in situ (AIS) 4 ราย (ร้อยละ 2.7), cervical adenocarcinoma 4 ราย (ร้อยละ 2.7), complex hyperplasia with atypia 2 ราย (ร้อยละ 1.3) และ endometrial adenocarcinoma 5 ราย (ร้อยละ 3.3)*

สรุป *: ความชุกของการเกิดรอยโรคที่มีความสำคัญทางคลินิกในผู้ป่วยที่มีผล pap smear เป็น AGUS คือร้อยละ 24.5 และพบมะเร็งระยะลุกลามร้อยละ 6.0*