Reporting of "LSIL with ASC-H" on cervicovaginal smears: Is it a valid category to predict cases with HSIL follow-up?

G. Kir[1], H. Cetiner[1], A. Gurbuz[2], A. Karateke[2]

[1]Department of Pathology and [2]Obstetrics and Gynecology, Zeynep Kamil Maternity Hospital, Istanbul (Turkey)

Summary

Recently it has been shown that there is a 15-30% risk of associated cervical intraepithelial neoplasia (CIN 2-3 or greater) for a low-grade squamous intraepithelial lesion (LSIL) diagnosis. We tried to define a subgroup of "LSIL with atypical squamous cells of undetermined significance. High-grade squamous intraepithelial lesion (LASC-H)" in cervicovaginal screening which may aid in predicting the cases associated with high risk cannot be ruled out. In the years between 2001 and 2003 a total of 21,342 cervicovaginal smears were evaluated. The smears with pure LSIL and LASC-H diagnosis which had histologic follow-up were selected. The cases with diagnosis of LASC-H contained numerous typical cells of LSIL and only a few cells with features suggesting high-grade squamous intraepithelial lesion (HSIL). Eight (61%) of 13 cases with a diagnosis of LASC-H but three (11%) of 27 cases with a diagnosis of pure LSIL resulted in CIN 2-3 histology ($p < 0.05$).

Diagnosis of LASC-H may be a valid diagnostic category in distinguishing patients with LSIL that would have HSIL in follow-up.

Key words: Cervical intraepithelial neoplasia; LSIL; ASC-H.

Introduction

The majority of women with a low-grade squamous intraepithelial lesion (LSIL) have no cervical lesions or have cervical intraepithelial neoplasia (CIN 1) that has a high rate of regression [4]. However, recently it has been shown that approximately 15-30% of women with LSIL will have histologic CIN 2-3 or greater [1-4]. In predicting these cases human papilloma virus (HPV) DNA testing is not recomended because 83% of women with LSIL have oncogenic HPV types. Repeat cytology is not recomended because there is a 53-76% likelihood that repeat cytology will be abnormal. There is a risk of loss to follow-up over multiple visits and there is a 15-30% risk of associated CIN 2-3 or greater. Thus the recommended management option for LSIL has become immediate colposcopy [1].

In this study we tried to define a LSIL subgroup in cervicovaginal screening which might aid the detection of LSIL cases associated with histologic CIN 2-3. There are cases which are not easily classified as either purely LSIL or a definitely high-grade squamous intraepithelial lesion (HSIL). These cases typically contain numerous cells of LSIL and only a few cells with features suggesting HSIL. One is left with the question, is the presence of only rare cells with features suggesting HSIL sufficient to classify the patients as HSIL? In our laboratory we made the diagnosis of "LSIL with atypical squamous cells of undetermined significance, cannot rule out high-grade squamous intraepithelial lesion (LASC-H)" on these cases.

Revised manuscript accepted for publication December 20, 2003

Materials & Method

The cytopathology files of the Pathology Department of Zeynep Kamil Maternity Hospital were searched for cervicovaginal smears (CVS) diagnosed as LASC-H between 2001 and 2003. During this time a total of 21,342 CVS were evaluated. LASC-H diagnoses which had histologic follow-up were selected. Cervical biopsies, endocervical curettage and/or cervical cones performed within three months of the cytologic diagnosi formed the basis of this study. The average patient age was 37 (range 18-76 years old). Cytologic diagnosis and specimen adequacy were classified using the Bethesda nomenculature system for cervical cytology [6]. The term atypical squamous cells cannot exclude a high-grade squamous intraepithelial lesion (ASC-H). It is a new diagnostic category included within epithelial cell abnormalities and reflects a mixture of true HSIL and its mimics.

The number of cells suitable with LSIL and cells suspicious of HSIL were estimated and rated on a score of 1 to 3 with "1" representing fewer than five cells, "2" representing five to ten cells and "3" representing more than ten cells. For the purposes of this study the histologic diagnosis of condyloma and CIN I will be classified as LSIL and CIN II and CIN III as HSIL. CVS with a diagnosis of LASC-H were divided into two groups: cases with a follow-up diagnosis of histologic LSIL and those with a follow-up diagnosis of histologic HSIL. Two pathologists (GK, HC) blindly reviewed all cases, using a multiheaded microscope; the cytomorphologic features were studied and recorded. The distrubution of biopsy results between the different groups were analysed by Fisher's exact test and chi-square analysis, where appropriate. A p value of less than 0.05 was considered statistically significant. The analyses were performed using Microsta statistical program for Windows.

Results

Follow-up data on 27 cases with pure LSIL and 13 cases with LASC-H are presented in Table 1. Eleven

(27%) of a total of 40 LSIL diagnoses (purely LSIL and LASC-H) resulted in a biopsy diagnosis of HSIL. There were numerous typical pure LSIL cells (score 3) and a only a few ASC-H cells in the LASC-H category with a HSIL follow-up (Figure 1). The frequent cytomorphologic features of ASC-H cells of the LASC-H category with a HSIL follow-up had a high nucleo-cytoplasmic ratio, hyperchromasia, coarse unevenly dispersed chromatin, prominent nuclear membrane irregularities, immature metaplastic cytoplasm and lack of nucleoli and mature metaplastic cytoplasm (Figure 2).

Of the 27 tissue specimens with a pure LSIL diagnosis on cervicovaginal smears, four (14%) cases were clinically insignificant lesions, 20 (74%) resulted in a diagnosis of LSIL and three (11%) were diagnosed as HSIL. Of the 13 specimens with a cytologic diagnosis of LASC-H, two (15%) were clinically insignificant lesions, three (23%) showed LSIL whereas eight (61%)were diagnosed as HSIL. Of the total 40 specimens with a cytologic diagnosis of LSIL, six (15%) were clinically insignificant lesions, 23 (57%) showed LSIL and 11 (27%) resulted in a diagnosis of HSIL. The distribution of LSIL and HSIL biopsy results between the three groups were significantly different ($p < 0.05$) (Table 1). There was a significant difference in distribution of biopsy results of the groups with diagnoses of LASC-H and total LSIL ($p < 0.05$). The positive predictive value (PPV) of diagnoses of "pure LSIL" and "LASC-H" was 11% and 61%, respectively. PPV of all cases with LSIL diagnoses was 27%. Table 2 lists the cytomorphologic features of LASC-H with HSIL follow-up. Representative cases are shown in Figure 1.

Table 1. — *Results of histologic follow-up.*

Diagnostic category (Cytology)	LSIL		LASH		Total LSIL	
	#	%	#	%	#	%
Biopsy number	27	100	13	100	40	100
No significant lesion	4	14.8	2	15.3	6	15
LSIL (Histology)	20	74	3	23	23	57.5
HSIL (Histology)	3	11.1	8	61.5	11	27.5
PPV (%)	11.1		61.5		27.5	

Table 2. — *Cytomorphologic features present in LASC-H cases with HSIL follow-up.*

Cytomorphologic features	#	%
LSIL cells - Score 1	–	–
LSIL cells - Score 2	1/8	12.5
LSIL cells - Score 3	7/8	87.5
ASC-H cells - Score 1	6/8	75
ASC-H cells - Score 2	2/8	25
ASC-H cells - Score 3	–	–
Cytologic features of ASC-H cells		
High nucleo/cytoplasmic ratio	7/8	87.5
Nucleoli	–	–
Coarse uneven chromatin	1/8	12.5
Hyperchromasia	6/8	75
Nuclear membrane irregularity	4/8	50
Mature metaplastic cytoplasm	2/8	25
Immature metaplastic cytoplasm	6/8	75

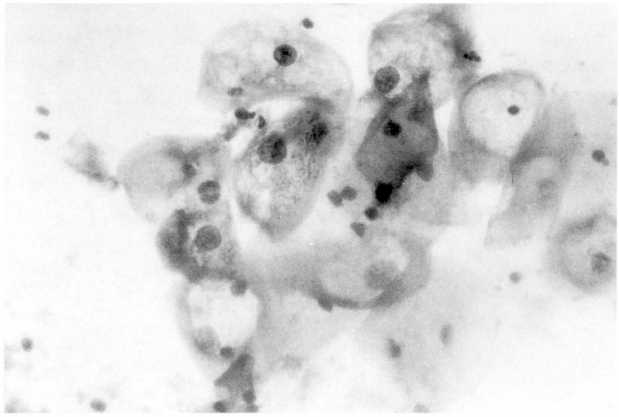

Fig. 1

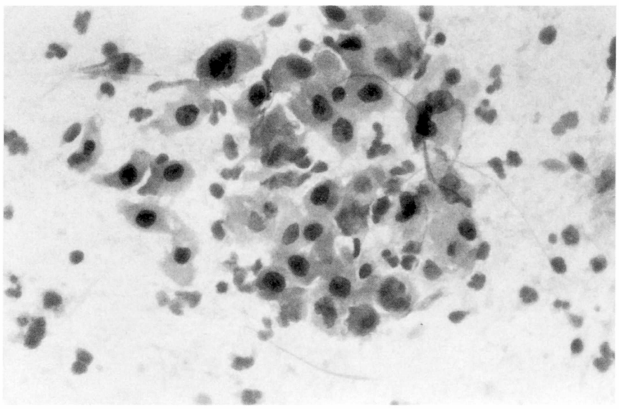

Fig. 2

Figure 1. — Numerous typical pure LSIL cells in the LASC-H category (Pap x 400).
Figure 2. — ASC-H cells of the LASC-H category with a high nucleo-cytoplasmic ratio, hyperchromasia and immature metaplastic cytoplasm (Pap x 400).

Discussion

Management options for LSIL have included immediate colposcopy, cytology follow-up or triage with HPV DNA testing for oncogenic types [5]. Recently however it has been shown that there was a 15-30% risk of associated CIN 2-3 or greater. Thus the recommended management option for LSIL has become only immediate colposcopy [1]. If we could predict the patients with high risk, the remaining LSIL cases could be managed by conservative management options instead of immediate colposcopy. For diagnostically challenging cases which are not easily classified as LSIL or HSIL our laboratory defined a diagnosis of LASC-H. We showed that 61% of cases with a LASC-H diagnosis resulted in a histologic diagnosis of HSIL. PPV of this category was higher than PPV of pure LSIL and total LSIL cases.

ASC-H diagnosis has been reportedly associated with CIN 2-3 in approximately 24 to 96% of patients in different studies [7-12]. Thus PPV of our LASC-H diagnostic catogory was higher than PPV of LSIL and similar to the higher end of this range for ASC-H.

The cases diagnosed as LASC-H contained numerous typical cells of LSIL and only a few cells suspicious for HSIL. The frequently encountered significant cytomorphologic features of ASC-H cells belonging to LASC-H

diagnosis with a HSIL follow-up had a high nucleo-cytoplasmic ratio, hyperchromasia, coarse unevenly dispersed chromatin, prominent membrane irregularities, immature metaplastic cytoplasm and lack of mature metaplastic cytoplasm and nucleoli.

McGrath *et al.* [13] suggested a diagnostic category of mild-moderate dysplasia defined as cases with cells of LSIL and only few moderately dysplastic cells. On biopsy and/or Pap smear follow-up of 41% of the cases showed LSIL and 59% of cases showed HSIL.

In conclusion we suggest that diagnois of LASC-H on cervicovaginal cytology may be a valid diagnostic category that can predict a subgroup of patients with a cytologic diagnosis of LSIL which will result in a biopsy diagnosis of HSIL.

References

[1] The ASCUS-LSIL Triage Study (ALTS) Group: "A randomized trial on the management of low-grade intraepithelial lesion cytology interpretations". *Am. J. Obstet. Gynecol.,* 2003, *188*, 1393.

[2] Law K.S., Chang T.C., Hsuch S., Jung S.M., Tseng C.J., Lai C.H.: "High prevalence of high grade squamous intraepithelial lesions and microinvasive carcinoma in women with a cytologic diagnosis of low grade squamous intraepithelial lesions". *J. Reprod. Med.,* 2001, *46*, 61.

[3] Fallani M.G., Penna C., Fambrini M., Marchionni M.: "Cervical cytologic reports of ASCUS and LSIL. Cyto-histological correlation and implication for management". *Minerva Ginecol.*, 2002, *54*, 263.

[4] Lytwyn A., Sellors J.W., Mahony J.B. *et al.* (The HPV effectiveness in Low-grade Paps Study No 1 Group): "Comparison of human papilloma virus DNA testing and repeat Papanicolaou test in women with low-grade cervical cytologic abnormalities: a radomized trial". *C.M.A.J.,* 2000, *163,* 701.

[5] Kurman R.J., Henson D.E., Herbst A.L., Nosler K.L., Schifman M.E.: "Interim guidelines for management of abnormal cervical cytology: the 1992 National Cancer Institute work-shop". *JAMA,* 1994, *271,* 1866.

[6] Solomon D., Davey D., Kurman R. *et al.*: "The 2001 Bethesda system: terminology for reporting results of cervical cytology". *JAMA,* 2002, *287,* 2114.

[7] Malik S.N., Wilkinson E.S., Drew P.A. *et al.*: "Do qualifiers of ASCUS distinguish between low and high risk patients?". *Acta Cytol.,* 1999, *43,* 376.

[8] Genest D.R., Dean B., Lee L.R. *et al.*: "Qualifiying the cytologic diagnosis of "atypical squamous cells od undetermined significance" affects the predictive vakue of squamous intraepithelial lesion on subsequent biopsy". *Arch. Pathol. Lab. Med.*, 1998, *122*, 338.

[9] Schoolland M., Sterrett G.F., Knowless S.A.S. *et al.*: "The inconclusive-possible high grade epithelial abnormality" category in Papanicolaou smear reporting". *Cancer,* 1998, *84,* 208.

[10] Sherman M.E., Tabbara S.O., Scott D.R. *et al.*: "ASCUS rule out HSIL: cytologic features, histologic correlates and human papillomavirus detection". *Mod. Pathol.,* 1999, *12,* 335.

[11] Quddus M.R., Sung C.J., Steinhoff M.M. *et al.*: "Atypical squamous metaplastic cells: reproducibility, outcome and diagnostic features of Thin Prep Pap test". *Cancer,* 2001, *93*, 16.

[12] Sherman M.E., Solomon D., Schiffman M., for the ALTS Group: "Qualification of ASCUS, A comparison of equivocal LSIL and equivocal HSIL cervical cytology in the ASCUS LSIL triage study". *Am. J. Clin. Pathol.,* 2001, *116*, 386.

[13] McGrath C.M., Kurtis J.D., Gordon H.Y.: "Evaluation of mild-to-moderate dysplasia on cervical-endocervical (Pap) smear: a subgroup of patients who brigde LSIL and HSIL". *Diagn. Cytopathol.*, 2000, *23,* 245.

Address reprint requests to:
K. GOZDE, M.D.
Soyak Gokyuzu Konutlari
B-Blok D:46
Kosuyolu Istanbul 81150
(Turkey)