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Vulval intraepithelial neoplasia and periungual Bowen's disease concordant for mucosal (HPV-34) and epidermodysplasia verruciformis (HPV-21) human papillomavirus types

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Summary

Human papillomavirus (HPV) infection is associated with genital malignancy and specific cutaneous malignancies. We report a case of an HPV-associated concurrent vulval intraepithelial neoplasia and periungual Bowen's disease in a young immunocompetent Afro-Caribbean woman with no known risk factors for either disease. HPV genotyping studies detected multiple α and β papillomaviruses with concordance for HPV-34 [a high-risk (HR) mucosal type], and HPV-21 [an epidermodysplasia verruciformis (EV) type] in both vulval and finger tissue. Although the HR-mucosal viruses detected are likely to have a pathogenic role in vulval intraepithelial neoplasia, this is the first report of concordance for EV HPV types in both genital and nongenital skin premalignancies. This case, in the context of accumulating epidemiological and experimental data in cutaneous SCC, raises the question of whether EV HPV may contribute to vulval malignancy, and further study is merited.

Human papillomavirus (HPV) infection is associated with genital malignancy and specific cutaneous malignancies. We report a case of an HPV-associated concurrent vulval intraepithelial neoplasia and periungual Bowen's disease in a young immunocompetent woman where HPV genotyping studies showed concordance for a high-risk mucosal and an EV type HPV.

Report

A 23-year-old Jamaican student presented in June 2003 with a 4-year history of an enlarging vulval lesion, and an 11-year history of a slowly extending lesion on her left index finger. She was a nonsmoker and had never been sexually active. Her medical history was unremarkable, without abnormal response to vaccinations, unusual childhood illness or prolonged wart infection. There was no relevant family history; in particular, her mother had never had genital or cervical disease. Examination revealed an extensive verrucous vulval lesion extending perianally (Fig. 1), and a hyperkeratotic, hyperpigmented plaque with associated nail dystrophy on the left index finger (Fig. 2).

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Excision biopsy of the vulval lesion revealed vulval intraepithelial neoplasia (VIN)-3, but no microinvasive squamous cell carcinoma (SCC). However, digital biopsy showed SCC *in situ* (Bowen's disease; BD). Cervical smear, routine blood tests, haemoglobin electrophoresis, CD4:CD8 T cell ratio, testing for human immunodeficiency virus (on two occasions) and human T-cell lymphotropic virus, hepatitis serology and a screen for sexually transmitted infections were normal or negative. At 6 months, recurrent disease was apparent at the left labium majus and interlabial sulcus, and was treated with topical imiquimod 5% cream applied 3 times weekly for 16 weeks. Despite this, an enlarging nodule developed on the left labium majus, biopsy of which showed VIN-3 with areas of incipient invasion. Surgical excision again showed VIN-3 but no invasive carcinoma.

The digital BD was treated with imiquimod concurrently with the vulva, but disease progression was evident after 3 months. This area was therefore treated by nail removal, a single cycle of curettage and electrocautery, and two cycles of topical photodynamic therapy using methylaminolaevulinate and a noncoherent red light source (633 nm $\pm$ 15 nm; Paterson PDT Omnilux, Phototherapeutics limited, Altrincham, UK) with an irradiance of 80 mW/cm² and total dose of 75 J/cm². Despite this, hyperkeratosis remained, and the patient underwent radical excision of the skin of the distal phalanx. BD but no invasive carcinoma was seen histologically. The patient had no evidence of digital disease 3 months later but was treated with topical imiquimod to the vulva and was maintained on acitretin.

We examined fresh-frozen lesional tissue for the presence of HPV DNA by degenerate PCR, using a technique that detects a broad spectrum of cutaneous, mucosal and epidermodysplasia verruciformis (EV) HPV types.¹ Four distinct HPV types were detected in the Bowen's disease and three distinct types in the VIN (Table 1). There was concordance for HPV-34 [a high-risk (HR) mucosal type], and HPV-21 (an EV type) in both tissues.

The HPV family of DNA tumour viruses are important human carcinogens. Phylogenetic classification largely reflects tissue-specific tropism, with mucosal (α), EV (β) and other cutaneous (γ , μ and ν) viruses.² Mucosal types HPV 16 (and related types including 31 and 58), 18 and 34 are termed high risk (HR), as they have the ability to immortalize human keratinocytes and are overwhelmingly implicated in causing cervical carcinoma and intraepithelial neoplasia. HPV-34 was first described in a female patient with periungual BD who had a history of cervical carcinoma.³

The EV viruses are associated with epidermodysplasia verruciformis, an inherited predisposition to cutaneous SCC in sun-exposed sites on a background of extensive and atypical warts. There is increasing evidence that HPV, and EV HPV types in particular, may play a cofactor role in SCCs of nongenital skin. Mucosal HPV types are not frequently implicated in cutaneous SCC except for the periungual site, where they have consistently been isolated, often in association with genital disease. There have been 9 previous reports describing 13 patients in which the same mucosal HPV type was isolated from anogenital and digital dysplasia or malignancy.⁴⁻⁷ HPV-16 was identified in 85% patients (11/13), including one co-infection with HPV-18. HPV-58 and HPV-35 have each been reported once. In these reports, genital disease invariably predated digital disease, and autoinoculation of mucosal HPV from genital to digital skin has been postulated. It has been suggested that periungual skin is susceptible to such infection due to the propensity of the fingers and nail unit to trauma. In contrast, in our patient, digital disease occurred in childhood and appeared to predate genital disease by at least 8 years.

While EV HPV types are now recognized to be ubiquitous in normal nongenital skin and hair follicles from early childhood, the source of the HR mucosal types is uncertain. One possibility is that mucosal HPV was acquired through vertical transmission from the

patient's mother. Vertical transmission with subsequent persistent HPV-16 infection has been demonstrated in infants born to mothers positive for HPV-16 in the cervix.⁸ Furthermore, hair follicles in the genital skin can act as a reservoir for HR-mucosal HPV types.⁹ Thus, a speculative explanation for this unusual sequence of clinical and virological events in our patient may be autoinoculation of vertically transmitted HR mucosal HPV types together with autoinoculation of acquired EV HPV types, genital hair-follicle carriage, and subsequent development of vulval disease. In addition to HPV-21 and -34, HR mucosal type 31 was isolated from vulval tissue, and HR mucosal type 58 and EV types 21 and 49 isolated from the finger in our patient. Such multiple HPV coinfections are well recognized in immunosuppressed patients. It is possible that an immune paresis, perhaps specific for HPV, could account for this unusual case, but to date no such underlying condition has been found.

This is the first report of multiple, simultaneous infection by both HR mucosal and EV HPV types in vulval and finger premalignancies. While the presence of one or more of the (concordant or not) HR mucosal types in the VIN or BD is likely to be causal, the contribution of EV infection is less clear. The presence of these viruses may be incidental, and does not necessarily imply a pathogenic role. In a pilot study of patients with current or previous genital warts, mucosal types 6 and 11 were identified in pubic or perianal but not eyebrow hair, whereas EV viruses were found in similar proportions in pubic and eyebrow hair,¹⁰ suggesting a possible bystander role for the EV types. Concordance for EV HPV-21 may, however, be relevant in the light of accumulating data concerning the role of EV HPV in cutaneous SCC. EV HPV carriage in normal skin and hair follicles is a risk factor for SCC,¹¹ and preliminary seroepidemiological studies also confirm an association between EV HPV seropositivity and SCC risk. It has been demonstrated that EV HPV DNA is present and transcriptionally active in a proportion of SCC tumour cells, and that viral load is highest in premalignant lesions.¹² Functional studies have provided further support for a possible cofactor role for EV HPV in skin carcinogenesis, through diverse mechanisms including inhibition of apoptosis, expression of an invasive phenotype and abrogation of DNA repair,¹³ not all of which necessarily interact with UVR. Thus, we propose that a possible contribution of EV HPV to vulval malignancy warrants further study.

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Figure 1.
Vulval disease at presentation with extensive hyperpigmented, hyperkeratotic, verrucous lesion, which also extended perianally.

Figure 2.
Plaque affecting left index finger with associated linear nail dystrophy.

Table 1

Results of HPV genotyping of finger and vulval tissue.

Site	HPV type	Papillomavirus genus2	Primer pair used for detection1
Vulva	21	β papillomavirus	CP65/CP68
	31	α papillomavirus	MY11/GP6
	34	α papillomavirus	CN1F/CN1R
Finger	21	β papillomavirus	CP65/CP68
	34	α papillomavirus	CN1F/CN1R
	49	β papillomavirus	EN3F/EN3R
	58	α papillomavirus	MY11/GP6

Degenerate PCR and direct sequencing was performed using a panel of nine primer pairs (seven nested, one semi-nested and one single round) and terminator cycle sequencing (ABI Prism d-rhodamine; Applied Biosystems). HPV genotype was assigned after comparison of the consensus sequence with the GenBank database using the GCG Blast program.