The Korean Journal of Pathology 2010; 44: 528-35
DOI: 10.4132/KoreanJPathol.2010.44.5.528

Evaluation of Low-Grade Squamous Intraepithelial Lesions, Cannot Exclude High-Grade Squamous Intraepithelial Lesions on Cervical Smear

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Received : September 8, 2009
Accepted : August 5, 2010

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Background : We examined cervicovaginal smears that contained definite low-grade squamous intraepithelial lesion (LSIL) cells and rare atypical cells suggestive of high-grade SIL (HSIL) (ASC-H) or contained borderline dysplastic cells between LSIL and HSIL. Such lesions were classified as LSIL-H. This study aimed to investigate the cytologic and histologic characteristics of LSIL-H category and we evaluated the associated clinical risk. **Methods :** The histologic outcomes of LSIL-H were compared with those of LSIL and ASC-H. Both the cytologic and histologic findings of LSIL-H that were confirmed as cervical intraepithelial neoplasia 2 (CIN2) or greater (CIN2+) were investigated. **Results :** LSIL-H accounted for 0.09% of the Pap tests. On the follow-up histology, the most frequent outcome was CIN2, and the risk of CIN2+ was higher than that for ASC-H. In the cases of LSIL-H that was histologically confirmed as CIN2+, most of the atypical cells suggestive of HSIL were cytologically similar to those of CIN2, and the corresponding cervical tissues were characterized by small CIN2+ lesions in a large background of flat condyloma/CIN1. The LSIL-H cases not confirmed on initial colposcopically-directed biopsy required further follow-up. **Conclusions :** LSIL-H may be a valid diagnostic category with distinctive features that are different from LSIL or ASC-H. LSIL-H needs further follow-up for the proper management.

Key Words : Cervix uteri; Cytology; Vaginal Smears; Cervical intraepithelial neoplasia

The 2001 Bethesda System (TBS) for reporting on the cervical cytology of squamous intraepithelial lesions (SIL) has been simplified into two categories: low-grade (LSIL) and high-grade (HSIL).[1] The rationale for the two tiers of LSIL and HSIL is partly based on the principle that a reduced number of diagnostic categories improves the interobserver and intraobserver reproducibility. The TBS atlas has been updated and it provides detailed interpretative criteria to improve the reproducibility of cytologic reports.[2] Yet there are occasional cases that cannot be clearly categorized as LSIL or HSIL. One report on the reproducibility of the subclassifications of SIL found that the agreement rate between LSIL and HSIL ranged from 81% for conventional smears to 93% for ThinPrep cytology preparations.[3] Most of the non-consensus cases were SILs that were difficult to grade. For these SILs of an indeterminate grade, the TBS atlas recommends an interpretation of 'SIL, grade cannot be determined.'[2]

Recent studies have documented cases of SIL of an indeterminate grade that typically exhibit unequivocal cells of LSIL and a small number of atypical cells suggestive of HSIL (ASC-H) under the terminology of 'mild-to-moderate dysplasia',[4] 'LSIL, cannot exclude HSIL (LSIL-H)'[5-7] and 'LSIL with ASC-H (LSIL-H)'.[8,9] In our department, for the Papanicolaou (Pap) smears that show cells that are definitely LSIL and rare atypical cells that are suggestive of HSIL, or for the smears that show borderline cells between LSIL and HSIL, our reporting system has included the categories of 'LSIL, cannot exclude HSIL' and 'SIL, consistent with (c/w) cervical intraepithelial neoplasia 1 to 2 (CIN1-2)', but there are no detailed cytologic criteria to differentiate between the two categories. For this study, we pooled these categories as 'LSIL-H'. The objective of the current study was to evaluate the clinical risk for LSIL-H on the follow-up cervical histology and to investigate the cytologic and histologic characteristics associated with the LSIL-H category.

MATERIALS AND METHODS

Sample collection

We searched the cytopathology files of our department for the LSIL-H Pap smears, including the 'LSIL, cannot exclude HSIL' and the 'SIL, c/w CIN1-2', and these specimens were obtained between January 2005 and March 2007. A total of 184 LSIL-H smears (0.09%) were identified among a total of 208,318 Pap tests. The 184 LSIL-H smears included the cytologic results of 52 LSIL, cannot exclude HSIL and 132 SIL, c/w CIN1-2. Among them, 144 smears had follow-up histologic samples obtained within 6 months: these were 65 cases of colposcopically-directed biopsies only and 79 cases of cone biopsies and/or hysterectomies with/without colposcopically-directed biopsies. For this study, the 65 smears having follow-up histologic samples by colposcopically-directed biopsies only were excluded due to the absence of subsequent conization or hysterectomy, and the 79 LSIL-H smears that had follow-up cervical histology with conization and/or hysterectomy were selected. Thirty-one smears were prepared by the conventional Pap test and 48 smears were prepared by liquid based cytology using SurePath™ (TriPath Imaging, Inc., Burlington, NC, USA). Fifty-four cytological specimens were obtained from the ordinary cevicovaginal portion for a routine Pap test, and 25 specimens were obtained from the endocervix by using a brush at colposcopy. The follow-up histology was reviewed by a pathologist to confirm the original diagnosis. If there was disagreement over the diagnosis, then three pathologists attempted to reach a consensus. There were four cases of CIN1-2 on follow-up histology, but they were revised as CIN1 in one case and CIN2 in three cases for this study. As controls, the Pap smears of 166 LSIL, 160 ASC-H and 38 HSIL, c/w CIN2 were randomly retrieved with using the same criteria as that for the study materials. The control group of 38 HSIL Pap smears was cytologically c/w CIN2 and they were histologically confirmed to be CIN2 or greater (CIN2+) on the follow-up cervical conization and/or hysterectomy.

Evaluation of LSIL-H

The histologic outcomes of the 79 cases of LSIL-H were compared with those of the 166 LSILs and 160 ASC-H controls. Both the cytologic and histologic features of the 38 LSIL-H smears that were confirmed to have histologic CIN2+ on the follow-up histology were compared with those of the 38 control smears of the HSIL, c/w CIN2. The histologic outcomes of the 38 HSIL controls were CIN2 in 21 cases and CIN3 in 17 cases. The following cytologic features were evaluated by a cytotechnologist and a pathologist: the presence of human papillomavirus cytopathic cells (koilocytes and multinucleated cells) and the number of ASC-H or the number of borderline cells between LSIL and HSIL (single cells $\geq$ 10 and cell groups $\geq$ 4). For histologic comparison, the presence of flat condyloma and the size of the CIN2+ lesions were estimated by a pathologist. For the size of the CIN2+ lesion, this was obtained by multiplying the longitudinal length by the transverse length of the lesion. The dimensions of the longitudinal and the transverse lengths were measured in the conization and/or hysterectomy material, including colposcopically directed biopsy. The transverse length was calculated by sections of the tissue blocks consecutive CIN2+ and multiplying this by the average thickness of the block (about 2.5 mm).

RESULTS

Clinical risk of LSIL-H

Table 1 presents the histologic outcomes of each cytological category. A benign histological outcome for the LSIL-H smears (6.3%) was markedly low compared to that of the smears of LSIL (33.1%) and ASC-H (34.4%). The frequency of abnormal histological lesions differed among the categories. The most frequent histologic outcome was CIN2 (51.9%) in the LSIL-H smears, flat condyloma/CIN1 (48.8%) in the LSIL smears, and CIN3 or greater (CIN3+) (46.9%) in the ASC-H smears. The risk of flat condyloma/CIN1 in the LSIL-H smears (11.4%) was intermediate between the LSIL (48.8%) and ASC-H (3.1%) smears. The risk of CIN3+ in the LSIL-H smears (30.4%) was also in-

Table 1. Histologic outcomes for LSIL-H as compared to that for LSIL and ASC-H

Cytology	Histologic diagnosis (%)				Total (%)
	Benign	Flat condyloma/CIN1	CIN2	CIN3+	
LSIL-H	5 (6.3)	9 (11.4)	41 (51.9)	24 (30.4)	79 (100.0)
LSIL	55 (33.1)	81 (48.8)	23 (13.9)	7 (4.2)	166 (100.0)
ASC-H	55 (34.4)	5 (3.1)	25 (15.6)	75 (46.9)	160 (100.0)

LSIL-H, low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; ASC-H, atypical cells suggestive of high-grade squamous intraepithelial lesion; CIN3+, cervical intraepithelial neoplasia 3 or greater.

termediate between the LSIL (4.2%) and ASC-H (46.9%) smears. One patient with LSIL-H had a focal, superficial microinvasive squamous cell carcinoma that was confirmed on hysterectomy after the diagnosis of CIN3 in the colposcopic biopsy. The corresponding LSIL-H smear of this case showed many keratinizing dysplastic cells, grade cannot be determined, as well as LSIL cells. There was no case of microinvasive carcinoma among the controls of LSIL or ASC-H.

Cytologic and histologic characteristics of LSIL-H

Tables 2 and 3 present the cytologic features of the LSIL-H smears that were confirmed to have histologic CIN2+ (Fig. 1), and these smears were compared with the control smears of HSIL, c/w CIN2 (Fig. 2). All of these study and control cases were confirmed to have histologic CIN2+ on the follow-up conization and/or hysterectomy. Evidence of LSIL such as koilocytotic atypia and multinucleated cells were frequently found in the LSIL-H smears (78.9% and 71.0%, respectively) compared to that of the smears of HSIL, c/w CIN2 (18.4% and 18.4%, respectively). The number of abnormal cells that were atypical cells suggestive of HSIL or borderline cells between LSIL and HSIL was less in the LSIL-H smears (single cells, 28.9%; clusters, 0%) than that in the smears of HSIL, c/w CIN2 (single cells, 76.3%; clusters, 50%) (Table 2). With regard to the degree of nuclear atypia, the atypical cells suggestive of HSIL or the borderline cells between LSIL and HSIL in the LSIL-H were less severe than those of the HSIL, c/w CIN2 (Table 3). The most common nuclear features of the LSIL-H smears were a moderate degree of atypia such as an increased N/C ratio, hyperchromasia and coarse chromatin, and a mild degree of nuclear membrane irregularity. However, the most common nuclear features of the HSIL smears, c/w CIN2 were a severe degree of atypia such as an increased N/C ratio, hyperchromasia and coarse chromatin, and a moderate degree of nuclear membrane irregularity.

Table 4 shows the histologic characteristics of the LSIL-H smears that were confirmed to represent CIN2+ on the follow-up conization and/or hysterectomy. Condylomatous change in

Table 2. The overall cytologic features of LSIL-H confirmed as histologic CIN2+ and as compared with those of HSIL, c/w CIN2

Cytolgic features	LSIL-H (n = 38) (%)	HSIL, c/w CIN2 (n = 38) (%)
Evidences of LSIL		
Koilocyte (+)	30 (78.9)	7 (18.4)
Multinucleation (+)	27 (71.0)	8 (18.4)
Suggestive of HSIL		
Single cells (≥ 10)	11 (28.9)	29 (76.3)
Clusters (≥ 4)	0 (0.0)	19 (50.0)

LSIL-H, low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion; CIN2+, cervical intraepithelial neoplasia 2 or greater; HSIL, high-grade squamous intraepithelial lesion; c/w CIN2, consistent with CIN2; LSIL, low-grade squamous intraepithelial lesion.

Table 3. Nuclear features of the atypical cells suggestive of HSIL

Nuclear atypia	Degree of atypia (%)		
	Absent or Mild	Moderate	Severe
LSIL-H (n = 38)			
Increased N/C ratio	5 (13.2)	25 (65.8)	8 (21.1)
Hyperchromasia	7 (18.4)	24 (63.2)	7 (18.4)
Coarse chromatin	14 (36.8)	20 (52.6)	4 (10.5)
Nuclear membrane irregularity	23 (60.5)	14 (36.8)	1 (2.6)
HSIL, c/w CIN2 (n = 38)			
Increased N/C ratio	2 (5.3)	14 (36.8)	22 (57.9)
Hyperchromasia	1 (2.6)	13 (34.2)	24 (63.2)
Coarse chromatin	3 (7.9)	17 (44.7)	18 (47.4)
Nuclear membrane irregularity	4 (10.5)	23 (60.5)	11 (28.9)

HSIL, high-grade squamous intraepithelial lesion; LSIL-H, low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion; c/w CIN2, consistent with cervical intraepithelial neoplasia 2.

Table 4. The histologic characteristics of LSIL-H confirmed as histologic CIN2+ and as compared to those of HSIL, consistent with CIN2

Cytology	Presence of flat condyloma (%)	CIN2+ size, mm^2
LSIL-H (n = 38)	37 (97.4)	52.9
HSIL[a] (n = 38)	29 (76.3)	116.7

[a]HSIL, consistent with CIN2.
LSIL-H, low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion; CIN2+, cervical intraepithelial neoplasia 2 or greater; HSIL, high-grade squamous intraepithelial lesion.

Table 5. Follow-up conization results after colposcopically-directed biopsy for LSIL-H

Initial colposcopic biopsy	Conization			
	Benign	Flat condyloma/CIN1	CIN2	CIN3+
Benign (n = 13)	4	1	4	4
Flat condyloma/CIN1 (n = 10)	5	2	3	0
CIN2 (n = 32)	10	5	14	3
CIN3+ (n = 17)	0	0	2	15
Total (n = 72)	19	8	23	22

LSIL-H, low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion; CIN3+, cervical intraepithelial neoplasia 3 or greater.

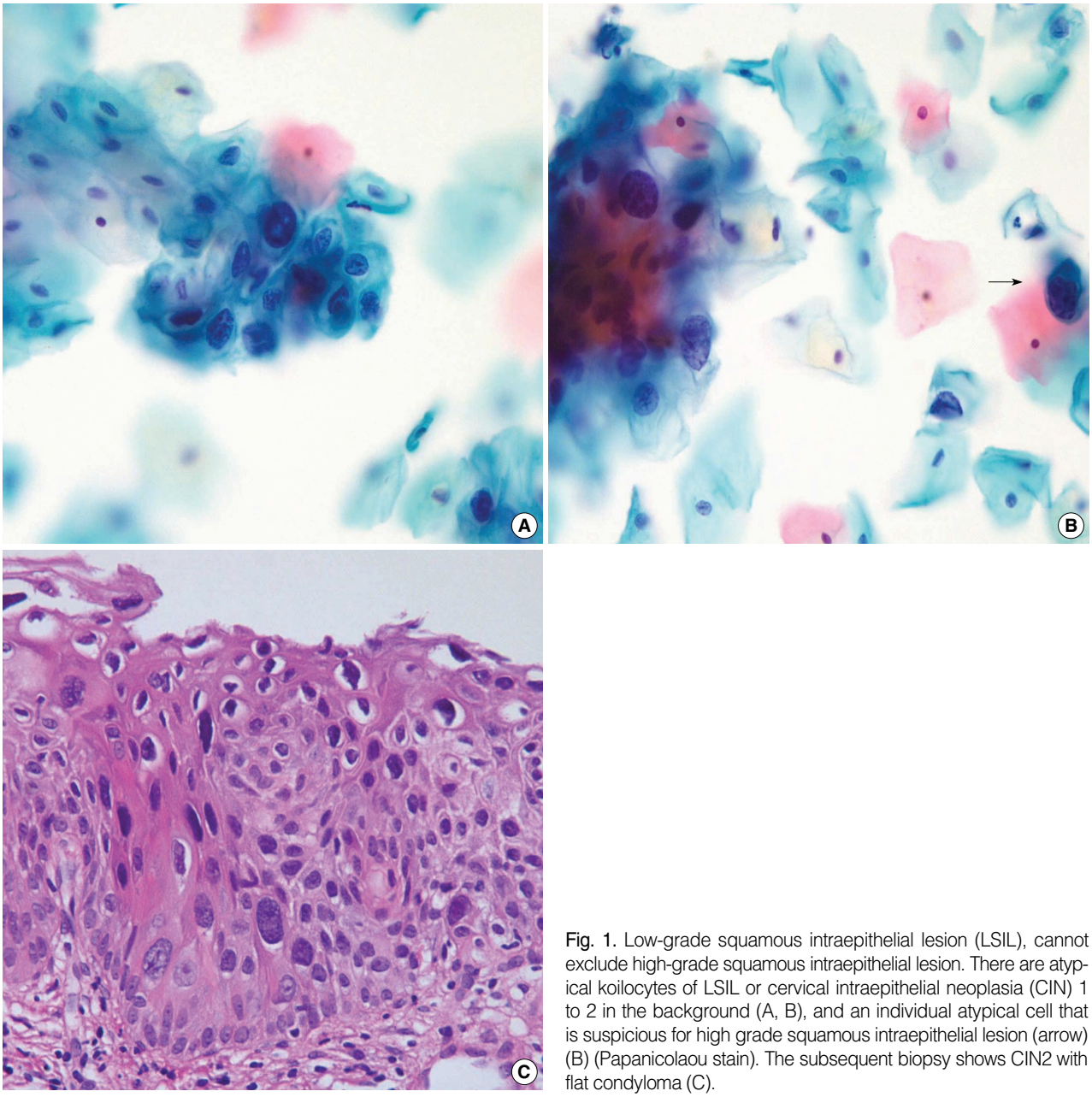

Fig. 1. Low-grade squamous intraepithelial lesion (LSIL), cannot exclude high-grade squamous intraepithelial lesion. There are atypical koilocytes of LSIL or cervical intraepithelial neoplasia (CIN) 1 to 2 in the background (A, B), and an individual atypical cell that is suspicious for high grade squamous intraepithelial lesion (arrow) (B) (Papanicolaou stain). The subsequent biopsy shows CIN2 with flat condyloma (C).

the histologic tissues was more frequently found in the LSIL-H smears (97.4%) than that in the smears of HSIL, c/w CIN2 (76.3%). The average size of the histologic CIN2+ lesions was smaller in the LSIL-H smears (52.9 mm^2) than that in the smears of HSIL, c/w CIN2 (116.7 mm^2).

There were 72 patients who underwent both colposcopic biopsy and subsequent conization, and we evaluated the clinical significance of the conization in the LSIL-H smears of these patients (Table 5). Eleven (47.8%) of 23 patients who had benign or flat condyloma/CIN1 at the initial colposcopically-directed biopsy were found to have CIN2 or CIN3 on conization; especially, four patients were confirmed to have CIN3 on conization. Among 32 patients diagnosed as CIN2 according to the initial colposcopically-directed biopsy, three were up-graded to CIN3 on conization. From these results, fourteen (31.1%) of all 45 patients who were confirmed to have CIN2 and CIN3+ had an up-graded diagnosis of high grade CIN2 or CIN3 by the subsequent conization.

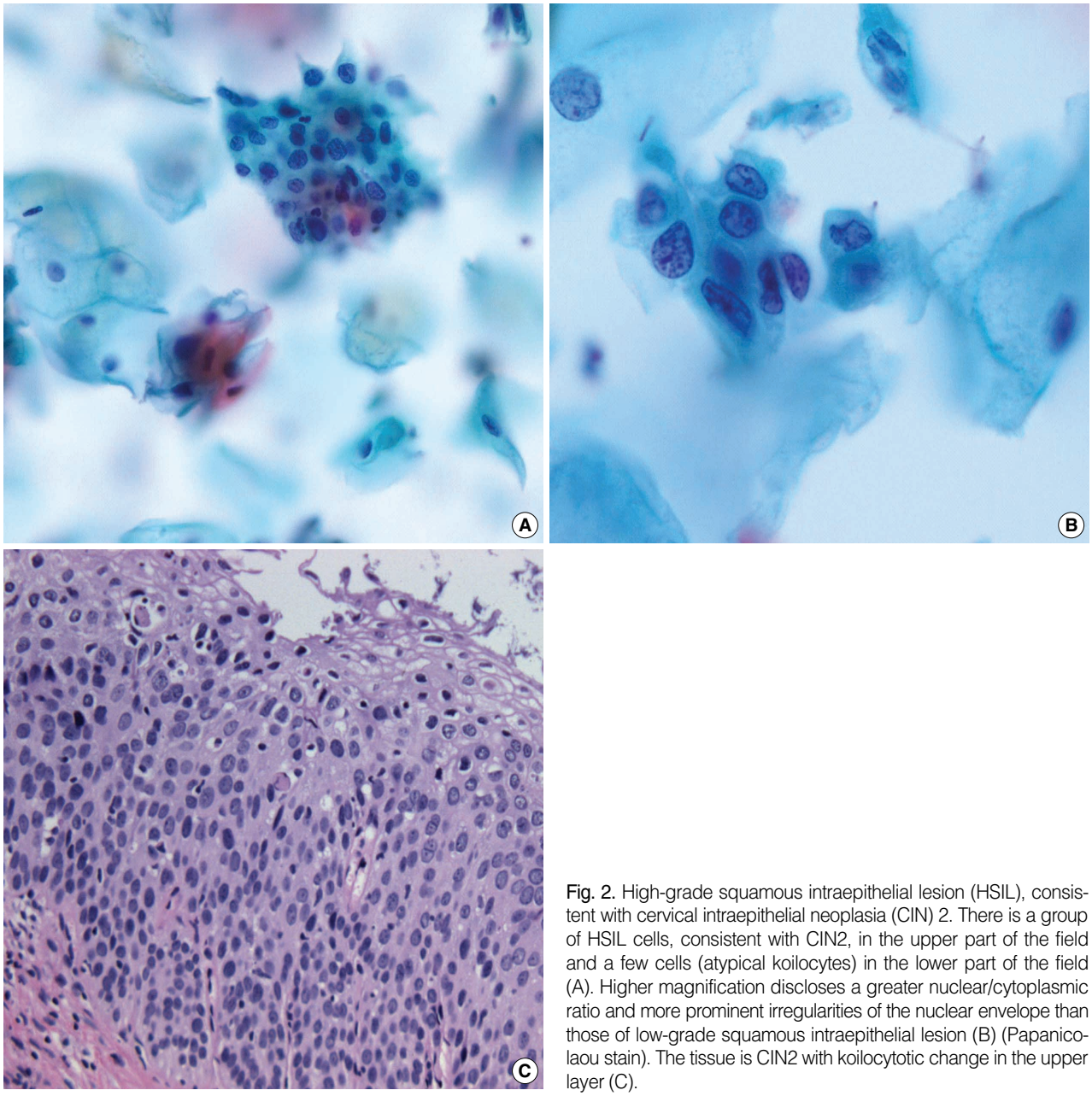

Fig. 2. High-grade squamous intraepithelial lesion (HSIL), consistent with cervical intraepithelial neoplasia (CIN) 2. There is a group of HSIL cells, consistent with CIN2, in the upper part of the field and a few cells (atypical koilocytes) in the lower part of the field (A). Higher magnification discloses a greater nuclear/cytoplasmic ratio and more prominent irregularities of the nuclear envelope than those of low-grade squamous intraepithelial lesion (B) (Papanicolaou stain). The tissue is CIN2 with koilocytotic change in the upper layer (C).

DISCUSSION

We studied 79 cases of LSIL-H smears that were followed by histological confirmation (conization and/or hysterectomy) within 6 months. The LSIL-H smears showed a different clinical risk from the control LSIL and ASC-H smears. First, the detection rate of benign lesions on the follow-up histology was markedly lower in the LSIL-H smears (6.3%) than that in the smears of LSIL (33.1%) and ASC-H (34.4%). As compared with the LSIL and the ASC-H smears, the main reason for this may be the fact that the cytological characteristics of LSIL-H typically exhibit unequivocal cells of LSIL and a small number of atypical cells suggestive of HSIL. It is reasonable that the presence of unequivocal cells of LSIL on cytology can cause an increased detection rate of flat condyloma or more severe lesion on histology. Therefore, the detection rate of benign lesions on the follow-up histology will be low in the LSIL-H smears. Second, the most common histological diagnosis on the follow-up cervical histology was CIN2 for the LSIL-H smears. This finding is different from those of the LSIL and ASC-H smears, for which the most com-

mon histological diagnosis was flat condyloma/CIN1 and CIN-3+, respectively. Third, for the LSIL-H smears, the detection rate of flat condyloma/CIN1 or CIN3+ on the follow-up histology was intermediate between the cases of LSIL and ASC-H smears. Therefore, LSIL-H is considered to be a distinct cytologic category.

In the current study, the detection rate of CIN2+ on the follow-up histology of the LSIL-H smears (82.3%) was higher than that for the LSIL (18.1%) and ASC-H (62.5%) smears. This was caused by the predominantly high rate of histological CIN2 (51.9%) in the LSIL-H. These findings are slightly dissimilar to other studies that reported an intermediate risk in the LSIL-H smears for the detection of high-grade CIN on the follow-up histology. Elsheikh *et al.*[6] reported that the LSIL-H smears (40.7%) had an intermediate risk of CIN2+ between the LSIL smears (13%) and the HSIL smears (74%) on the follow-up histology, but the risk was similar to that of the ASC-H smears (44%). A recent paper shows generally similar findings to those of our data, even though the positive rates are different between the cytologic categories.[10] They reported that the CIN-2+ rate (33.14%) observed in association with LSIL-H was higher than the rate of LSIL (16.11%) but it was lower than the rate of HSIL (69.03%) and it was similar or slightly higher than the rate observed in the ASC-H (26.33%).[10] They also showed that the rate of CIN3+ observed on the follow-up of LSIL-H (11.24%) was lower than the rate of CIN3+ in the ASC-H (17.79%). Our study showed a high detection rate of CIN2+ in the LSIL-H, as compared to the previous studies.[6,10] The dissimilarity between the current study and the previous studies may be due to different study materials. In the previous studies, the follow-up histological materials were obtained by biopsy specimens (including cervical biopsy, endocervical curetting, loop electrosurgical excision and cone excision), yet in the current study, the histology materials included only confirmatory histologic materials of cone biopsies and/or hysterectomies. It is reasonable that the detection rate of high-grade CIN should be higher in the follow-up conization/hysterectomy than that in the colposcopic biopsy only. In fact, if the materials of the colposcopically-directed biopsies only are included in this study, the detection rate of CIN2+ on the follow-up histology of the LSIL-H smears (58.3%) was similar or slightly lower than that of the ASC-H smears (62.5%) (data not shown).

Certain Pap smears could be classified as LSIL-H for two reasons. Firstly, there are occasional 'borderline' cases that lie between LSIL and HSIL on both the Pap smears and the histological samples, although examination of the morphologic features usually classifies the smears as either LSIL or HSIL. In a study that focused on the cervical biopsy-cytology correlation and that was performed by the College of American Pathologists, the diagnosis SIL of an indeterminate grade occupied 3.3% of all the SIL diagnoses.[11] LSIL-H smears may belong to SIL, grade cannot be determined. Nasser *et al.*[5] revealed that dysplastic cells with a borderline N/C ratio appeared in 18% of the LSIL-H smears. Similarly, we used the cytologic result of 'LSIL, cannot exclude HSIL' together with 'SIL, c/w CIN1-2,' without detailed cytologic criteria to differentiate between the two categories, and we found four histologic results of CIN1-2 on the follow-up histology. They were revised to CIN1 or CIN2 for this study. Second, for the cases of LSIL-H that contain numerous cells of LSIL and rare cells suggestive of HSIL, it could be assumed that the cervical tissue has a small portion of high-grade CIN in a large background of low-grade lesion of flat condyloma or CIN1. Our follow-up histology data showed that the size of CIN2+ on the follow-up histology was smaller in the LSIL-H cases as compared with that of the pure cases of HSIL, c/w CIN. At the same time, condylomatous change on the follow-up histology was more frequently found in the cases of LSIL-H than that in the cases of HSIL, c/w CIN. Taken together, our results support the assumption that in many cases of HSIL-H, the cervix has a small, high-grade CIN admixed with large flat condyloma/CIN1.

In the current study, the LSIL-H smears accounted for 0.09% (184/208,318) of all the Pap tests, which was a somewhat lower frequency than that reported by Elsheikh *et al.*[6] (0.15%, 194/126,911), Shidham *et al.*[9] (0.19%, 146/77,979), McGrath *et al.*[4] (0.2%, 108/48,687) and Owens *et al.*[7] (0.5%, 113/21,220). Elsheikh *et al.*[6] described that LSIL-H was the least frequent of all squamous cell abnormalities and it accounted for 0.15% of all Pap test interpretations and 2.5% of the squamous cell carcinomas. Although the prevalence of LSIL-H has varied across the reports, there was no significant difference among them. The similar prevalence indicates that the cytologic definition of LSIL-H is relatively well established as a Pap smear that typically contains definitive cells of LSIL and a few atypical cells that are suggestive, but not diagnostic of HSIL, and/or the Pap smear has borderline dysplastic cells that are between LSIL and HSIL. However, the diagnostic criteria for cells suggestive of HSIL were not exactly same between the previous studies. For example, Nasser *et al.*[5] described atypical squamous metaplastic cells (62%), atypical keratinized cells (20%) and dysplastic cells with a borderline N/C ratio (18%) as the cytologic criteria of the cells suggestive of HSIL. However, Elsheikh *et al.*[6] excluded the cells of dyskeratosis or keratinizing dysplasia, and included

rare dysplastic cells (usually < 5 cells), atypical metaplastic squamous cells and cells with an N/C ratio intermediate between LSIL and HSIL as the criteria. The cytological details for the morphologic criteria of LSIL-H need to be better defined to set up LSIL-H as a valid diagnostic category.

We observed that the nuclear atypia in LSIL-H cells suggestive of HSIL was less severe than that of the pure cases of HSIL, c/w CIN2. The most frequently encountered morphologic findings of the LSIL-H cells suggestive of HSIL were a moderate degree of nuclear atypia such as an increased N/C ratio, hyperchromasia and coarse chromatin, and a mild degree of nuclear membrane irregularity. These cytologic findings resemble those of CIN2. Accordingly, we agree with McGrath *et al.*[4] that LSIL-H cells with features suggestive of HSIL usually represent CIN2.

The 2001 consensus guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP) recommended colposcopy for women with a Pap smear diagnosis of LSIL or HSIL. However, the ASCCP guidelines do not address the management of women with a Pap smear diagnosis of SIL of an indeterminate grade. Elsheikh *et al.*[6] suggested that the same management guidelines for ASC-H should be applied to patients with LSIL-H because both tend to have poorly reproducible cytological interpretation and a clinical risk of CIN2+ on the follow-up histology that is intermediate between LSIL and HSIL. Shidham *et al.*[9] reported that a management algorithm comparable to that for ASC-H and HSIL would be appropriate for the LSIL-H cases, and they suggested a management algorithm for women with LSIL-H. Similarly, based on our data, the management of the LSIL-H cases that are diagnosed as benign or flat condyloma/CIN1 on the initial colposcopically-directed biopsy needs to be emphasized. A sizable percentage (47.8%) of patients who had LSIL-H and who were confirmed to have CIN2+ on the follow-up histology were identified by conizaton after originally being diagnosed with benign or flat condyloma/CIN1 on the initial colposcopic biopsy. Accordingly, we suggest that the management of women with LSIL-H that is not confirmed on the initial colposcopically-directed biopsy may require further follow-up, just like cases of ASC-H or HSIL. However, because the LSIL-H cases appeared to have small CIN2 on the cytology and histology, further large studies are necessary to avoid excess management and to identify the real nature of the LSIL-H entity.

In conclusion, the Pap smears of LSIL-H accounted for 0.09% of all the Pap tests in this current study and these smears had characteristic findings. On the follow-up histology, the risk of detecting CIN2+ was higher than that for ASC-H, but the most common histological outcome was CIN2. The cytological features of the atypical cells suggestive of HSIL were usually those of CIN2, and most cervical lesions of the LSIL-H smears had a small focus of high-grade CIN admixed with a relatively large area of flat condyloma/CIN1. For proper management, the LSIL-H smears not confirmed on the initial colposcopic biopsy need further follow up. Therefore, LSIL-H represents a valid diagnostic category that is defined as a LSIL smear containing rare atypical cells suggestive, but not diagnostic of HSIL.

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