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[999] Biomarker (ProEx™ C, p16^{INK4A} and Mib-1) Distinction of High Grade Squamous Intraepithelial Lesions (HSIL) from Its Mimics

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Background: Topoisomerase II alpha (TOP2A) and minichromosome maintenance protein 2 (MCM2) are proteins associated with aberrant S-phase induction. The current study evaluated the performance of these biomarkers (ProEx™ C-TriPath Oncology, Burlington, NC) in the context of p16^{INK4A} and MiB-1 to distinguish high-grade squamous intraepithelial lesions (HSIL) from HSIL mimics.

Design: 96 archived cervical biopsies in which immunostains for p16 and/or MiB-1 were employed to resolve a diagnosis of HSIL vs. reactive epithelial changes were analyzed for ProEx C. Immunostains for ProEx C, p16 and MiB-1 were available for 95, 96 and 59 samples, respectively, and were classified according to distribution (on a graded system of percentage cell involved), intensity (weak or strong), and staining pattern (horizontally continuous vs. discontinuous for p16 and vertical extent in terms of layers involved for MiB-1 and ProEx C). p16 staining of >5% positive cells was scored positive; MiB-1 and ProEx C staining extending beyond the lower third was scored as positive. H-E stained slides were reviewed independently by three pathologists, scored for the presence or absence of SIL and compared across pathologists by Kappa statistic. A diagnosis of SIL or absence of SIL (NoSIL) was based on agreement by at least 2 of 3 pathologists. Chi-square test was used for statistical comparison between biomarker immunostaining and consensus diagnosis of SIL.

Results: Agreement in diagnosis of SIL across pathologists in this selected series ranged from fair to moderate (kappa=0.37 to 0.57). All three biomarkers correlated positively with the consensus diagnosis of SIL (p<0.001). Positive staining for ProEx C, p16 and MiB-1 was observed in 87% (N=52/60), 84% (N=51/61) and 94% (34/36) of SIL and negative in 71% (N=25/35), 63% (N=22/35) and 52% (N=12/23) of diagnoses of NoSIL. The combination of p16/ProEx C predicted more SIL (92%, N=33/36) and NoSIL (61%, N=14/23) than p16 plus MiB-1 (94%, N=34/36 and 43%, N=10/23), but this difference was not statistically significant.

Conclusions: ProEx C appears to have the best combination of sensitivity plus specificity for distinguishing HSIL from its mimics. The combination of p16/ProEx C may be a better discriminant than p16/Mib-1 pending confirmation by a larger case series.

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