Human Papillomavirus (HPV) Genotypes in Condylomas, Intraepithelial Neoplasia, and Invasive Carcinoma of the Penis Using Laser Capture Microdissection (LCM)-PCR

A Study of 191 Lesions in 43 Patients

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Abstract: Laser capture microdissection-polymerase chain reaction (LCM-PCR) supported by $p16^{INK4a}$ was used for the first time to demonstrate human papillomavirus (HPV) DNA in histologically specific penile lesions, which were as follows: squamous hyperplasia (12 lesions, 10 patients), flat lesions (12 lesions, 5 patients), condylomas (26 lesions, 7 patients), penile intraepithelial neoplasia (PeIN) (115 lesions, 43 patients), and invasive squamous cell carcinomas (26 lesions, 26 patients). HPV was detected by whole-tissue section and LCM-PCR. LCM proved to be more precise than whole-tissue section in assigning individual genotypes to specific lesions. HPV was negative or very infrequent in squamous hyperplasia, differentiated PeIN, and low-grade keratinizing variants of carcinomas. HPV was strongly associated with condylomas, warty/basaloid PeIN, adjacent flat lesions, and warty/basaloid carcinomas. A single HPV genotype was found in each lesion. Some condylomas and flat lesions, especially those with atypia, were preferentially associated with high-risk HPV. Unlike invasive carcinoma, in which few genotypes of HPV were involved, there were 18 HPV genotypes in PeIN, usually HPV 16 in basaloid PeIN but marked HPV heterogeneity in warty PeIN (11 different genotypes). Variable and multiple HPV genotypes were found in multicentric PeIN, whereas unicentric PeIN was usually related to a single genotype. There was a correspondence among HPV genotypes in invasive and associated PeIN. $p16^{INK4a}$ was positive in the majority of HPV-positive lesions except condylomas containing LR-HPV. $p16^{INK4a}$ was usually negative in squamous hyperplasia, differentiated PeIN, and low-grade keratinizing variants of squamous cell carcinomas. In summary, we demonstrated that LCM-PCR was a superior research technique for investigating HPV genotypes in intraepithelial lesions. A significant finding was the heterogeneity of HPV genotypes in PeIN and the differential association of HPV genotypes with subtypes of PeIN. The presence of atypia and high-risk HPV in condylomas and adjacent flat lesions suggests a precursor role, and the correspondence of HPV genotypes in invasive carcinomas and associated PeIN indicates a causal relation. Data presented support the bimodal hypothesis of penile cancer carcinogenesis in HPV-driven and non-HPV-driven carcinomas and justify the current WHO pathologic classification of PeIN in special subtypes.

Key Words: human papillomavirus, laser microdissection, polymerase chain reaction, penile neoplasm, penile squamous cell carcinoma, penile intraepithelial neoplasia, condyloma

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Penile carcinoma is rare with an estimated 22,000 new cases reported worldwide each year, but the incidence varies widely from country to country and within regions. The highest rates are in Africa, South America, and Asia (2 to 4/100,000 inhabitants).[1] Penile cancer has been associated with a number of environmental risk factors.[2] As with the vulva and head and neck, penile carcinomas are thought to develop through 2 carcinogenic pathways: a non-human papillomavirus (HPV)-related pathway and an HPV-related pathway. Overall, HPV prevalence in penile cancer is between 33% and 63%, with HPV being more prevalent in developed countries.[3–6] It has been suggested that the 2 pathways of penile carcinogenesis show different histologic features.[7,8] The new WHO histologic classification of penile carcinoma reflects this and separates invasive neoplasia into HPV related and non-HPV related. In the first group, tumors with warty or basaloid morphology predominate, and in the second group there are more differentiated keratinizing variants of squamous cell carcinomas (SCC) and sarcomatoid carcinomas.[9,10] Penile intraepithelial neoplasia (PeIN) is

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