Commentary
Volume 10:02, 2025

Journal of Molecular Histology & Medical Physiology

ISSN: 2684-494X

Open Access

Cervical Biopsy Interpretation in HPV-associated Lesions: Histopathological Challenges

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Introduction

Human papillomavirus (HPV) infection is the central etiological factor in the pathogenesis of cervical intraepithelial neoplasia (CIN) and cervical cancer, representing a major global health concern. While screening programs utilizing cytology and HPV testing have substantially reduced the incidence and mortality of cervical cancer in developed regions, histopathological interpretation of cervical biopsies remains the definitive method for diagnosis, grading and guiding clinical management. However, the histopathological assessment of HPV-associated lesions is fraught with interpretive challenges, including morphological overlap with benign mimics, interobserver variability and issues surrounding lesion grading and progression potential. These challenges underscore the need for standardized criteria, adjunctive biomarkers and greater awareness of HPV-associated histologic patterns among pathologists [1].

Description

Cervical biopsies are typically performed to evaluate abnormal cytologic findings or positive high-risk HPV test results and the histopathological goal is to confirm the presence and grade of CIN, which is classified as CIN 1 (low-grade), CIN 2, or CIN 3 (high-grade). The hallmark of HPV-associated lesions is the presence of koilocytosis cells exhibiting nuclear atypia and perinuclear halos along with architectural disarray and maturation disturbances within the squamous epithelium. While CIN 1 is confined to the lower third of the epithelium and exhibits mild atypia, CIN 2 and CIN 3 progressively involve the upper layers, with increased nuclear atypia, loss of polarity and mitotic activity. However, these features are not always clearly demarcated and considerable overlap exists between reactive changes, immature squamous metaplasia and true dysplasia. A significant histopathological challenge lies in differentiating CIN from benign mimickers such as reparative epithelium, atrophic changes, inflammation-induced atypia and tangentially sectioned tissue. Reactive changes may show enlarged nuclei and mitotic activity, raising concern for dysplasia, but lack the consistent nuclear enlargement, hyperchromasia and maturation arrest seen in true neoplasia. Atrophic epithelium, particularly in postmenopausal women, may appear basaloid with increased nuclear-cytoplasmic ratios, mimicking high-grade lesions. These scenarios demand careful assessment of the overall architecture, mitotic location and chromatin quality, often requiring correlation with clinical history and cytology [2].

Another persistent issue is the reproducibility of CIN grading, particularly between CIN 2 and CIN 3, which have different clinical management implications. CIN 2 is considered a biologically heterogeneous entity, with some lesions regressing and others progressing to invasive cancer. This ambiguity contributes to interobserver variability, even among experienced pathologists. In response, the Lower Anogenital Squamous Terminology (LAST) project proposed a two-tiered system low-grade and high-grade squamous intraepithelial lesions (LSIL and HSIL) to harmonize histologic and cytologic nomenclature and improve diagnostic clarity. While widely adopted, this system does not eliminate the inherent biological continuum of HPV-related lesions and decisions regarding patient management often still rely on conventional three-tiered CIN classification. To improve diagnostic accuracy, adjunctive use of immunohistochemical biomarkers such as p16^INK4a^ and Ki-67 has become increasingly common. Overexpression of p16 is considered a surrogate marker of oncogenic HPV activity and is particularly useful in distinguishing high-grade lesions from mimics. Diffuse, block-positive p16 staining supports a diagnosis of HSIL, whereas patchy or absent staining favors a benign or low-grade lesion. Ki-67, a proliferation marker, is also helpful in assessing the extent of proliferative activity, with increased suprabasal expression suggesting neoplasia. Despite their utility, these markers are not infallible and should be interpreted within the morphologic context to avoid overdiagnosis [3].

HPV genotyping and *in situ* hybridization further contribute to lesion stratification, particularly in research and equivocal cases. High-risk HPV subtypes, especially HPV 16 and 18 are strongly associated with high-grade lesions and invasive carcinoma and their detection can provide prognostic information. However, routine HPV typing in biopsy specimens is not universally performed due to cost and limited incremental value over morphological and immunohistochemical findings in most settings. The evaluation of glandular lesions and Adenocarcinoma *In Situ* (AIS) introduces additional complexities. These lesions may be subtle, exhibit skip areas and be under-recognized in superficial biopsies. AIS often coexist with HSIL and may be overlooked if not specifically considered. Furthermore, benign endocervical glands affected by inflammation or hormonal changes can exhibit nuclear enlargement and pseudostratification, mimicking neoplastic changes. Special stains and deeper levels are often necessary in such cases and awareness of subtle architectural and cytologic cues is essential for accurate diagnosis. Interobserver variability, while inherent to all histopathology, is particularly significant in cervical pathology due to the subjective nature of grading and the prevalence of borderline lesions. Studies have shown moderate agreement among pathologists in diagnosing CIN 2, emphasizing the importance of second opinions, consensus review and continued training. Digital pathology and machine learning algorithms are being developed to assist in lesion detection and grading, but their clinical integration remains in early stages [4,5].

Conclusion

In conclusion, the interpretation of cervical biopsies in HPV-associated lesions poses a number of histopathological challenges due to the morphological diversity of HPV-related changes, overlap with benign conditions and variability in lesion progression. Accurate diagnosis requires a combination of morphologic expertise, familiarity with HPV biology and judicious use of ancillary techniques such as p16 immunohistochemistry. As cervical cancer prevention efforts evolve, pathologists play a crucial role in the effective management of HPV-related disease and continued efforts toward standardization and innovation in diagnostic practice are essential for improving patient outcomes.

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Received: 03 March, 2025, Manuscript No. jmhmp-25-168577; **Editor Assigned:** 05 March, 2025, PreQC No. P-168577; **Reviewed:** 17 March, 2025, QC No. Q-168577; **Revised:** 24 March, 2025, Manuscript No. R-168577; **Published:** 31 March, 2025, DOI: 10.37421/2684-494X.2025.10.284

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Zysset, Ismael. "Cervical Biopsy Interpretation in HPV-associated Lesions: Histopathological Challenges." *J Mol Hist Med Phys* 10 (2025): 284.