Problem of atypical Squamous Cells of Undetermined Significance Diagnosis

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Abstract

Objective: To assess the histologic correlates of atypical squamous cells of undetermined significance (ASCUS) Pap smear and analyze its impact on the accuracy of Pap smear.

Study design: A total of 7,546 women were screened for early detection of cervical cancer. The women with ASCUS diagnosis were further qualified as ASCUS favor reactive, ASCUS favor LSIL (low grade squamous intraepithelial lesion) and ASC-H (cannot exclude HSIL) according to the Bethesda 1991 system and the Bethesda 2001 system of reporting. ASCUS favor reactive were followed up by a repeat smear examination and persistent ASCUS cases were taken up for colposcopy and biopsy if indicated. All ASCUS favor LSIL and ASC-H cases were taken up for immediate colposcopy.

Results: On cytohistologic correlation of diagnosed ASCUS cases, the total 80 ASCUS favor reactive cases, 37 showed chronic cervicitis with or without squamous metaplasia, the accuracy 50.41%. The total 24 ASCUS favor LSIL, 8 showed HPV (human papilloma virus) infection/ CIN 1 (cervical intraepithelial neoplasia)/ CIN1+HPV infection, the accuracy 77.24%. The total 19 ASC-H, 5 showed CIN2 / CIN3 / CIN2, CIN3 + HPV infection, the accuracy 85.36%.

Conclusion: Our data showed a good accuracy in ASC-H group. ASCUS is a problem to define, diagnose, reproduce and manage. The diagnosis of ASCUS is wide, ranging from a totally chronic cervicitis, HPV infection and CIN. Careful attention to subtle cytomorphologic characteristics may be helpful for a more definitive subdivision of ASCUS terminology into ASC-US and ASC-H.

Key words: ASCUS, ASC-H, Pap smear, accuracy

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Introduction

The term “atypical squamous cells of undetermined significance (ASCUS)” was first introduced with the Bethesda System (TBS) 1988, and was maintained in TBS 1991. ASCUS originally in TBS 1988 was defined as “cellular abnormalities that are more marked than those attributable to reactive changes but that quantitatively or qualitatively fall short of a definite diagnosis of squamous intraepithelial lesion (SIL)”\(^1\). TBS 1991 revision defined ASCUS category to ASCUS favor reactive, ASCUS favor SIL and ASCUS not otherwise specified\(^2\). In TBS 2001, ASCUS was replaced with atypical squamous cells (ASC) which divided into 2 subcategories, 1) undetermined significance (ASC-US), which defined change suggestive of low-grade SIL (LSIL) 2) cannot exclude high-grade SIL (ASC-H)\(^3\), which considered suspicious for high-grade SIL (HSIL). ASCUS terminology is a problem to distinguish between cytologic atypia due to benign reactive or inflammatory processes and atypia associated with preneoplastic lesions. The frequency of ASCUS varied from 3.48-4.77\(^{\%}\)^4. Variation in the number of ASCUS cases reflects the difficulty in differentiating benign cellular change, ASCUS favor reactive, ASCUS favor LSIL and ASC-H. The purpose of this study was to evaluate the histologic correlates of ASCUS group and analyze its accuracy of each subcategories diagnosis.

Materials and Methods

During a period of 1 year (August 2007-July 2008), a total of 7,546 ThinPrep and conventional Pap smears in Thammasat University Hospital were screened for early detection of cervical cancer. A total of 286 Pap smears (3.8\%) were diagnosed as ASCUS favor reactive, ASCUS favor LSIL and ASC-H by TBS 1991 and TBS 2001. A total of 123 cases had definitive histologic diagnosis. ASCUS favor reactive was followed-up by a repeat smear examination and persistent ASCUS cases were taken up for colposcopy and biopsy. All ASCUS favor LSIL and ASC-H cases were taken up for immediate colposcopy and biopsy.

Results

The cytologic findings of ASCUS favor reactive (Fig. 1 A, B) showed grouping of atypical metaplastic cells with slightly enlarged nuclei, smooth nuclear outlines and prominent

![Fig. 1](image)

**Fig. 1** ASCUS favor reactive. (A) Atypical metaplastic cells with enlarged nuclei and prominent nucleoli. (B) Atypical intermediate cells with enlarged nuclei and smooth nuclear outline. (A, Conventional smear B, ThinPrep; Papanicolaou stain x600)
nucleoli which was highly predictive of reactive cell change. The pattern frequently demonstrated an inflammatory background. The nuclear chromatin was fine, little or no nuclear hyperchromasia and minimal or no nuclear membrane irregularities. The ASCUS favor LSIL showed atypical cells that were difficult to morphologically distinguish from LSIL, those cellular abnormalities more marked than the reactive, inflammatory changes but that were inadequate the diagnostic criteria for SIL (Fig. 2). The ASCUS favor LSIL with questionable HPV infection showed squamous cells with borderline changes and it cannot give definitive HPV change in LSIL (Fig. 3). The ASC-H cases showed immature metaplastic cells with high nuclear/cytoplasmic (N/C) ratio, increased nuclear hyperchromasia, nuclear membrane irregularities and these cytologic features difficult to distinguish from HSIL (Fig. 4 A, B)

Fig. 2 ASCUS favor LSIL. Marked atypical intermediate cells with minimal irregular nuclear outline and inadequate criteria for LSIL. (Conventional smear; Papanicolaou stain x600)

Fig. 3 ASCUS favor LSIL with questionable HPV infection. Koilocytelike change of two atypical intermediate cells with perinuclear cavity. (Conventional smear; Papanicolaou stain x600)

Fig. 4 ASC-H. (A) Single atypical metaplastic cell with irregular nuclear membrane. (B) Small group of immature squamous metaplastic cells with irregular nuclear membrane and high N/C ratio (A, B, ThinPrep; Papanicolaou stain x600)
Table 1 summarizes the cytohistologic correlation results in 123 women. The total 80 ASCUS favor reactive cases; 37, 41, 2 showed chronic cervicitis with or without squamous metaplasia, HPV infection/CIN 1/CIN 1 + HPV infection, CIN 2/CIN 2 with HPV infection, respectively, the accuracy was 50.4%. The total 19 ASCUS favor LSIL; 4, 2 showed HPV infection/CIN 1, CIN 3/CIN 3 with HPV infection, respectively. The total 5 ASCUS favor LSIL with questionable HPV infection; 4 showed HPV infection/CIN 1 with HPV infection. The accuracy of ASCUS favor LSIL and ASCUS favor LSIL with questionable HPV infection were 77.24%. The total 19 ASC-H; 2, 3 showed CIN 2 with HPV infections, CIN 3/CIN3 with HPV infection respectively, the accuracy was 85.36%.

### Discussion

We conclude our cytologic finding of each subcategories ASCUS diagnosis. ASCUS favor reactive involves nuclear enlargement 2-3 times in squamous cells, finely granular chromatin with or without prominent nucleoli. The nuclear envelope is smooth and regular. There may be variation in nuclear size. The ASCUS favor LSIL may reflect insufficient smear sampling of LSIL, presence of a few atypical cells of CIN1 or a few koilocytelike changes in ASCUS favor LSIL with questionable HPV infection. Cytologic features within the ASC-H category include disorganized groups of hyperchromatic cells, atypical immature and mature squamous metaplasia, and small atypical cells with high N/C ratio.

Alli et al. reported the significant cytomorphologic criteria in ASC-H with a CIN follow-up (compared with reactive cell change follow up) were fewer atypical cells, a high N/C ratio, more nuclear chromasia, more coarse, more nuclear membrane irregularities, lack of nucleoli and lack of an inflammatory background. Mokhtar et al. concluded that ASC-H is an important group in TBS 2001 and the cytopathologic features most strongly associated with HSIL was the presence of coarse nuclear chromatin. These cytomorphologic findings are similar to our criteria to diagnose ASCUS favor reactive, ASCUS favor LSIL or ASC-H subcategories. Various studies including this study suggest that the significant criteria to interpret subcategory ASCUS due to nuclear details, such as chromatin pattern (fine or
coarse), prominent nucleoli (presence or absence), nuclear membrane (smooth or irregularity) and nuclear crowding.

Our data from Table 1, the histological diagnosis in ASCUS favor reactive showed many cases of HPV infection with or without CIN, a few cases of CIN 2 with or without HPV infection, its accuracy was only 50%. The ASC-H group had a good accuracy (85.36%). The variation in cytohistologic correlation reported by this study and various studied\textsuperscript{5-7,9} may be due to many factors; such as the patient population, the diagnostic criteria utilized, the experience and the skill of the cytotechnologists and cytopathologists. Each Pap smear was carefully examined and gives definitive diagnosis. The few cases that are difficulty in interpretation to reactive cell change or SIL should be diagnosed as ASC-US or ASC-H.

**Conclusion**

Our data showed a good accuracy in ASC-H group. ASCUS is a problem to define, diagnose and manage. The diagnosis of ASCUS is wide, ranging from a totally chronic cervicitis, HPV infection and CIN. Careful attention to interpret cytomorphologic characteristics may be helpful for a more definitive subdivision of ASCUS terminology into ASC-US and ASC-H.

**References**

บทคัดย่อ

ปัญหาการวิจัย: เซลล์แทรกซ้อนโรคปกติที่ไม่ระบุอย่างชัด

วัตถุประสงค์: เพื่อทบทวนผลการวิจัยของเซลล์แทรกซ้อนจากเปปไตรไทช์ของกลุ่ม ASCUS กับเซลล์เนื้อเยื่อต่าง ๆ ที่มีความ

วิธีการ: กลุ่มตัวอย่างติดตามทั้งหมด 4,326 กรณี ตรวจพบเปปไตรไทช์ เพื่อตรวจหาความเป็นปกติ งานวิจัยด้วย

ผลการวิจัย: ผลขั้นตอนกลุ่ม ASCUS, favor reactive จำนวน 43 ราย พบว่า 37 ราย มีการเปลี่ยนแปลงรูปต่างกับภาวะ squamous metaplasia ที่มีความแน่นอนจากการวิจัยด้วยเปปไตรไทช์ ร้อยละ 86.31 กลุ่ม ASCUS, favor LSIL จำนวน 25 ราย พบว่า 9 รายมีผลขั้นตอนเป็นการติดเชื้อ HPV อย่างถาวรหรือ CIN ๓ อย่างน้อย หรืออย่างมากกั้น มีความแน่นอน ร้อยละ 85.68 จำนวน 14 ราย ของกลุ่ม ASC-H พบว่า 9 ราย มีผลขั้นตอนเป็น CIN ๒ หรือ CIN ๒ และ ๓ ร่วมกันการติดเชื้อ HPV ที่มีความแน่นอน ร้อยละ 85.68

สรุป: ในการศึกษาพบว่ากลุ่ม ASC-H มีความแน่นอนมากกว่า กลุ่ม ASCUS มีความแน่นอนน้อยกว่า เป็นกลุ่มที่มี

คำเฉพาะ: ASCUS, ASC-H, เปปไตรไทช์, ความแน่นอน