Low-Grade Squamous Intraepithelial Lesion and Mimics

TERMINOLOGY
- Squamous cell changes associated with HPV infection
- Includes koilocytosis, mild dysplasia/cervical intraepithelial lesion grade 1 (CIN 1)

ETIOLOGY/PATHOGENESIS
- Most low-grade squamous intraepithelial lesions (LSILs) are due to high-risk HPV (HR-HPV) types (85% per ASC-US Low-Grade Triage Study); others due to low-risk types 6 and 11
- HPV-16 dominates in HR-HPV(+) group

CLINICAL ISSUES
- Asymptomatic; presents as abnormal Pap smear/test
- Often regresses spontaneously over period of 1-2 years
- Persistence is indicator for coexistent high-grade squamous intraepithelial lesion (HSIL), which is biologically independent event

CYTOPATHOLOGY
- Mature cell types (i.e., superficial or intermediate)

- Nuclear enlargement > 3x size (area) of intermediate cell nucleus with mild increase in nucleus:cytoplasm ratio
- Variable hyperchromasia, size, shape, and number (binucleated and multinucleated)
- Coarsely granular and uniformly distributed or densely opaque and smudged
- Nuclear contours are smooth or slightly irregular
- Sharply delineated perinuclear clearing with peripheral rim of densely stained cytoplasm (koilocyte) is characteristic but not requirement for diagnosis
- Cytoplasm may be densely keratinized (orangeophilic)
- Perinuclear halos in absence of nuclear abnormalities do not qualify for a diagnosis of LSIL
- Terminology for cytology and histology unified after lower anogenital squamous terminology conference in 2012
- Interpretive traps include navicular cells, radiation changes, early herpes viral changes, tight halos of reactive changes

(Left) This ThinPrep Pap test demonstrates a group of uni- and bi-nuclear koilocytes with an optically clear halo and nuclear enlargement, hyperchromasia, and contour irregularities. The nuclei are not centrally located within the halos. (Right) Low-grade squamous intraepithelial lesion (LSIL) on ThinPrep shows cells without the koilocytic cytoplasmic clearing but with nuclear features, including enlargement, hyperchromasia, and contour irregularities. Koilocytes are seen in the lower part of the image.

(Cervical biopsy section shows LSIL/cervical intraepithelial lesion grade 1, characterized by nuclear crowding and irregularity limited to the lower 1/3 of the cervical epithelium. Koilocytes are seen in the upper 1/2 of the biopsy. (Right) Tight halos from reactive changes secondary to Candida overgrowth. These reactive halos are small, not optically clear, and the nucleus tends to be centrally located within the halo. Unlike koilocytes, there is no peripheral cytoplasmic condensation.)

LSIL, Koilocytes on ThinPrep

LSIL

Cervical Biopsy With LSIL

Tight Halos, Not LSIL
Gynecologic Cytopathology: Squamous Cell Abnormalities and Mimics

Low-Grade Squamous Intraepithelial Lesion and Mimics

TERMINOLOGY

Abbreviations
- Low-grade squamous intraepithelial lesion (LSIL)

CLINICAL ISSUES

Presentation, Treatment, and Prognosis
- Often regresses spontaneously over period of 1-2 years
- Country-/continent-specific management guidelines are available
- Reporting rates per CAP surveys range from 1.1-6.2% on liquid-based cytology and 0.0-4.3% for conventional smears; median for liquid-based cytology is 2.7%

CYTOPATHOLOGY

Cellularity, Pattern, and Background
- Variable cellularity with cells in clumps, small groups, or single in clean or inflammatory background
- Cases with LSIL and rare cells suggestive of HSIL can be reported as LSIL and ASC-H or just ASC-H or LSIL; cannot rule out HSIL (LSIL-H); Bethesda 2014 does not sanction new category of LSIL-H due to potential confusion

Cells
- Mature cell types (i.e., superficial or intermediate cells)

Nuclear Details
- Nuclear enlargement > 3x size (area) of intermediate cell nucleus with mild increase in nucleus:cytoplasm ratio
- Variable hyperchromasia, size, shape, and number (binucleated and multinucleated)
- Coarsely granular and uniformly distributed or densely opaque and smudged
- Smooth or slightly irregular nuclear contours
- Nucleoli usually absent or inconspicuous

Cytoplasmic Details
- Sharply delineated perinuclear clearing with peripheral rim of densely stained cytoplasm (koilocyte) is characteristic but not requirement for diagnosis
- Cytoplasm may be densely keratinized (orangeophilic)
- Perinuclear halos in absence of nuclear abnormalities do not qualify for a diagnosis of LSIL

Cytology-Histology Correlation
- LSIL on biopsy (a.k.a. mild dysplasia or CIN 1)
- Terminology for cytology and histology unified after lower anogenital squamous terminology conference in 2012
- Some overlap with CIN 2 possible
- Utilize p16 to further clarify issue on histology
- Lack of block staining = LSIL/CIN 1

ANCILLARY TESTS

PCR
- HR-HPV testing may be useful for triage in certain age groups and clinical scenarios (per ASCCP guidelines)

DIFFERENTIAL DIAGNOSIS

Navicular Cells
- Yellow-tinged, large halo due to glycogen
- True koilocytes have clear halo and nuclear features

Hyperkeratosis
- Nuclear changes of LSIL are not seen

Tight Halos Due to Inflammation/Infections
- Slight nuclear enlargement (< 3x) and smooth contours

Herpes Viral Infection
- Early infection may lack characteristic viral cytopathic effect

Radiation Effect
- Nuclear enlargement, chromatinic smudging, altered shapes

SELECTED REFERENCES


(Left) LSIL on SurePath Pap shows nuclear enlargement, hyperchromasia, smudged chromatin, nuclear contour irregularities, and ↑ nucleus:cytoplasm ratio but no cytoplasmic clearing. (Right) Pap smear shows navicular cells with yellow-tinged coloration to the cytoplasmic clearing. Nuclear changes of LSIL are absent in this mimic.