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Clinical importance of "low-grade squamous intraepithelial lesion, cannot exclude high-grade squamous intraepithelial lesion (LSIL-H)" terminology for cervical smears☆

5-year analysis of the positive predictive value of LSIL-H compared with ASC-H, LSIL, and HSIL in the detection of high-grade cervical lesions with a review of the literature

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ABSTRACT

Objective. We compared follow-up biopsy findings and positive predictive values (PPVs) for cervical intraepithelial neoplasia 2 or worse (CIN 2+) in cases that were cytologically interpreted as low-grade squamous intraepithelial lesions (LSIL); high-grade squamous intraepithelial lesions (HSIL); LSIL, cannot exclude HSIL (LSIL-H); and atypical squamous cells, cannot exclude HSIL (ASC-H) during a 5-year period to evaluate the clinical significance of LSIL-H as a distinct cytological category.

Methods. All Pap tests with a diagnosis of LSIL-H, ASC-H, LSIL, and HSIL (January 1, 2004–July 20, 2009) were retrieved from our computer database. PPVs of cytological diagnostic categories for detecting CIN 2+ were compared.

Results. Of all Pap tests ($n=163{,}315$), 1713 cases that had histological confirmation were included in the study. The LSIL-H diagnosis represented only 0.23% ($n=387$) of all Pap tests and 9.3% of all cytological SILs ($n=4119$). LSIL alone was associated with a significantly lower risk for CIN 2+ (PPV = 21%) as compared with LSIL-H (PPV = 40%). The results showed that the risk of CIN 2+ was intermediate for LSIL-H compared with unqualified LSIL ($p<0.005$) and HSIL ($p<0.0001$).

Conclusions. The current study is one of the largest LSIL-H series to date. Because of its intermediate status between LSIL and HSIL, LSIL-H should be considered a distinct diagnostic category, and specific cytomorphological criteria should be defined. The results suggest that an LSIL-H diagnostic category would aid in more rapid detection and treatment in some patients with CIN 2+.

Introduction

The Bethesda System (TBS 2001) for cervical cytology reporting classifies squamous intraepithelial lesions (SIL) into two categories: low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL). However, in practice, occasional "borderline" cases and diagnostic dilemmas may occur between over-diagnosing LSIL and under-diagnosing HSIL. No diagnostic category for such cases is included in the TBS 2001, and a diagnosis of "SIL, grade cannot be determined" is recommended without explaining on which side of the diagnostic boundary they should reside [1–3].

A number of terminologies have been coined to describe this type of abnormal Papanicolaou (Pap) test. They include; (a) LSIL with atypical squamous cells, cannot exclude HSIL (ASC-H), (b) ASC-H without any references to LSIL, (c) LSIL, cannot exclude HSIL (LSIL-H), (d) HSIL or LSIL, and (e) LSIL with rare atypical cells suggestive but not diagnostic of HSIL [4–8]. For these cases that appear to bridge LSIL and HSIL, we prefer using "LSIL, cannot exclude HSIL (LSIL-H)" terminology for diagnosis.

The Bethesda classification for SILs not only provides standardized terminology and guidance for clinical management, but also reflects the biological differences between these lesions, and these biological differences affect patient management. HSIL persists, with some cases progressing to carcinoma, whereas most cases of LSIL may regress

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spontaneously. Therefore, HSIL is usually treated with the loop electrocautery excision procedure (LEEP) or cervical conization, whereas LSIL is followed closely by Pap smear and/or biopsy.

For these reasons, the SIL grade detected by the Pap test has important clinical implications and it seems that there is a need for an intermediate, separate diagnostic category for borderline cases between LSIL and HSIL.

Only a limited number of reports, including some in abstract form [4–24], have examined the significance of LSIL-H.

The objective of the current study is to evaluate the value of the diagnosis of LSIL-H in Pap smears to predict cervical intraepithelial neoplasia (CIN) 2 or more severe lesions (CIN 2+) in follow-up surgical biopsies in comparison to ASC-H, LSIL, and HSIL diagnostic categories.

Materials and methods

All Pap tests with an LSIL-H diagnosis during the 5-year period from January 1, 2004 to July 20, 2009 were retrieved from our computer database. For comparison, we also retrieved all cases of ASC-H, LSIL, and HSIL that were evaluated during the same period. Of these, only cases that had histological confirmation were included in the study.

All samples were stained using standard Pap stain, screened by a cytotechnologist, and reported by a (cyto)pathologists based on the Bethesda 2001 criteria [2].

The gold standard used was the follow-up biopsy. The cytology results were correlated with subsequent biopsies. As outside clinics did not always send their biopsies to our laboratory, we could not correlate the biopsy results in all cases. The histological diagnosis of CIN 1 was classified as mild dysplasia, and CIN 2 and 3 as moderate and severe dysplasia, respectively. When multiple biopsies were available, only the most severe diagnosis was recorded.

The LSIL-H diagnostic category was used when ASC-H features seen in a background of unequivocal LSIL, as well as features described in the LSIL-H publications [4–8,25,26].

Positive predictive values (PPVs) of the cytological diagnostic categories in the detection of CIN 2+ were compared using the chi-square test. p-values <0.05 were considered statistically significant.

Results

During the 5-year study period, 163,315 Pap tests were processed and evaluated in our laboratory. For all Pap tests, the rates of LSIL-H, ASC-H, LSIL, and HSIL were 0.23% ($n=387$), 0.19% ($n=314$), 2.00% ($n=3271$), and 0.28% ($n=461$), respectively.

A cyto-histo correlation was available for 185 LSIL-H (57.2%), 127 ASC-H (40.4%), 1137 LSIL (47.8%), and 264 HSIL (34.7%) interpretations. Only these 1713 cases (38.6% of all cases), which had histological confirmation, were included in the study (Table 1). The studied 1713 Pap tests included 908 (53.0%) conventional smears and 805 (46.9%) liquid-based cytologic preparations (ThinPrep®, Cytyc Corp.). The follow-up histologic tissue samples were from colposcopically-guided biopsy in 884 (51.6%), LEEP-conization-endocervical curettage in 786 (45.8%) and rarely hysterectomy specimens in 43 (2.5%) patients.

Table 1
Pap test interpretations of the study group cases that had histological follow-up.

Cytologic interpretation	Number of cases (n) (%)
LSIL-H	185 (10.7%)
ASC-H	127 (7.4%)
LSIL	1137 (66.3%)
HSIL	264 (15.4%)
Total	1713 (100.0%)

LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; LSIL-H, LSIL, cannot exclude HSIL; ASC-H, atypical squamous cells, cannot exclude HSIL.

The LSIL-H diagnosis represented only 0.23% ($n=387$) of all Pap tests and 9.3% of all cytologic SILs ($n=4119$) (Fig. 1) that were evaluated during the study period.

The histological follow-up for cytological diagnostic categories is shown in Table 2. For patients with an ASC-H interpretation on a Pap test, the most frequent histological outcome was CIN 2+ (43% of cases), followed by benign findings (31% of cases). For patients with an LSIL interpretation, the most frequent biopsy diagnosis was CIN 1 (57% of cases), followed by a benign diagnosis (22%); CIN 2+ was detected in 21% of cases with an LSIL interpretation on the Pap test. The most frequent histological outcome for patients with LSIL-H was CIN 1 (41% of cases), followed by CIN 2+ (40%). A benign diagnosis was given in only 19% of LSIL-H cases.

The results showed that a benign interpretation was more common in patients with an ASC-H (31%) as compared with LSIL-H (19%). LSIL-H was associated with a higher incidence of CIN 1 (41%) than was HSIL (14%) in follow-up cervical biopsy results. In the majority of patients with an HSIL interpretation (81%), CIN 2+ was detected in a subsequent cervical biopsy.

A comparison among the cytological categories for positive and negative predictive value (Table 3, Fig. 2) showed that the risk of CIN 2+ was intermediate for LSIL-H compared with unqualified LSIL ($p<0.005$) and HSIL ($p<0.0001$). Further comparisons between LSIL-H and ASC-H revealed that LSIL-H was more frequently associated with a definitive histological diagnosis of any CIN (CIN 1+) compared with ASC-H ($p<0.0001$). LSIL alone was associated with a significantly lower risk for CIN 2+ (PPV = 21%) than was LSIL-H (PPV = 40%). The rate of associated CIN 2+ differed significantly from that of LSIL-H (40%) and LSIL (21%) ($p<0.005$), but was similar to that of ASC-H (43%) and LSIL-H (40%).

Discussion

Only a limited number of studies have examined the significance of LSIL-H [4–24], and according to the literature, the current study is one of the largest LSIL-H series to date.

LSIL-H comprised only 0.23% of all Pap tests evaluated during the study interval. This rate was reported as 0.35% by Alsharif et al. [22], 0.19% by Shidham et al. [6], 0.15% by Elsheikh et al. [7], 0.15% by Booth et al. [9], and 0.2% by McGrath et al. [4]. The rate in the current study was similar to these reported rates.

In the College of American Pathologists (CAP) Interlaboratory Comparison Program in Cervicovaginal Cytology, the discrepancy rate between low- and high-grade lesions ranged from 9.8 to 15% [27]. Perhaps the absence of an intermediate diagnostic category such as LSIL-H between LSIL and HSIL caused this discrepancy.

The reported PPVs of LSIL-H, ASC-H, LSIL, and HSIL cytological diagnosis in the detection of CIN 2+ are shown in Table 4. We observed that the CIN 2+ rate after a diagnosis of LSIL-H (PPV = 40%) was higher than that of LSIL (PPV = 21%) and lower than that of HSIL (PPV = 81%) (Table 3, Fig. 1). As seen in Table 4, it is quite remarkable that our CIN 2+ rate was highest in cases interpreted as HSIL. If the rates are compared with each other, despite the use of different types of Pap test preparation techniques and definitions for LSIL-H, our rate (40%) was similar to the rates reported by Elsheikh et al. (40.7%) [7], Owens et al. (39.5%) [18], DiFurio et al. (40%) [13], Jain et al. (42%) [12], and Power et al. (40%) [11].

The histological CIN 2+ rates in women with LSIL and ASC-H cytology are similar to those in most other studies [6,7,11,14,16,18,19,21,22,27]. In the current study, Pap smears reported as ASC-H and LSIL-H predicted CIN 2+ with similar accuracy (40% and 43%, respectively).