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Condylomata acuminata, Bowenoid papulosis, and squamous cell carcinoma, all positive for human papillomavirus type 16/18 DNA, coexisting in the genital area: a case report*

Efstathia Pasmatzi[1] ✉, George Badavanis[1], Nikiforos Kapranos[2], Alexandra Monastirli[1], Assimina Apostolidou[1], Dionysios Tsambaos[1]

[1]*Department of Dermatology, School of Medicine, University of Patras, Patras, Greece.* [2]*Laboratory for Molecular Histopathology, Athens, Greece.*

Abstract

In an attempt to raise awareness among physicians of the importance of early diagnosis and treatment of penile cancer and its precursor lesions, we report the unique case of a male patient with condylomata acuminata, Bowenoid papulosis, and squamous cell carcinoma, all HPV 16/18–positive, coexisting in his genital area.

Keywords: human papillomavirus, condyloma acuminatum, Bowenoid papulosis, squamous cell carcinoma

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Introduction

Human papillomaviruses (HPVs) constitute a large and heterogeneous group of non-enveloped small circular double-stranded DNA viruses with a life cycle closely associated with keratinocytes undergoing terminal differentiation (1). HPVs affect the stratified squamous epithelia of the skin and cause a large spectrum of benign and malignant mucocutaneous disorders (2).

More than 200 HPV types have been identified so far (3). Among them, about 50 are capable of affecting the genital tract in both sexes, being classified as "low-risk" and "high-risk" according to the degree of their oncogenic potential (4). Thus, "low-risk" HPV types are thought to cause mostly benign clinical manifestations, whereas "high-risk" ones are associated with anogenital cancer (5, 6).

Genital HPV infection in men is the most common sexually transmitted disease; it occurs on the penis of 16 to 69% of healthy men (depending on the methodology applied and the population studied) and may progress to clinical manifestations that are classified into three distinct groups: a) condylomata acuminata, b) penile intraepithelial neoplasia (PIN), which encompasses three clinically distinct variants (Bowenoid papulosis, or BP; erythroplasia of Queyrat, or EQ; and Bowen's disease, or BD, sharing the histological features of squamous cell carcinoma, or SCC, in situ), and c) SCC (7, 8).

We report herein the first case of coexisting condylomata acuminata, BP, and SCC, all HPV 16/18–positive, in the genital area of a male patient.

Case report

A 62-year-old Caucasian, heterosexual, HIV-negative man presented to the Department of Dermatology at the Patras University Medical Center with quite a remarkable 6-year history of "warts" in the genital area. Because some of the initial lesions disappeared within several months, the patient thought that all the lesions would resolve over time; therefore he did not seek any medical advice and care. However, not only did the skin lesions show no sign of resolution, but they progressively increased in number and size. About 2 years prior to the patient's presentation, a preexisting lesion on the penis shaft started growing rapidly and progressively transformed into an extensive ulcer. It was only when this penile lesion showed extreme deterioration that the patient managed to overcome his fear and shame and seek medical help. He had a history of diabetes mellitus, hypertension, and hyperlipidemia, but no history or evidence of infectious, autoimmune, or neoplastic disorders.

Physical examination revealed the following clinical manifestations (Fig. 1): 1) several small flesh-colored papules on the left

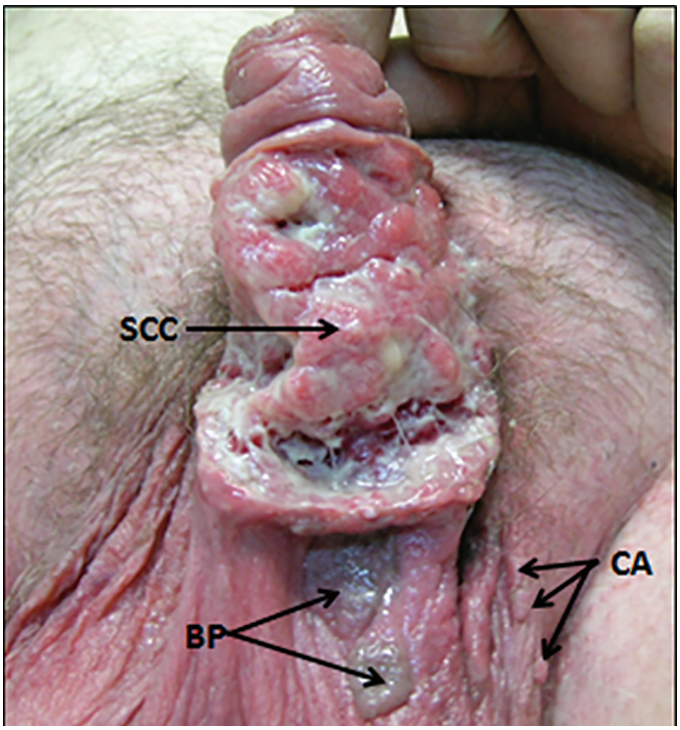

Figure 1 | Small flesh-colored papules on the left inguinal area (condylomata acuminata, CA); multiple reddish-gray shiny papules coalescing into two annular plaques located on the subscrotal area (Bowenoid papulosis, BP); a large, multinodular, erosive, hemorrhagic, and locally destructive mass that affects the penis shaft, producing a yellowish discharge (squamous cell carcinoma, SCC).

✉ Corresponding author: pasmatzi@otenet.gr; efipas@upatras.gr

*Dedicated to the memory of Professor Dr. John Varakis, Department of Anatomy, School of Medicine, University of Patras, Patras, Greece.

inguinal area, 2) multiple reddish-gray shiny papules coalescing into two annular plaques located on the subscrotal area, 3) a large, multinodular, erosive, hemorrhagic, and locally destructive mass on the penis shaft producing a yellowish discharge, and 4) large and indurated inguinal and axillary lymph nodes.

Microbiological examination of secretion samples derived from the lesion on the penis shaft revealed the presence of *Proteus vulgaris* and *Serratia marcescens*. Based on the results of the antibiogram, the patient was given a 14-day course of intravenous administration of ciprofloxacin (500 mg × 2/day) and clindamycin (400 mg × 3/day), which led to a complete resolution of inflammation and exudate.

Routine laboratory tests, including a complete blood count, blood chemistry, urinalysis, and immunological and serological investigations—tests for syphilis, herpes simplex virus 1 and 2 (HSV 1 & 2), human immunodeficiency virus 1 and 2 (HIV 1 & 2), hepatitis A, B, and C, and cytomegalovirus (CMV)—were either negative or within normal limits. Chest X-ray and bone scanning investigations, electrocardiogram, and colonoscopy were unremarkable. Whole-body computer tomography (CT) revealed large inguinal, axillary, and paratrachial lymph nodes and right pleura thickening.

Histological examination of skin biopsy specimens obtained from the lesions on the left inguinal area, the subscrotal region, and the penis shaft revealed the features of condylomata acuminata, BP, and SCC respectively (Figs. 2a–c). *In situ* hybridization performed on routinely formalin-fixed and paraffin-embedded specimens using commercially available biotinylated HPV-DNA probes (Rembrand Kit, PanPath, Amsterdam, Netherlands) revealed the presence of HPV types 16/18 in the nuclei of keratinocytes in all lesions (Figs. 2d–f).

Because we informed the patient about the results of the histopathological, imaging, and routine laboratory investigations performed and suggested urgent surgical intervention, he requested his transfer to the urology department at a hospital in his hometown, where he underwent a radical penectomy, after which he was lost to follow up.

Discussion

Condylomata acuminata are the most common clinical manifestation of HPV infection that primarily involves the skin and mucosae of the anogenital region, affecting about 1% of sexually active adults worldwide with increasing incidence (9, 10). Condylomata

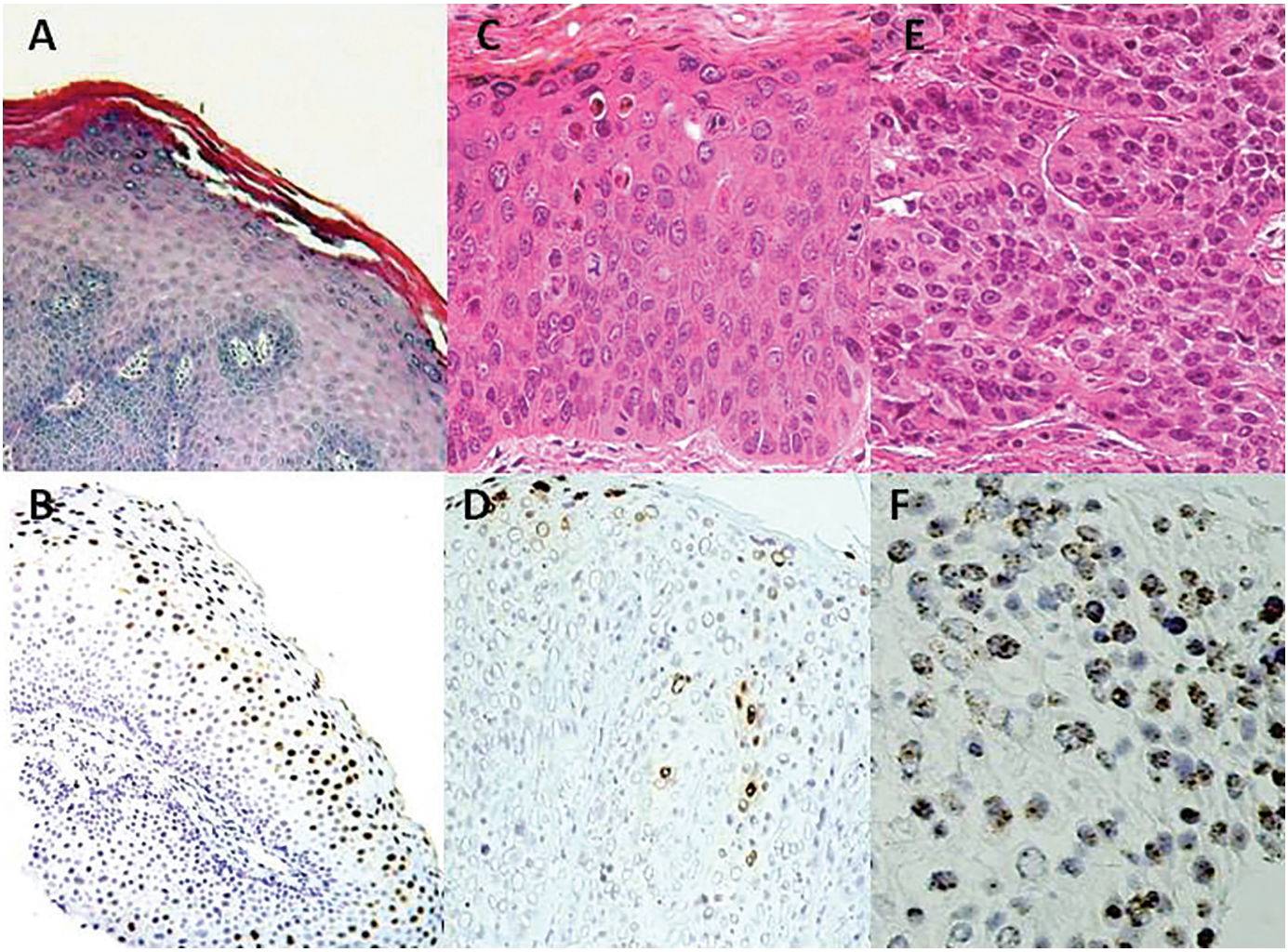

Figure 2 | Condylomata acuminata: (A) histological section showing orthokeratosis and epidermal hyperplasia with papillomatosis, acanthosis, and koilocytes in the granular and the upper spinous layer (H&E, original magnification 100×); (B) hybridization *in situ* showing clear positivity for HPV types 16/18 in many epidermal cell nuclei (DAB/peroxidase, original magnification 100×); Bowenoid papulosis: (C) histological section showing full thickness replacement of epidermis by large dyskeratotic or atypical cells with loss of polarity and atypical mitoses (H&E, original magnification 400×); (D) hybridization *in situ* showing rare, and mostly superficial intranuclear epidermal cell positivity for HPV types 16/18 (DAB/peroxidase, original magnification 400×); squamous cell carcinoma: (E) histological section showing squamous cells with eosinophilic cytoplasm, severe nuclear atypia, and many mitoses; keratin pearl formation is not evident (H&E, original magnification 400×); (F) hybridization *in situ* for HPV types 16/18. The signal is localized in almost all neoplastic cell nuclei and has the form of intranuclear dots, suggesting integration of HPV DNA in the host cell genome (DAB/peroxidase, original magnification 600×).

acuminata are acquired through sexual contact with an affected person and are highly infectious, with a transmission rate of about 65% (11, 12). In uncircumcised men, condylomata acuminata most commonly affect the glans penis, coronal sulcus, preputial cavity, and frenulum, whereas in circumcised men they mostly occur on the penile shaft (13).

Clinically, they are characterized by usually asymptomatic flesh-colored, red, or brown, solitary or confluent, smooth-surfaced or warty papules, and their histological features include acanthosis, parakeratosis, koilocytosis, and papillomatosis. In about 30% of clinically evident condylomata acuminata, spontaneous regression can occur within 12 to 24 months, whereas in other cases condylomata acuminata may persist for months or years and occasionally progress to intraepithelial neoplasia or even to life-threatening invasive SCC, as reported for the first time by Buschke and Loewenstein (1931) 90 years ago (14, 15).

In immunocompromised individuals (e.g., HIV-infected patients and organ transplant recipients), condylomata acuminata are more often seen (compared to healthy individuals), occur even in unusual localizations, and reveal a high tendency to recurrence and malignant transformation (16). In up to 95% of condylomata acuminata cases, HPV types 6 and 11 are the main etiological agents of the disease; in rare instances, however, other HPV types, even high-risk ones, are also implicated in the mechanisms of the development of condylomata acuminata (Table 1) (13, 17, 18, 38–46).

In 1970, Lloyd (19) was the first to describe an uncommon skin condition primarily affecting the anogenital area of sexually active individuals that was characterized by pink, red, or brown, solitary or confluent verrucous papules. These lesions clinically resembled those of condylomata acuminata or lichen planus and were histologically similar to BD (19). Several years later, Wade et al. (20) recognized this disorder as a distinct nosological entity, for which they introduced the term *Bowenoid papulosis* (BP). This was previously regarded as a benign disorder, which in immunocompetent individuals occasionally reveals spontaneous regression; however, today it is well known that BP is a variant of high-grade intraepithelial neoplasia or SCC *in situ* caused by HPV infection that, if left untreated, may progress to BD and invasive SCC after some years of persistence (21, 22). BP is primarily due to HPV16 and/or HPV18 infection, with a prevalence of up to 69.2%, and less frequently due to a variety of other HPV types, as shown in Table 1 (23, 24, 47–54).

Penile carcinoma is a relatively rare and devastating tumor that predominantly affects elderly men. It has the highest incidence between 50 and 70 years of age and accounts for 0.3 to 0.5% of all male malignancies in Europe and the United States (25–27). SCC represents 95% of all penile carcinomas and usually originates from the epithelium of the inner prepuce and glans and less often on the penile shaft; its invasive form manifests as a painful ulcerative and/or papillary lesion, which progressively grows and is associated with discharge, bleeding, or foul odor (28).

Penile SCC may develop either de novo or subsequent to malignant transformation of precursor lesions. Recent epidemiological studies have shown that the occurrence of penile SCC is related to HPV infection and multiple risk factors; thus, two major causative pathways are thought to be implicated in penile SCC development: a) the HPV-associated pathway, probably involving sexual contact, and b) a non-HPV-associated pathway related to risk factors such as lack of circumcision in childhood, cigarette smoking, phimosis, poor penile hygiene and trauma, multiple sexual partners, balanitis xerotica obliterans, lichen sclerosus et atrophicans, and ultraviolet A phototherapy of the genital area (15, 29–32).

In view of these pathways, penile carcinomas are classified by the Union for International Cancer Control (UICC) into HPV-associated and non-HPV-associated (33). The reported overall prevalence of HPV infection in penile SCC varies between 11.6 and 100% due to the heterogeneity of this tumor and differences between the studies performed with regard to the methodology applied and the characteristics of the populations studied (34, 35). The following histologic subtypes of HPV-associated penile SCCs are recognized: basaloid, papillary basaloid, warty, warty basaloid, clear-cell, and lymphoepithelioma-like carcinoma, with the basaloid and warty penile SCC subtypes showing the strongest HPV-association (13, 36). Worldwide, HPV 16 (followed by HPV 18 and HPV 6) is identified in the majority of HPV-mediated penile SCCs (34, 35) irrespective of geographic area, whereas on some occasions other HPV-genotypes are also etiologically implicated in the pathogenesis of these tumors, as shown in Table 1 (55–61).

Although the exact mechanisms underlying HPV-induced penile carcinogenesis are still far from being clearly understood, there is no doubt that viral oncoproteins E6 and E7 transcribed in HPV-affected epithelial cells play a critical role in this process. Indeed, apart from their disruptive effects on centrosome synthesis (6), viral E6 and E7 oncoproteins target tumor protein 53 (p53) and retinoblastoma 1 (RB1) tumor suppressor proteins, respectively, which negatively regulate the mitotic activity of the affected cells, resulting in uncontrolled cell cycle progression and an inhibition of DNA repair and apoptosis (26, 37).

To the best of our knowledge, this is the first time that the coexistence of condylomata acuminata, BP, and SCC in the genital region of a male patient has been reported, with all these disorders being positive for HPV 16/18, as demonstrated by *in situ* hybridization. The possibility that these HPV-associated diseases developed de novo independently of each other cannot be definitely ruled out. However, in view of their persistence and long duration as well as the common causative factor (HPV 16/18), which is capable of inducing a neoplastic phenotype in the affected epithelial cells, it seems reasonable to suggest that these lesions are etiologically related to each other and represent clinical manifestations of different stages of a single HPV-related cutaneous carcinogenesis process.

Table 1 | Distribution of HPV types in HPV-associated genital diseases in men.

Disease	Distribution of HPV types*	References
Condylomata acuminata	**6**, **11**, 16, 18, 30, 31, 32, 33, 34, 35, 39, 40, 41, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 74, 79, 81, 82, 83, 84	13, 17, 18, 38, 39, 40, 41, 42, 43, 44, 45, 46
Bowenoid papulosis	1, 2, 6, 11, 13, **16**, **18**, 31, 32, 33, 34, 35, 39, 42, 43, 44, 51, 52, 53, 58, 67	23, 24, 46, 47, 48, 49, 50, 51, 52, 53, 54
Squamous cell carcinoma	6, 8, 11, 12, **16**, 17, **18**, 20, 23, 31, 32, 33, 34, 35, 39, 40, 44, 45, 51, 52, 56, 58, 59, 66,68, 70, 73, 74	5, 34, 35, 55, 56, 57, 58, 59, 60, 61

*Numbers in bold represent HPV types with the highest prevalence.

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