Distinctive Immunohistochemical Profile of Penile Intraepithelial Lesions: A Study of 74 Cases

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Abstract: Several classification schemes for penile precancerous lesions have been proposed, but none of them seems to correlate with the current understanding of penile cancer pathogenesis. Recently, a system, which takes into account morphologic features and purported etiopathogenesis, was proposed, separating penile intraepithelial neoplasia (PeIN) in differentiated and warty/basaloid subtypes. This study was designed to seek an immunohistochemical profile that can be helpful in the classification and differential diagnosis of penile epithelial abnormalities and precancerous lesions using the aforementioned system. The immunohistochemical panel included stains for $p16^{INK4a}$, p53, and Ki-67. For $p16^{INK4a}$ immunostaining, only full-thickness positivity in all epithelial cells was considered as positive; for p53 and Ki-67 immunostaining, patchy or diffuse nuclear positivity above the basal layer was considered as positive. Seventy-four lesions in 59 patients were selected and classified as follows: differentiated PeIN, 34 cases; squamous hyperplasia (SH), 21 cases; basaloid PeIN, 15 cases; and warty PeIN, 4 cases. The mean age of patients was 64 years. Forty-two lesions (56.8%) were located in the glans and 32 (43.2%) in the foreskin. Overexpression of $p16^{INK4a}$ was useful for distinguishing SH from warty/basaloid PeINs (0% vs. 94.7%, $P < 0.0001$) but not SH from differentiated PeINs (0% vs. 5.9%, $P = 0.519$). In addition, $p16^{INK4a}$ allowed the distinction of differentiated and warty/basaloid PeINs (5.9% vs. 94.7%, $P < 0.0001$). Immunohistochemistry results for p53 allowed the separation of SH and differentiated PeIN (9.5% vs. 44.1%, $P = 0.0078$) and SH and warty/basaloid PeIN (9.5% vs. 55.6%, $P = 0.0042$). Ki-67 immunostain was useful for distinguishing SH from differentiated PeIN (52.6% vs. 89.7%, $P = 0.0062$) and SH from PeIN with warty and/or basaloid features (52.6% vs. 100%, $P = 0.0011$). There seems to be a distinctive immunohistochemical profile for associated and precursor epithelial lesions of the penis. SH was $p16^{INK4a}$ and p53 negative, with variable Ki-67 positivity. Differentiated PeIN was $p16^{INK4a}$ negative and Ki-67 positive, with variable p53 positivity. Basaloid and warty PeINs were consistently $p16^{INK4a}$ and Ki-67 positive, with variable p53 positivity. The use of a triple $p16^{INK4a}$/p53/Ki-67 immunohistochemical panel was found to be helpful in the classification, differential diagnosis, and morphologic standardization of penile intraepithelial lesions.

Key Words: penile intraepithelial neoplasia, carcinoma in situ, squamous hyperplasia, differentiated penile intraepithelial neoplasia, warty/basaloid penile intraepithelial neoplasia

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Historically, criteria for nomenclature and diagnosis of penile precursor lesions have been variable and confusing.[8,9] Erythroplasia of Queyrat and Bowen disease, albeit morphologically similar under the microscope, are clinical terms used for lesions arising either in the mucosal or cutaneous penile surface, respectively.[17] The usage of these terms is common in current urological practice.[4,7,17] Akin to the terminology in use for cervical precancerous lesions, the denomination of penile squamous intraepithelial lesion, further categorized in low-grade and high-grade variants, was proposed for precursor lesions of the penis and morphologic criteria for diagnosis were given.[8,9] Despite the simplicity and reproducibility of such a classification system, it shows no correlation with the current understanding we have about the bimodal pathogenic pathway of penile carcinomas.[4,13,14,16,21] In this respect, whereas most precancerous and infiltrating carcinomas of the uterine cervix are composed of basaloid and nonkeratinizing cells,[25,26] in our experience less than one half of penile squamous cell carcinomas (SCCs), either in situ or invasive, exhibit such morphologic appearance.[6,11,13,21] Furthermore, most cervical in situ and invasive carcinomas show evidence of human papillomavirus (HPV) infection,[1] whereas the virus is found in only 22% to 42% of all invasive penile carcinomas,[11,13,21] with a reported higher incidence (60% to 100%) in noninvasive lesions.[4,12] Reasons for this discrepancy are not apparent, but they may be related to geographical differences in the predominant type of in situ lesions.[23] Recently, we proposed a new classification system for penile precursor lesions, separating them into 4 categories:

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