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REVIEW

Significance of Atypical Squamous Cells and Atypical Glandular Cells: Similar but Dissimilar

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Since 1988 when the Bethesda System (TBS) was first adopted[1], two modifications were subsequently carried out in 1991 and 2001[2,3]. One of the major changes in TBS 2001 is the revision of a terminology used for atypical squamous and glandular cells. TBS 2001 replaced "atypical squamous cells of undetermined significance (ASCUS)" and "atypical glandular cells of undetermined significance (AGUS or AGCUS)" in TBS 1988 and 1991 with simply "atypical squamous cells (ASC)" and "atypical glandular cells (AGC)", respectively. Attempts have always been made to qualify or subcategorize these equivocal diagnoses in a manner to indicate that it can define a patient at increased risk of significant clinical lesions which generally include high grade pre-invasive and invasive cancers. These two acronyms are similar for being classified as cells which are more atypical than reactive response but are not justified to be classified as preinvasive or invasive lesions. However, they are dissimilar in terms of having different cytologic backgrounds and underlying histopathology as well as clinical implication. When these abnormal cytologic diagnoses and their qualifiers or subcategories are given, a gynecologist who confronts with the women should thoroughly understand the messages from a cytopathologist through his/ her report of these cytologic interpretations. Some important issues of these two particular cytologic abnormalities will be briefly pointed out here in a light of hope that this will lead to an optimal management for a woman.

Background

ASC

Overall, the prevalences of atypical squamous cells generally range from 2-5%[4-6]. TBS 1988 initiated the category of "atypical squamous cells of undetermined significance" (ASCUS) for cells that are more abnormal than merely reactive changes but do not meet qualitative and quantitative criteria for squamous intraepithelial lesion (SIL)[1]. Although qualifying ASCUS as reactive or SIL was encouraged, most cases were reported as not otherwise specified (NOS). With a further attempt to define risk of this cytologic classification, TBS 1991 then emphasized the responsibility of the cytopathologist to communicate whether a reactive or a premalignant/ malignant process was favored for ASCUS[2]. With more emerging data showing that the diagnosis of ASCUS had poor interobserver reproducibility[7-10] and with a concern that all ASC should be considered to be suggestive of SIL, TBS 2001 eliminates ASCUS favor reactive and replaces ASCUS with ASC[3].

The ASC of TBS 2001 is subcategorized into ASC, of undetermined significance (ASC-US) and ASC, cannot exclude high-grade SIL (ASC-H). Cells of ASC-US have size of intermediate or superficial squamous cells with nuclear changes suggestive but not diagnostic

of LSIL. The diagnosis of ASC-US should exclude any cytology suggestive of HSIL and it denotes that specific diagnosis cannot be made. After ASCUS favor reactive which was mostly associated with normal histology or unimportant histopathologic lesions was deleted, the 2001 ASC-US is comparable to previous categories of ASCUS-NOS or ASCUS favor SIL[11]. ASC-H is far less common than ASC-US, accounting for 5% to 10% of all ASC cases[12,13]. Cells of ASC-H generally have size of metaplastic cells lying singly or in clusters suggestive of HSIL but lack criteria for definitive interpretation.

AGC

Overall, the prevalences of atypical glandular cells are much less common than atypical squamous cells, ranging from 0.1-0.6%[14-20]. TBS 1988 used the term "atypical glandular cells of undetermined significance" (AGUS or AGCUS) for any glandular cells having nuclear atypia which is more severe than reactive changes but lacks definite features of invasive adenocarcinoma. It was suggested that supplementary note of "favor reactive" or "favor premalignant/ malignant" could be used to provide additional information to the clinician. Of note, adenocarcinoma in situ (AIS) was also included in AGCUS of TBS 1988 and 1991. This AGCUS or AGUS of TBS 1988 and 1991 has similar sound with ASCUS but has much different cytologic and clinical backgrounds. Hence, AGUS was replaced by AGC in TBS 2001 in order to avoid confusion with ASCUS. Furthermore, AGC favor reactive was deleted because the term "reactive" may mislead a gynecologist to an undermanagement while AGC, favor neoplastic which definitely requires further investigation is separated from simple AGC (AGC, NOS). AIS which was included in AGUS category is also detached from AGC and is set as another category due to its distinctive cytologic features and good reproducibility. Cytologic features of AIS are similar to those of adneocarcinoma e.g. increased cellularity, crowded clusters or rosettes with anisonucleosis, nuclear enlargement, nuclear hyperchromasia, overlapping nucleus, and feathering but AIS lacks features of invasion, such as, tumor diathesis[21-23].

Some unique features of AGUS or AGC should be recognized. Firstly, AGC can derive from endocervix, endometrium, or any other sites lined by glandular epithelium; hence, an awareness of a more specific suggestion on the site of origin is certainly helpful for a clinical investigation or management. Secondly, a report of AGC together with ASC or SIL is not uncommon (which could be found in approximately half of AGC)[24]. This should alert a gynecologist to conduct a thorough evaluation for all possible sites of these cytologic abnormalities. Lastly, AGC itself can have various underlying pathology of either squamous or glandular lesions. Some studies even demonstrated higher incidence of squamous than glandular lesions[19,24-26]. This higher incidence of squamous lesions was found more commonly in women aged less than 35 years and in AGC associated with a squamous abnormality (as mentioned) than simple AGC as the only diagnosis[24,27]. This high incidence of squamous cell lesions in AGC might be partly explained by a common event of squamous lesions involving glandular epithelium which can give the cytomorphology of round cell clusters with smooth peripheral contours and nuclear pseudostratifications mimicking endocervical glandular lesions[25].

Clinical significance

The main objective of cervical cytologic screening is to detect preinvasive or early invasive cancer. Thus, abnormal cytologic classification is generally based on the possibility or associated risk of significant histopatholgy which is generally defined as cervical intraepithelial neoplasia (CIN) 2-3, squamous or adenocarcinoma in situ, and invasive carcinoma. The clinician should recognize risks of significant lesions from each cytologic classification for an appropriate clinical management.

ASC

ASC was found to be the most common (nearly 40%) of all cytologic abnormalities associated with underlying high grade histopathology or cancer[6]. Data of our own institution, which found 2% prevalence of ASCUS, demonstrated that 53% of these women had underlying histopathology of SIL or cancer. These were

significant clinical lesions of > CIN 2 and cancer in approximately 10%. We also reviewed other series and found the figures ranged from 22-72% (for all SIL), being significant lesions 3-20% and cancer in 2-4%[28].

Type of ASC is the most important predictor of their underlying histopathology. Many studies demonstrated higher incidence of dysplastic lesions in ASCUS, favor SIL or ASC-H than ASCUS, favor reactive or ASC-US: 13-40% vs 3-11%[12, 28-29]. One study by Kietpeerakul et al reported significantly higher incidence of high-grade lesions (CIN 2-3, AIS, and invasive cancer) in women with ASC-H than those with ASC-US: 69% vs 23%[30]. The authors in that study also reviewed other reports and found CIN 2-3 and cancer in 10-74% and 2-8% of ASC-H, respectively. Some features which are generally found in ASC-H are strongly associated with underlying histopathologic lesions > CIN 2 when they are prominent; these features are e.g. focal nuclear notching, grooving, or irregularity[12].

AGC

Having been mentioned that AGUS or AGC have different clinical backgrounds from ASCUS or ASC because it carries higher and various risks of significant glandular or squamous pathology[24]. From data of our own institution and other reports, histopathology was identified in approximately 9-58% of AGUS[14,15,20,26,27,31]. These were clinical significant lesions, including > CIN 2, AIS, and atypical endometrial hyperplasia in approximately 8-53% and cancer in 4-24%[14,15,20,26,27,31].

Risk of significant lesions may be inaccurate without adequate duration of follow-up or appropriate care according to a management guideline. One study reported 4% risk of gynecological cancers from over 8,000 women who had AGC from screening cytology after a long follow-up period of 6 years[26]. The relative risks for gynecologic cancers were as high as 2-18 folds compared to normal population[26]. Another study found that women with AGC were undermanaged in both initial and secondary evaluations especially in women aged > 35 years[27].

The most important predictor of significant pathology of AGC is its qualifier; underlying pathology was identified in 29-74% of AGUS or AGC, favor neoplasia compared to 10-33% in those with AGUS, favor reactive or AGC, NOS[20,24,27,29]. Regarding the primary sites of cancers in women with AGC, many studies reported different results. Some found endometrial cancers as the most common gynecologic malignancy in 50-58%[17,20,29] while others demonstrated cervical cancer as more common in 55-84% especially in women aged < 40 years, in AGC, NOS or AGC suggesting endocervical in origin[25,26].

Management

One should always bear in mind that a reduction in cervical cancer incidence and mortality is not simply achieved by cancer screening. An appropriate management and follow-up of abnormal cervical cytology is also crucial. One study reported among 9,000 women with abnormal cytology that nearly 20% of women were lost to follow-up care and nearly 40% received suboptimal care[32]. Factors associated with this problem were from both parties of the women themselves and the health care system: lower degrees of cytologic abnormality, fear, lack of understanding or social support, smaller health care facilities, inconvenient clinic hours, male health providers, and insensitive staff[32,33]. A clinician should be aware of these problems to obtain an optimal ultimate outcome of cervical cancer reduction.

From the TBS 1991 workshop, the group called for the guidelines regarding management of atypical squamous cells of undetermined significance and low-grade lesions. One leading medical organization "The American Society for Colposcopy and Cervical Pathology (ASCCP)", in collaboration with other medical panel organizations, has developed care maps of cervical cytology abnormalities management based on quality of evidence and strength of recommendation to derive special terms of recommendations as the followings: a) recommended b) preferred c) acceptable and d) unacceptable[34]. The most updated recommendation is released in 2007[35]. A clinician should be familiar with these terms of recommendations, so a standard clinical management for women can be offered. Although the most important issue to be considered for management is how the equivocal

diagnosis is qualified, specific or individualized management may vary depending on economic background and availability of the human instrumental resources assuming that the yield of early detection for significant lesions or cancer is achieved. The followings are summaries of the ASCCP's guidelines for management of ASC and AGC.

ASC

Based on dissimilar risks of having significant histologies, the ASCCP has outlined management of ASC-US and ASC-H differently.

ASC-US

Either HPV-DNA testing for high-risk oncogenic HPV, repeat cervical cytologic testing, or colposcopy are acceptable for women aged > 20 years.

1. Reflex HPV-DNA testing is the preferred option if liquid-based cytology (LBC) has been undertaken. This "reflex HPV-DNA testing" can be achieved by submitting the liquid-based specimen for cytology, and subsequently proceeding with the HPV-DNA test if the cytologic result is ASC-US.
2. Repeat cervical cytologic testing is recommended at 6 month and 12 month. With 2 consecutive negative results, routine screening is allowed. With any follow-up cytologic lesions ≥ ASC-US, colposcopy is recommended.
3. With negative findings of CIN from colposcopy, repeat cytology at one year is recommended.

Few important issues must be noted for women with ASC-US:

1. Diagnostic excisional procedures including loop electrosurgical excision procedure (LEEP) are unacceptable without a tissue biopsy diagnosis of CIN 2-3.
2. Adolescents aged ≤ 20 years are recommended to have annual cytologic follow-up instead of a 6-month cytology test. HPV DNA testing and colposcopy are unacceptable for these adolescents. The results of HPV testing in this young age group should not influence their management. Colposcopy should be performed later if the follow-up cytology is ≥ HSIL at 12 month or is ≥ ASC-US at 24 month.
3. Immunosuppressed, postmenopausal, or pregnant women > 20 years with ASC-US should be managed as normal women. Two exceptions in pregnant women are: a) deferring colposcopy until at least 6 weeks postpartum is acceptable and b) endocervical curettage is unacceptable during pregnancy.

ASC-H

Colposcopy is recommended for women with ASC-H. Without lesions of CIN 2-3, follow-up with HPV DNA testing at 12 months or cytological testing at 6 month 12 month is acceptable. Further management depends on the results of these subsequent tests:

1. Colposcopy is recommended for those who are positive for HPV-DNA or are found to have ≥ ASC-US from a follow-up.
2. Routine cytologic screening is recommended for those with negative HPV test or with 2 consecutive negative cytologic tests from a follow-up.

AGC

Due to different risk of underlying significant lesions, the ASCCP has different guidelines of management for AGC from those of ASC. The followings tests are recommended as initial investigation for women with AGC.

1. Colposcopy with endocervical sampling is *recommended* for women with AGC of all subcategories, with additional endometrial sampling in women aged ≥ 35 years or in women aged < 35 years but are at risk for neoplastic endometrial lesions.
2. Endometrial and endocervical sampling are *recommended* for women with atypical endometrial cells. Colposcopy can be performed as an initial evaluation altogether or be deferred until no pathology is identified from endometrial and endocervical sampling.

3. HPV DNA test at the time of colposcopy is *preferred* in women with atypical endocervical, endometrial, or glandular cells not otherwise specified (NOS).
4. HPV DNA testing alone or repeated cervical cytology is *unacceptable* for the initial management of all subcategories of AGC.
5. The initial evaluation of AGC for pregnant women is the same as non-pregnant women (colposcopy with or without HPV test) except that endocervical curettage and endometrial biopsy are *unacceptable*.

Unlike ASC, an emphasis must be made on subsequent evaluation or follow-up for women with AGC who do not have underlying histopathology of CIN or glandular neoplasia at an initial investigation. Having been mentioned earlier that one study reported increased risk of gynecologic cancers in these women with AGC after a long term follow-up[26], surveillance is warranted even without any revealed pathology in that immediate setting. Regarding the management after negative primary investigations, it depends on the qualifier of AGC: AGC, NOS vs AGC, favor neoplasia and are detailed as the followings.

AGC, NOS

Management may be stratified according to the results of HPV-DNA test.

1. If the HPV DNA test is positive, a repeat cytology and HPV DNA testing at 6 months is *recommended*.
2. If the HPV DNA test is negative, a repeat cytology and HPV DNA testing at 12 months is *recommended*.
3. If HPV test is not done, repeat cytologic testing at 6-month intervals is *recommended*.

Colposcopy is *recommended* for any women who have positive high risk HPV or those who have ≥ ASC-US from subsequent tests. For those with 4 consecutive negative results, routine cytologic screening is allowed.

AGC, favor neoplasia

A diagnostic excisional procedure is recommended for women with atypical endocervical or glandular cells, favor neoplasia if invasive disease is not identified during the initial colposcopic workup. The type of diagnostic excisional procedure used in this setting should provide an intact specimen with interpretable margins. Concomitant endocervical sampling done in the same setting is *preferred*.

Conclusion

Although ASC and AGC are considered as the mildest forms of cervical cytologic abnormalities, their clinical significance must be recognized. ASC and AGC have different cytologic backgrounds as well as underlying histopathology and clinical outcomes; hence, their management options are dissimilar. A gynecologist should clearly understand the message from the cytopathologist particularly the specific subgroups or qualifiers of each, so an optimal care for women with these abnormal cervical cytology can be provided appropriately. National policy makers should understand and address the problems why women with abnormal cervical cytology cannot adhere to the follow-up program aside from the shortage of primary cervical cancer screening. These issues will certainly lead to an ultimate result of cervical cancer reduction in the country.

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ความสำคัญของ Atypical Squamous Cells และ Atypical Glandular Cells: ความเหมือนและความแตกต่าง

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แม้ระบบ Bethesda จะแบ่ง ASC (atypical squamous cells) และ AGC (atypical glandular cells) เป็นเซลล์ผิดปกติที่อยู่ในระดับเดียวกัน คือ ได้รับการจัดเป็นเซลล์ที่มีความผิดปกติมากกว่า reactive แต่น้อยกว่า squamous intraepithelial lesions หรือ adenocarcinoma in situ แต่ ASC และ AGC มีความแตกต่างกันอย่างมากทั้งในแง่ลักษณะทางเซลล์วิทยา ความสัมพันธ์กับผลทางพยาธิวิทยาที่มีความสำคัญทางคลินิกตลอดจนแนวทางการตรวจวินิจฉัยเพิ่มเติมและการตรวจติดตาม นอกจากนั้นชนิดของ ASC ที่แบ่งกลุ่มย่อยออกเป็น ASC, of Undetermined Significance (ASC-US) และ ASC, cannot exclude HSIL (ASC-H) และชนิดของ AGC ที่แบ่งเป็น AGC, not otherwise specified (AGC, NOS) และ AGC favor neoplastic (AGC, FN) ก็มีความสำคัญทั้งทางพยาธิวิทยาและทางคลินิกแตกต่างกัน แพทย์ผู้ทำการรักษาควรระลึกถึงความแตกต่างของกลุ่มเซลล์ทั้ง 2 ชนิดนี้รวมทั้งกลุ่มย่อยชนิดต่างๆ เพื่อจะได้ให้การดูแลสตรีที่มีผลเซลล์ผิดปกติเหล่านี้ได้อย่างเหมาะสมต่อไป
