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■ ORIGINAL ARTICLE ■

Outcome of "Atypical Squamous Cells" in Cervical Cytology: Follow-up Assessment by Loop Electrical Excision Procedure

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Background: We have retrospectively assessed the incidence and outcome of women diagnosed during a hospital-based cytology screening program with "atypical squamous cells (ASC)" and followed-up with loop electrical excision procedure (LEEP). **Methods:** We analyzed 173,947 cases of cervical smears' follow-up cytology and histology findings. Previous or archival cytology with LEEP results were retrieved for 390 women with ASC of undetermined significance (ASC-US) and 112 with ASC, cannot exclude high-grade squamous intraepithelial lesion (ASC-H). **Results:** On the follow-up cytology, of the 390 women initially diagnosed with ASC-US, 130 (33.3%) had no follow-up records of smears before LEEP; smears of 18 (4.6%) were negative for cytologic abnormalities, 193 (49.5%) were ASC-US, 24 (6.2%) were ASC-H, 111 (28.5%) were low grade squamous intraepithelial lesion (SIL), and 44 (11.4%) were high grade SIL. LEEP findings in these 390 women showed that 183 (46.9%) were negative, 73 (18.7%) were graded as cervical intraepithelial neoplasia (CIN) 1, 25 (6.4%) as CIN 2, 102 (26.2%) as CIN 3, and 7 (1.8%) had carcinoma. LEEP was performed in 112 women initially diagnosed with ASC-H; 36 (32.1%) were negative, 4 (3.6%) were graded as CIN 1, 7 (6.3%) as CIN 2, 60 (53.6%) as CIN 3, and 5 (4.5%) with carcinoma. **Conclusions:** Patients with ASC-H smears were at increased risk of SIL or carcnoma compared with patients with ASC-US. Careful follow-up is required in ASC patients.

Key Words: Cervix uteri; Cytology; Loop electrical excision procedure; Atypical squamous cell

The significance of atypical squamous cells of undetermined significance (ASC-US) diagnosis on cervical cytologic smears and the clinical management of patients with ASC-US are unclear. There has been a strong consensus to replace ASC-US with a new category, "atypical squamous cells (ASC)", defined as "cytologic changes that are suggestive of squamous intraepithelial lesion (SIL) and are quantitatively insufficient for a definitive interpretation."[1] The ASC can be further subdivided into "those of undetermined significance (ASC-US)" and "those where a high-grade squamous intraepithelial lesion (HSIL) cannot be excluded (ASC-H)." The ASC-US category includes cytologic changes that are suggestive of SIL but lack criteria for a definitive interpretation, whereas the ASC-H one does those that are suggestive of HSIL but also lack criteria for a definitive interpretation.

As might be expected, based on the concept that the ASC-US is an equivocal category, the ASC is not an interpretation that can particularly be reproduced from either an inter- or intra-observer viewpoint. This has been well verified in a number of studies. In the National Cancer Institute (NCI), atypical squamous cells of undetermined significance–low-grade squamous intraepithelial lesion (ASCUS-LSIL) Triage Study (ALTS), estimates of reproducibility within a well-controlled "expert" environment show similar kappa rates (kappa value = 0.46) for correlations between the observers on both cytology and histopatholgic specimen.[2] In an earlier study of Sherman *et al*.,[3] a group of five experts showed a similar variability with a lack of the unanimity in an entire study set of putative ASC-US cases. Variability in diagnosis agreement remains concerning the diagnosis of ASC-US.[4] In addition, treatment of patients with this diagnosis is still a major point of controversy.[5] Several authors have addressed this issue by analyzing the cytohistological correlation with this cytological diagnosis.[6-8] To date, however, information retrieval from biopsy results as well as the variability of therapeutic methods has constantly been a limiting factor. It has been proven that a cervical biopsy is poor in predicting

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the actual status of underlying cervical intraepithelial lesion.

Given the above background, we conducted this study by taking advantage of selected cases treated by loop electrical excision procedure (LEEP) in the absence of previous biopsy to evaluate the incidence and outcome of ASC by a retrospective histopathological analysis of LEEP samples of women in a hospital-based cytology screening program and to correlate the histological findings with the last cytological categories proposed for ASC diagnosis.

MATERIALS AND METHODS

From January 2004 to December 2007, 173,947 conventional or liquid-based cervical smears were performed at the Obstetrics and Gynecology clinic and then sent for analysis to the cervical cytology laboratory of the Asan Medical Center. We've used the liquid-based cytology (LBC) with an automated system (AutoPap, TriPath Imaging, Inc., Burlington, NC, USA) since January 2006 and a conventional cytology technique during a period ranging from January 2004 to December 2005. These smears were immediately wet-fixed, stained using the standard Papanicolau technique (Pap), screened by cytotechnicians and then assessed by cytopathologists. In cases of LBC with an automated screening system, the case followed the protocol of AutoPap primary screening system (TriPath Imaging, Inc.).[9] Atypical cases were reviewed by cytotechnologist and then referred to cytopathologist. The final cytologic abnormalities reported by pathologists included ASC-US, atypical glandular cells of undetermined significance, LSILs, HSILs and malignant disease.

According to Bethesda system,[1] ASC-US in conventional cytology are criteria as shown below:

1) Nuclei are approximately two and one half to three times the area of the nucleus of a normal intermediate squamous cell.

2) Slightly increased ratio of the nuclear to cytoplasmic area.

3) Minimal nuclear hyperchromasia and irregularity in chromatin distribution or nuclear shape.

4) Nuclear abnormalities associated with dense orangeophilic cytoplasm.

The appearance of ASC-US is similar between the smears and liquid-based cytology. That is, cells may appear larger rather than more flat on smears.

ASC-H cells are usually sparse. Small cells have high nuclear/cytoplasmic ratios accompanied by a crowded sheet pattern. In a LBC, ASC-H cells may appear quite small, with nuclei whose size is only two to three times greater than that of the neutrophil nuclei.

The cytology and histology laboratory databases of the Asan Medical Center were searched for follow-up data in patients who had been initially diagnosed with ASC-US or ASC-H. But the cytology and histology slides were not reviewed. Patients were excluded if they had been diagnosed with higher-grade cervical smears (such as LSIL and HSIL) prior to diagnosis of ASC-US or ASC-H on Pap smears, if LEEP or biopsy had been performed before diagnosis of ASC-US/ASC-H or if LEEP had not been performed.

Chi-square and Fisher's tests were used with a 95% confidence interval.

RESULTS

Pap smears obtained from 173,947 women were examined in our laboratory (Table 1). Of these, 7,125 (4.1%) women and 383 (0.2%) were diagnosed with ASC-US and ASC-H, respectively. During the same time frame (January 2004 to December 2007), the ratio of SIL to carcinoma was 17.7 : 1 and that of ASC to SIL was 2.01 : 1.

In addition, 2,810 patients underwent LEEP during the same period, 648 (23.1%) and 216 (7.7%) of whom were diagnosed with ASC-US and ASC-H, respectively. A follow-up cytology with LEEP results was retrieved in 390 women with ASC-US and 112 with ASC-H.

The mean age of patients was 43.51 years (range, 22 to 73 years) in the ASC-US group and 46.94 years (range, 26 to 76 years) in the ASC-H group. Median follow-up period following the diagnosis of ASC was 24.1 months (range, 0 to 68.5 months) in the ASC-US group and 2.76 months (range, 0 to 13.1 months) in the ASC-H group. The mean length of period elapsed from ASC to LEEP was 8.07 months in the ASC-US

Table 1. Cytological diagnoses in adequate cervical smears (n = 173,947)

Cytologic diagnosis	No. of cases (%)
Negative for SIL/Malignancy	162,330 (93.32)
ASC-US	7,125 (4.09)
ASC-H	383 (0.21)
AGC	162 (0.09)
LSIL	2,949 (1.68)
HSIL	787 (0.49)
Carcinoma	211 (0.12)

SIL, squamous intraepithelial lesion; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; AGC, atypical glandular cells; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion.

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group and 1.98 months in the ASC-H group. The mean number of subsequent cervical smears was 1.69 (range, 0 to 14) in the ASC-US group and 0.3 (range, 0 to 4) in the ASC-H group.

On the second smear examination, of the 390 women who had been initially diagnosed with ASC-US, 130 (33.3%) had no follow-up records of Pap smears. In addition, the other remaining patients had the following results: 68 (17.4%) were negative, 94 (23.8%) were again diagnosed with ASC-US, 14 (3.6%) were diagnosed with ASC-H, 64 (16.4%) were diagnosed with LSIL, 20 (5.7%) were diagnosed with HSIL and none were diagnosed with squamous cell carcinoma. At the last cytology prior to LEEP, of the 260 patients, 18 (6.9%) were negative for epithelial abnormalities, 63 (24.2%) were diagnosed with ASC-US, 24 (9.2%) were diagnosed with ASC-H, 111 (42.7%) were diagnosed with LSIL and 44 (16.9%) were diagnosed with HSIL, but none were diagnosed with squamous cell carcinoma.

Based on the LEEP findings, of the 390 women who had been initially diagnosed with ASC-US, 183 (46.9%) were negative, 73 (18.7%) were graded as cervical intraepithelial neoplasia (CIN) 1, 25 were graded (6.4%) as CIN 2, 102 (26.2%) were graded as CIN 3, and seven (1.8 %) had carcinoma (Table 2).

Of the 112 women who were diagnosed with ASC-H on cervical Pap smears, 91 (81.3%) underwent LEEP without a follow-up cytology. On the follow-up cytology of the 112 women who had been initially diagnosed with ASC-H, smears of four (3.6%) were negative for cytologic abnormalities, two (1.8%) were positive for ASC-US, 97 (86.6%) were positive for ASC-H, three (2.6%) were positive for LSIL, and six (5.4%) were positive for HSIL.

Of the 112 women who were diagnosed with ASC-H and underwent LEEP, 36 (32.1%) were negative, four (3.6%) were graded as CIN 1, seven (6.2%) were graded as CIN 2, 60 (53.6%) were graded as CIN 3, and five (4.5%) were diagnosed with carcinoma (Table 3).

DISCUSSION

Quality assurance monitoring of ASC reporting has been stressed. In screening general populations, ASC should not exceed 5% of the total specimens and the ratio of ASC to SIL should not exceed 2 : 1 to 3 : 1. Furthermore, ASC-H should not account for >10% of the total ASC.[10] In evaluating outcomes in women who were diagnosed with ASC-US/ASC-H on cervical smears in a single institution in Korea, these criteria were met.

Many studies have been conducted to show the rate of CIN in a follow-up interpretation of ASC.[11] According to these studies, there was a great variability in the rate of CIN at a follow-up and it ranged from as low as 10% to as high as 80%. Most of the studies have shown that it ranges between 30% and 60%. As might be expected, with the prepondenderance of ASC-US in the population, most cases of CIN are in the CIN 1 category, generally ranging between 60% and 95%. Based on our understanding of the biology of cervical carcinogenesis, however, more than CIN 2 is an important point for the detection of the disease. Studies have shown that more than CIN 2 accounts for 0-40% of total cases of CIN detected at a follow-up. In the ALTS, the proportion of cases of more than CIN 2

Table 2. Follow-up LEEP findings for ASC-US

Cytologic diagnosis[a]	LEEP conization					Total
	NTP	CIN 1	CIN 2	CIN 3	Carcinoma	
NILM	13 (72.2)	1 (5.5)	0 (0.0)	4 (22.2)	0 (0.0)	18 (4.6)
ASC-US	106 (54.9)	23 (11.9)	10 (51.8)	49 (25.4)	5 (2.6)	193 (49.5)
ASC-H	11 (45.8)	3 (12.5)	0 (0.0)	10 (41.7)	0 (0.0)	24 (6.2)
LSIL	49 (44.1)	43 (38.7)	7 (6.3)	12 (10.8)	0 (0.0)	111 (28.5)
HSIL	4 (9.1)	3 (6.8)	8 (18.2)	27 (61.4)	2 (4.5)	44 (11.3)
Total	183 (46.9)	73 (18.7)	25 (6.4)	102 (26.2)	7 (1.8)	390 (100)

Values are presented as number (%).
LEEP, loop electrical excision procedure; ASC-US, atypical squamous cells of undetermined significance; NTP, no tumor present which means negative for cervical intraepithelial or malignancy; CIN, cervical intraepithelial neoplasia; NILM, negative for intraepithelial lesion or malignancy; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion.
[a]The cytologic diagnosis represents the last Pap results before LEEP conization.

Table 3. Follow-up LEEP findings for ASC-H

Cytologic diagnosis[a]	LEEP conization					Total
	NTP	CIN 1	CIN 2	CIN 3	Carcinoma	
NILM	2 (50.0)	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	4 (3.6)
ASC-US	0 (0.0)	0 (0.0)	0 (0.0)	2 (100)	0 (0.0)	2 (1.8)
ASC-H	33 (34.0)	3 (3.1)	7 (7.2)	49 (50.5)	5 (5.2)	97 (86.6)
LSIL	1 (33.3)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	3 (2.6)
HSIL	0 (0.0)	0 (0.0)	0 (0.0)	6 (100)	0 (0.0)	6 (5.4)
Total	36 (32.1)	4 (3.6)	7 (6.3)	60 (53.6)	5 (4.5)	112

Values are presented as number (%).
LEEP, loop electrical excision procedure; ASC-H, atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion; NTP, no tumor present which means negative for cervical intraepithelial or malignancy; CIN, cervical intraepithelial neoplasia; NILM, negative for intraepithelial lesion or malignancy; ASC-US, atypical squamous cells of undetermined significance; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion.
[a]The cytologic diagnosis represents the last Pap results before LEEP conization.

was 15.4%, which stands presently as our best benchmark.[12] In our clinical series of patient, on histopatholgic examinations of the subsequent tissue specimens, there was either a low- or a high-grade dysplasia in 53.7% and 67.8% of women who had been diagnosed with ASC-US and ASC-H, respectively, on Pap smears. At a follow-up, of women who had been diagnosed with ASC-US, 11.3% had a progression to HSIL and 26.2% did a histologically confirmed high-grade dysplasia. In addition, of women who had been diagnosed with ASC-H, 5.4 % had a progression to HSIL and 53.6% did a histologically confirmed high-grade dysplasia.

As compared with our results, previous studies have shown that 2,765 patients had an SIL rate of 28% and an HSIL rate of 11.3% at a follow-up with both cytologic and histologic examinations.[13] According to a study that was conducted by Kim *et al*.[14] in Korean patients, a histopathologic examination proved that 14.6% (13/89) of patients with ASC-US had an HSIL.

There are some gaps in the cytologic diagnoses between initially and at a follow-up. As we have previously mentioned, the first reason is that the diagnosis of "ASC" contains a lower reproducibility and a higher variability.[2] The second reason is that there is a possibility that the disease might truly progress or regress. In addition, the other reason might be due to sampling error.

Of note, higher SIL rates have been reported after short follow-up periods, which may be due to the regression of low-grade lesions.[15,16] It has been shown that low-grade cervical intraepithelial lesions are more likely to regress than to progress to HSIL or invasive carcinoma.[17] Rates of regression to normal are 68% for ASC-US, 47% for LSIL, and 35% for HSIL.[18] Presumably, many patients with ASC-US might have SIL if biopsies are performed several weeks after ASC-US cytology. These lesions may have regressed between the time point of the diagnosis of ASC-US and that of a follow-up 6-12 months later.

By contrast, of women who had initially been diagnosed with ASC-H on Pap smears, 67.8% had either a low- or a high-grade dysplasia in subsequent tissue specimens. Of the patients with ASC-H, 28.6% and 53.6% had a progression to HSIL and a histologically confirmed high-grade dysplasia, respectively. These findings are in agreement with previous reports.[18-20] Duncan and Jacob[19] showed that 46% of women with a smear diagnosis of ASC-H were found to have a high-grade dysplasia in tissue specimens. Consistently with previous reports,[21,22] our results showed that there was a positive value of 57.7% in predicting a histologically proven high-grade dysplasia in patients with ASC-H patients. This implies that ASC-H is an important diagnosis and it warrants an immediate further evaluation by colposcopy and/or biopsy.

In the management of ASC lesions, there is a broad consensus that women should be referred for immediate colposcopic evaluation, once they are diagnosed with ASC-H, because many of them are more likely to harbor high-grade lesions.[20,23,24] It is also recommended, however, that they undergo a repeated cervical cytology at a certain length of intervals, receive an immediate colposcopy, take DNA analysis for the detection of high-risk types of human papillomavirus (HPV) or undergo a single repeat cervical cytology combined with another adjunctive method.[24] In the current study, where 130 patients with ASC-US were enrolled but not followed up for cytology, we analyzed the reasons for a lack of a follow-up cytology or a punch biopsy although they directly underwent LEEP. Of them, 78 (60%) patients were referred to us for further evaluation and treatment. This is because they had been diagnosed with more than ASC-US at local clinic. In addition, 18 (13.8%) patients with ASC-US had a high-risk HPV and 34 (26.1%) did neither a history of ASC-US nor a high-risk HPV. In 34 patients, where a diagnosis of ASC was made, particularly including those where a diagnosis of ASC-US was initially made on the Pap cytology, the LEEP was not a first choice of treatment. We have therefore cautiously speculated that it is an acceptable practice in Korean patients from the viewpoints of not only the relationship between physicians and patients but also a fear for the malignant potential. There is a great tendency that Korean patients face the risk and thereby choose surgical excision for the treatment.

Recent studies have shown that the HPV typing test also had a significant effect in choosing the optimal treatment modality. In the ALTS trial,[12] HPV triage is at least as sensitive as immediate colposcopy in detecting CIN 3 in women with ASC-US. In addition, a meta-analysis also showed that HPV triage is a more sensitive modality than cytology in detecting CIN 2/3.[25] In the management of patients with ASC, particularly including those with ASC-US, the HPV status is a criticial clue. But one the limitations of the current study is that there were no attempts to identify the correlation between the HPV status and cytology of ASC. We have actually tried to identify such correlation, but failed to detect the statistical significance. This is because we have enrolled a smaller number of patients for the HPV test.

The other limitation is that we did not review the slides in differentially making a pathological diagnosis of ASC from the initial cytology or the follow-up diagnosis on the cytology or

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LEEP. It was therefore impossible to rule out the discrepancy in the classification of ASC-US between the pathologists.

Then, it deserves special attention whether ASC can be eliminated. Of note, over the years, a number of studies have been conducted to test a hypothesis that what would happen if we eliminate the use of an atypical category and force the cytologist to commit to making "normal" or "SIL" interpretations? In a study by Pitman *et al*.,[26] 100 cases of ASC-US were presented for interpretation to a group of expert cytologist. The rules of the study asked them to classify each as either negative or SIL. Of note, there was a significant reduction in the sensitivity for SIL/HSIL with rates ranging from 100% to 39% for the former and 100% to 41% for the latter. Presumably, overall, the elimination of ASC might lower the validity of the Pap test in detecting SIL. This is because it has been shown that the largest proportion of HSIL cases are detected initially from the ASC pool due to its high prevalence.[27] Following the introduction of the Bethesda System 2001 with the elimination of the "favor reactive" sub-classification, repeated studies have been conducted. The results may have an improvement in overall performance, but the current situation dictates that the equivocal category must stay for the present. In the future, as new methods of cervical screening are developed, combination of morphology and biomarkers may allow the elimination of this category.

In conclusion, there is still a controversy as to the category of ASC on the aspects of variability in the agreement between the diagnosis and treatment based on it. But we have confirmed that the positive value was relatively higher in predicting cases of more than CIN 2 at a follow-up. Additional studies are needed to better determine the actual risk of ASC in association with specific clinical parameters such as age, HPV status and viral load.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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