Ancillary Diagnostics in Gynecologic Cytology

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KEYWORDS

• Human papillomavirus • Hybrid capture • In situ hybridization • Squamous dysplasia
• Genomic testing

KEY POINTS

- The three main ways of detecting human papillomavirus are enhanced morphology though immunochemistry, detecting high risk HPV through hybrid capture, and identification of specific HPV types through genotyping.
- Immunochemistry for Ki67 and p16 assists in identifying high risk HPV through enhancing the morphologic evaluation of the Pap test.
- Management decisions are changing based on the genotyping identification of HPV 16 or 18.

ABSTRACT

Cytology has been the mainstay of cervical dysplasia and cancer screening in the United States. The specificity of a woman harboring a high-grade lesion when identified as high-grade squamous intraepithelial lesion on Pap test is high; however, the test suffers from low sensitivity. Epidemiology studies have demonstrated that human papillomavirus (HPV) types 16 and 18 account for most cervical squamous cell carcinomas. Tests have been developed to identify high-risk HPV, some specifically to identify HPV 16 and 18. Simultaneous to the increase in HPV detection methods, interdisciplinary groups are making recommendations on the managerial use of the tests.

INTRODUCTION

Cytology has been the mainstay of cervical dysplasia and cancer screening in the United States. Specimen collection is relatively easy and painless and the specificity of a woman harboring a high-grade lesion when identified as high-grade squamous intraepithelial lesion (HSIL) on Papanicolaou (Pap) test is very high. However, the Pap test suffers from a low sensitivity (50%–70%), and as such there has been an enormous effort to improve cervical screening tests and identify more women with high-grade lesions.[1] At the same time, large epidemiology studies have demonstrated that human papillomavirus (HPV) types 16 and 18 account for the vast majority of cervical squamous cell carcinomas, have the highest binding affinity to E6 and E7, are the most common persistent HPV infections, and tend to have the most rapid progression from infection to high-grade dysplasia to carcinoma.[2] As a result of the understanding of the biology of HPV infections, tests have been developed to identify high-risk HPV (hr-HPV) and some specifically to identify HPV 16 and HPV 18. These tests have come in the form of (1) morphologic enhancement via immunohistochemistry and in situ hybridization, (2) detection of pooled hr-HPV through hybrid capture techniques, and (3) identification of specific HPV types through genotyping. Simultaneous to the increase in HPV detection methods, interdisciplinary groups are making recommendations on the managerial use of the tests and subsequent management (**Table 1**).[3]

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Table 1
Comparison of human papillomavirus (HPV) tests

	Immunocytochemistry	Hybrid Capture	Genotyping
Morphologic test	Yes	No	No
Specifically Identifies HPV 16 and 18	No	No	Yes
May cross-react with low-risk HPV	Yes	Yes	No

CYTOLOGIC DIFFERENTIAL DIAGNOSIS

In the United States, cervical morphology via the Pap test is still the most common initial screening test for the detection of cervical cancer and findings are uniformly reported by laboratories using the Bethesda System Terminology.[4] The most common abnormal cytologic diagnosis in the Pap test is "Atypical Squamous Cells" (ASC). About half of these diagnoses are secondary to reactive changes, but our ability to appropriately categorize them into reactive or HPV-related groups on morphology alone is poor.[5] The category "Atypical Squamous Cells, cannot exclude a high-grade lesion" (ASC-H) more often is associated with high-grade squamous intraepithelial lesion than ASC, but still most cases have tissue biopsies less than cervical intraepithelial neoplasia (CIN) 2.[6] Immature squamous metaplasia and atrophy are great mimickers of high-grade squamous intraepithelial lesion and are a common benign explanation of an ASC-H interpretation.[4]

All of the cytologic uncertainty is compounded by the great variability in the histologic diagnosis of CIN 2 on biopsy.[7] Additionally, the natural biology of CIN 2 is variable and not predictable on morphology alone. Some CIN 2 lesions will regress, some will persist, and some will progress to invasive carcinoma. The differential diagnosis of CIN 2 is often CIN 1 or CIN 3.

ANCILLARY STUDIES

IMMUNOCYTOCHEMISTRY AND IN-SITU HYBRIDIZATION

Immunocytochemical markers have been studied as an approach to identifying the presence of hr-HPV testing by using unstained slides or cell blocks from residual material from liquid-based Pap tests.[8,9] The benefits of immunocytochemistry are ease of implementation, low cost, and potential for automation. The most robust biomarkers evaluated in the cytology literature of HPV-induced intraepithelial lesions include $p16^{INK4a}$, Ki-67 (MIB-1), minichromosome maintenance protein 2 (MCM2), and DNA topoisomerase IIα (TOP2A), all used as stand-alone immunocytochemical markers or in combination. For a more extensive summary of immunocytochemical markers, the reader is referred to the review by Pinto and colleagues.[9]

$P16^{INK4A}$

$p16^{INK4a}$ (p16) is a surrogate marker for infection with hr-HPV. It is a prototypic INK4 protein whose function is to inhibit cyclin-dependent kinase-mediated phosphorylation of the retinoblastoma (Rb) gene product leading to downregulation of cell proliferation. In the setting of persistent infection with hr-HPV, the E7 oncoprotein binds to the host Rb protein, which results in the inactivation of Rb and release and subsequent activation of the transcription factor E2F. These actions commit the cell to division. Simultaneously, E2F causes a marked increase in the production of p16; however, its inhibitory effect on cell proliferation is lost. This paradoxic overexpression makes p16 a sensitive biomarker for HPV infections caused by hr-HPV types.[9]

The overexpression of p16 in the setting of HPV infection is evident by accumulation of the protein in the nucleus and cytoplasm. In histologic sections, strong and diffuse nuclear or nuclear plus cytoplasmic staining with p16 from the basal cell layer upward correlates well with the presence of an HSIL (**Fig. 1**).[10] In cervicovaginal samples, a positive immunocytochemical stain is demonstrated by brown cytoplasmic staining with slightly darker brown nuclear staining. p16 staining identifies cells that may be missed by standard screening alone. However, because p16 positivity also can be seen in tubal metaplasia, squamous metaplasia, endometrial cells, and Trichomonas, interpretation of the stain requires correlation with the appropriate cytomorphologic criteria of dysplasia.[11–14]

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