Cervix
Common Diagnoses

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Pap Smear vs. Cervical Biopsy

Pap smear performed → screened by computer → then pap reviewed by a cytotechnologist → pap smear slides thought to be truly abnormal are given to a pathologist or a cytopathologist for final opinion.

Biopsy performed → slides given to a pathologist for interpretation and diagnosis.
ASCUS

Atypical squamous cells of undetermined significance.

This terminology is used to describe cells that are not normal in appearance. Yet, at the same time, the person reviewing the slide also does not deem them to be sufficient for a more definitive diagnosis (e.g. HSIL or LSIL).
ASC-H

Atypical squamous cells – cannot exclude high-grade dysplasia.

This terminology is used to describe situations in which some of the squamous cells appear atypical and raise concern for a possible high-grade dysplasia.
HR HPV+

The high-risk HPV molecular test looks for the presence of 13 or 14 of the most common high-risk HPV types.
Case #1

29 year old woman referred by family practice clinic for colposcopy. Recent pap: LSIL, HR HPV+

History: No prior abnormal pap results.

Colposcopy reveals an acetowhite area that gets biopsied.
Acute and chronic cervicitis

Cervix, biopsy:
Chronic active cervicitis with parakeratosis and reactive changes.
Transformation zone is identified.
No evidence of dysplasia or malignancy is identified.
Why was there no dysplasia identified within the biopsy specimen?
Possible explanations

1. LSIL pap was incorrectly diagnosed (false positive).
2. Biopsy was incorrectly diagnosed (false negative).
3. Lesion was in the block – but did not get sectioned (sampling error).
4. Inflammation can create similar appearance.
5. Lesion was not biopsied.
Possible ways to resolve this situation

1. LSIL pap was incorrectly diagnosed (false positive). One could ask that the pap be re-reviewed.
2. Biopsy was incorrectly diagnosed (false negative). One could ask that the biopsy slide be re-reviewed.
3. Lesion was in the block – but did not get sectioned (sampling error). Ask that deeper sections be obtained and reviewed.
4. Inflammation can create a similar appearance.
5. Lesion was not biopsied. (Repeat the pap in 12 months).
Case #2

30 year old woman – Self referred.
She had an abnormal pap smear 3 months ago, ASCUS HR HPV+. Moved shortly thereafter and did not follow-up. Now has settled in your community.
Colposcopy reveals an acetowhite area at 12 o’clock that gets biopsied.
HGSIL (CIN II-III)

Cervix, biopsy at 12 o’clock:
High-grade squamous intraepithelial lesion (CIN II-III).
Transformation zone is identified.
HGSIL vs. CIN II-III

Historically, -SIL terminology was used with cytology (pap smear) specimens (e.g. HSIL); -IN I, II or III terminology was used with histopathologic lesions (e.g. CIN III).

-- Pathologists may have also used squamous cell carcinoma in situ or CIS to describe the same high-grade squamous intraepithelial lesion (CIN III).
LAST Project Consensus

Back in March of 2012, the College of American Pathologists and American Society for Colposcopy and Cervical Pathology, in collaboration with 35 stakeholder organizations, convened a consensus conference called the Lower Anogenital Squamous Terminology (LAST) Project.
LAST Project Consensus

LAST recommended the terminology going forward should be: “low-grade” or “high-grade squamous intraepithelial lesion (SIL).”

--But, biopsy results using SIL terminology could be further qualified using the older “intraepithelial neoplasia” (IN) terminology in parentheses.
Case #3

20 year old woman –
She had an abnormal pap smear 11 months ago during a prenatal visit.
Pap diagnosis was ASC-H
Colposcopy did not reveal a discrete lesion so 4 quadrant biopsies are taken.
HGSIL (CIN II)

Cervix, biopsy at 12 o’clock:
High-grade squamous intraepithelial lesion (CIN II).
Transformation zone is identified.
Rate of and Risks for Regression of CIN-2 in adolescents and young women

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Abstract

Objective

To describe the natural history of CIN-2 in a prospective study of young women and to examine the behavioral and biologic factors associated with regression and progression.

Methods

Women aged 13 to 24 years referred for abnormal cytology and were found to have CIN-2 on histology were followed at 4-month intervals. Risks for regression defined as 3 consecutive negative cytology and histology visits and progression to CIN-3 were estimated using Cox proportional hazards regression models.

Findings

Ninety-five women with a mean age of 20.4 years (± 2.3) were entered into the analysis. Thirty-eight percent cleared by year 1, 63% by year 2 and 68% by year 3. Multivariable analysis found that recent N. gonorrhoeae infection (H.R. = 25.27 [95% C.I. 3.11, 205.42]) and medroxyprogesterone acetate use (per month) (H.R. = 1.02 [95% C.I. 1.003, 1.04]) were associated with regression. Factors associated with non-regression included combined hormonal contraception use (per month) (H.R. = 0.85 [95% C.I. 0.75, 0.97]) and persistence of HPV of any type (H.R. = 0.40 [95% C.I. 0.22, 0.72]). Fifteen percent of women showed progression by year 3. HPV 16/18 persistence (H.R. = 25.27 [95% C.I.2.65, 241.2, p = 0.005]) and HPV 16/18 status at last visit (H.R. = 7.25 [95% C.I. 1.07, 49.36]; p < 0.05) was associated with progression. Because of the small sample size, other co-variates were not examined.

Conclusion

The high regression rate of CIN-2 supports clinical observation of this lesion in young women.
Case #4

32 year old woman – abnormal pap smear ASCUS, HR HPV+. She has been your patient for 4 years. She has had prior abnormal pap smears (LSIL) and also biopsies showing LGSIL. No prior ASCUS or HR HPV+.

Colposcopy reveals an acetowhite area at 12 o’clock that gets biopsied.
Cervix, biopsies:
Low-grade squamous intraepithelial lesion (CIN I).
Transformation zone is identified.
Comment: To aid in the assessment of the biopsies, the p16 immunostain was performed. The p16 immunostain showed no block-positive staining.
What is the p16 immunostain?

In the lab, we use the p16 immunostain as a surrogate maker for transformed high-risk HPV related cervical lesions.

If the p16 stain shows a strong and diffuse block-positive staining pattern, the stain lends support to the diagnosis of HGSIL (CIN II-III).

If the p16 stain is negative or not block-positive (i.e. mottled/mosaic) the result favors LGSIL (CIN I) or a reactive process.
Cervix - p16 immunostain

Negative
Cervix – p16 immunostain

Mottled or Mosaic Staining Pattern
Case #5

59 year old woman – abnormal pap smear ASC-H, HR HPV+. She has been your patient for 4 years. She has had prior abnormal pap smears (LSIL) and also biopsies showing LGSIL, HR HPV+. Colposcopy reveals an acetowhite area at the 2-3 o’clock position that gets biopsied.
Atrophy

Cervix, biopsy at 3 to 4 o’clock position: Chronic cervicitis with reactive and atrophic change. Transformation zone is identified. No evidence of dysplasia or malignancy is identified.
Diagnoses That I Avoid

Cervix, biopsy at 6 o’clock:
Ectocervical squamous epithelium with HPV effect.
Transformation zone is identified.
What does this mean?
- Koilocytosis?
- Dysplasia?
Diagnoses That I Avoid

Cervix, biopsy at 4 o’clock:
Ectocervical squamous epithelium with CIN I-II.

What does this mean?
- Is it HGSIL and other fragments show LGSIL?
- Is it LGSIL that is p16+?
- Is it morphologically CIN II on H&E but p16 negative?
Diagnoses That I Avoid

Cervix, biopsy at 3 o’clock:
Ectocervical squamous epithelium with focal atypical squamous metaplasia.

What does this mean?
- Is it HGSIL arising in an area of metaplasia?
- Is it benign metaplasia that is inflamed and looks like dysplasia?
- Is it morphologically CIN II on H&E but p16 negative?
Case #6

47 year old woman with recent pap diagnosis of AGUS (atypical glandular cells of undetermined significance).

Patient referred by family practice physician.

Focal punctuation and abnormal vessels observed on colposcopy.

Endometrial biopsy, cervical biopsy, and endocervical curettage are performed.
Adenocarcinoma in situ

Endometrium, biopsy:
Proliferative pattern endometrium.
No atypical hyperplasia or malignancy identified.

Cervix, biopsy:
Adenocarcinoma in situ.

Endocervix, ECC:
Minute fragments of atypical endocervical glandular epithelium, compatible with AIS.
Case #7

54 year old woman with recent pap diagnosis of AGUS (atypical glandular cells of undetermined significance).

Patient referred by family practice physician.

No obvious lesion colposcopy.

Endometrial biopsy, cervical biopsy, and endocervical curettage are performed.
Endometrial adenocarcinoma

Endometrium, biopsy:
Endometrial adenocarcinoma, endometrioid type, FIGO grade 1 of 3

*if a large volume of tumor is present in both the ECC and endometrial biopsy – it is possible that the tumor an endometrioid type of endocervical adenocarcinoma...
Endometrial adenocarcinoma

Cervix, biopsy:
Chronic active cervicitis with reactive changes. Transformation zone is identified. No evidence of dysplasia or malignancy is identified.

Endocervix, ECC:
Scant fragments of negative endocervix.
Summary

Topics covered:

Atrophic and reactive changes, LGSIL (CIN I), and HGSIL (CIN II-III)
The role of the p16 immunostain.
Endocervical glandular lesions (AIS and adenocarcinoma).