Clear Cell Carcinoma of the Penis: An HPV-related Variant of Squamous Cell Carcinoma

A Report of 3 Cases

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Abstract: Penile clear cell carcinoma originating in skin adnexal glands has been previously reported. Here, we present 3 morphologically distinctive penile tumors with prominent clear cell features originating not in the penile skin but in the mucosal tissues of the glans surface squamous epithelium. Clinical and pathologic features were evaluated. Immunohistochemical stains were GATA3 and p16. Human papilloma virus (HPV) detection by in situ hybridization was performed in 3 cases, and whole-tissue section-polymerase chain reaction was performed in 1 case. Patients' ages were 52, 88, and 95 years. Tumors were large and involved the glans and coronal sulcus in all cases. Microscopically, nonkeratinizing clear cells predominated. Growth was in solid nests with comedo-like or geographic necrosis. Focal areas of invasive warty or basaloid carcinomas showing in addition warty or basaloid penile intraepithelial neoplasia were present in 2 cases. There was invasion of corpora cavernosa, lymphatic vessels, veins, and perineural spaces in all cases. p16 was positive, and GATA3 stain was negative in the 3 cases. HPV was detected in 3 cases by in situ hybridization and in 1 case by polymerase chain reaction. Differential diagnoses included other HPV-related penile carcinomas, skin adnexal tumors, and metastatic renal cell carcinoma. Features that support primary penile carcinoma were tumor location, concomitant warty and/or basaloid penile intraepithelial neoplasia, and HPV positivity. Clinical groin metastases were present in all cases, pathologically confirmed in 1. Two patients died from tumor dissemination at 9 and 12 months after penectomy. Clear cell carcinoma, another morphologic variant related to HPV, originates in the penile mucosal surface and is probably related to warty carcinomas.

Key Words: clear cell carcinoma, penile carcinoma, HPV

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There are several subtypes of penile squamous cell carcinomas according to the new WHO classification of tumors of the male genital system.[1] Because of their morphologic distinctiveness and sufficient evidence for a bimodal etiopathogenesis of penile cancer[2] the subtypes were grouped into human papilloma virus (HPV) and non-HPV-related carcinoma. In the first category are the basaloid, warty (condylomatous), warty-basaloid, papillary basaloid, and lymphoepithelioma-like carcinomas.[3–5] The importance of identifying these tumors is not only etiological or morphologic but has to do with the better prognoses reported for tumors associated with HPV in the penis and other sites.[6–15] Some studies found no prognostic difference in HPV-positive and HPV-negative patients.[16,17] Here we report 3 patients with penile clear cell squamous cell carcinomas associated with HPV, adding to the list of morphologically distinctive HPV-related penile squamous cell carcinomas.

MATERIALS AND METHODS

Clinical and pathologic materials from 3 patients diagnosed at the Instituto de Patología e Investigación were evaluated. Pathologic specimens consisted of 3 penectomies (2 total and 1 partial). An average of 15 sections per case were studied.

Immunohistochemical studies and in situ hybridization were performed at the Department of Pathology, Massachusetts General Hospital, Boston, MA, on 5-μm-thick tissue sections in a Bond III automated immunostainer (Leica Microsystems, Bannockburn, IL), using primary antibodies against GATA3 (L50-823, 1:250; Biocare Medical, Concord, MA) and p16 (16P04, 1:4; Ventana Medical Systems, Tucson, AZ) and DNA in situ hybridization probes against HPV16 and 18 (prediluted,

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