Development of multiple human papillomavirus-16-associated digital squamous cell carcinomas and human papillomavirus-16-associated oral squamous cell carcinoma in an immunocompetent adult

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Key words: cutaneous; digital; HPV; HPV16; human papillomavirus; mouth; nail; nail apparatus; nail unit; oral; periungual; SCC; SCC in situ; SCCis; squamous cell carcinoma; squamous cell carcinoma in situ; ungual.

INTRODUCTION

The oncogenic role of human papillomavirus (HPV) in anogenital and oropharyngeal squamous cell carcinoma (SCC) is well-established.[1] Skin and adnexal HPV-associated SCC primarily localizes to the hands and feet, particularly surrounding the nail bed.[2] Approximately 60% to 80% of nail SCCs are associated with high-risk HPV subtypes, most commonly HPV-16.[1] HPV-16 is also the subtype most often associated with oral SCC.[2]

Herein, we describe the case of an immunocompetent male who developed 12 digital SCC in situ (SCCis) lesions, and of 8 tested, all were positive for high-risk HPV and/or HPV-16. The patient also developed HPV-16-associated oral SCCis. Both the number of digital lesions and the concomitant presentation of cutaneous and oral HPV-16-associated SCCis in an immunocompetent adult make this case unique.

Abbreviations used:

HPV:	human papillomavirus
MMS:	Mohs micrographic surgery
SCC:	squamous cell carcinoma
SCCis:	squamous cell carcinoma in situ

CASE REPORT

A 30-year-old male presented with peeling fingernails. He had unsuccessfully self-treated his nails with antifungal nail varnish, tea tree oil, vinegar, and bleach. Examination was notable for loss of the left first and third fingernails and subungual, verrucous thickening. Nail clipping with periodic acid-Schiff stain was negative for fungi; however, fungal culture was positive for Aspergillus species. He was treated with itraconazole for 4 months and terbinafine for 6 weeks without improvement.

Three years later, he presented with nail plate loss and warty plaques encompassing the nail bed and hyponychium, extending under the proximal nailfold on the left first and third fingernail. The left fourth fingernail was notable for distal radial onycholysis and brown subungual debris, and the right second fingernail for radial onycholysis with a verrucous papule on the distal nail bed and lateral

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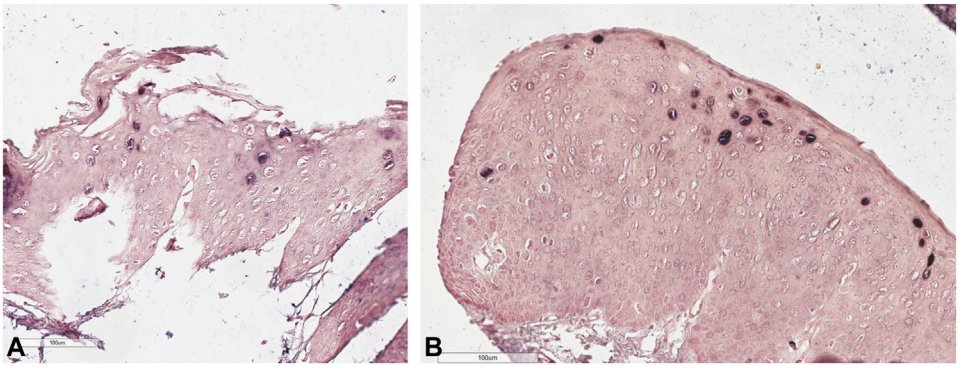

Fig 1. A, In situ hybridization testing of the right floor of the mouth with strong human papillomavirus (HPV)-16 expression using a *blue* signal with a *pink* counterstain. **B,** In situ hybridization testing of the *midline* anterior floor of the mouth with strong HPV-16 expression using a *blue* signal with a *pink* counterstain.

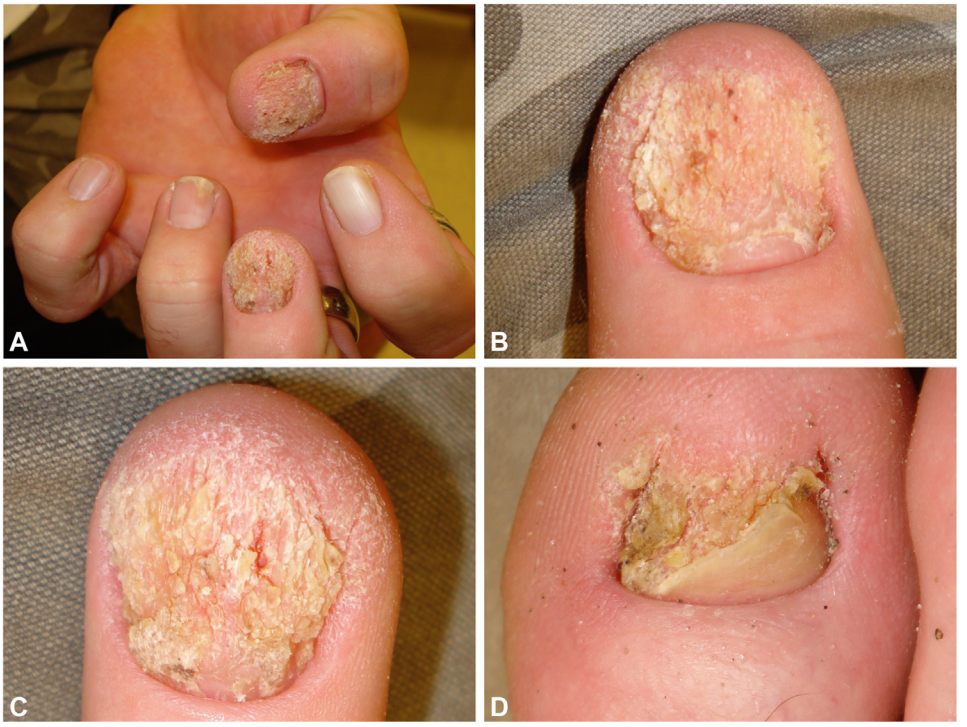

Fig 2. A, Left hand with hyperkeratotic, verrucous plaques with some discrete hemorrhagic areas on the first (**B**) and third (**C**) nail beds, leukonychia of the second nail, and onycholysis of the fourth nail. **D,** Verrucous, hyperkeratotic plaque on the right great toe nail bed.

nail sulcus. The right great toe nail bed and lateral sulcus showed medial verrucous change. Biopsies revealed SCCis, and tissue samples were positive for high-risk HPV by DNA probe. The patient underwent Mohs micrographic surgery (MMS) of the left thumb, left third digit, and right great toe. Topical imiquimod was trialed for 6 weeks without improvement on the remaining lesions prior to MMS.

Thirteen years later, the patient underwent biopsy of the right floor of the mouth revealing hyperkeratosis and moderate to severe epithelial hyperplasia. There was diffuse cytoplasmic and nuclear reactivity of the basilar two-thirds of the dysplastic epithelium with p16 immunoperoxidase evaluation. In situ hybridization testing for HPV-16 was strongly positive (Fig 1, *A*). Two years later, a small papillomatous area in the midline anterior floor of the mouth was biopsied, revealing severe dysplasia. Testing for HPV-16 was positive (Fig 1, *B*). Excision 6 months later revealed diffuse SCCis with minor salivary gland involvement.

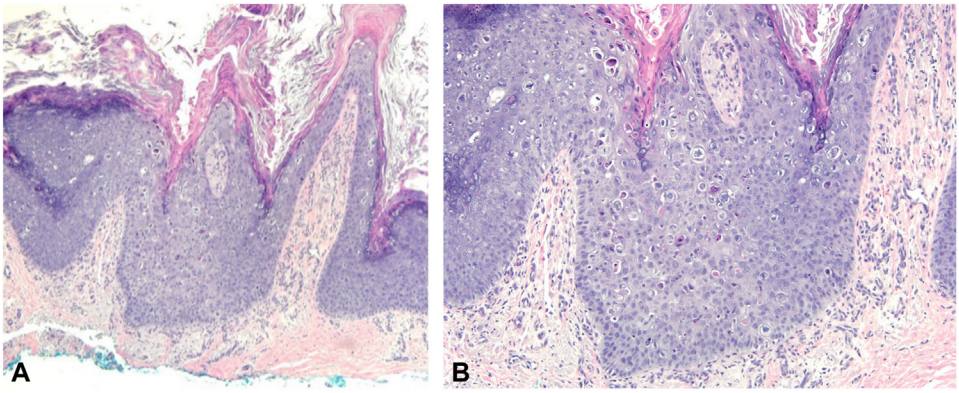

Fig 3. Hematoxylin and eosin (H&E) stained shave biopsy of the right great toe nail bed showing a broad atypical intraepidermal keratinocytic proliferation with dense overlying hyperkeratosis and parakeratosis ([**A**] 40×) and numerous koilocytes on the surface of the papillae with perinuclear clearing and wrinkled nuclei ([**B**] 200×).

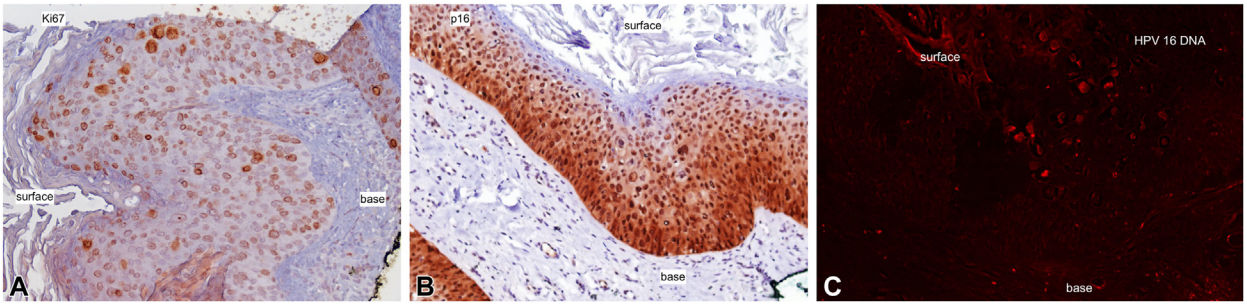

Fig 4. Squamous cell carcinoma in situ of the right great toe nail bed with strong epidermal Ki-67 expression (**A**) and p16 expression (**B**). **C,** In situ hybridization testing of the right great toe nail bed using a red fluorescent-based signal for human papillomavirus (HPV)-16.

Four months later, the patient presented with hyperkeratotic lesions on the right third finger overlying the proximal interphalangeal joint, the left thumb distal tip, and the nail bed of the left first, second, and third digits and right great toe (Fig 2). Biopsies revealed SCCis (Fig 3), and lesions were treated with MMS. Additional testing of the left thumb distal tip using the QuanDx MeltPro High-Risk HPV Genotyping Test was positive for HPV-16. Both p16 and Ki-67 expression of the right great toe were increased. In situ hybridization testing of the right great toe yielded positivity for HPV-16 (Fig 4). The patient was subsequently followed for 7 months without new lesions. Throughout 17 years of follow-up, he did not develop immunosuppressive conditions or conditions predisposing to SCC (xeroderma pigmentosum, multiple self-healing squamous epithelioma, oculocutaneous albinism, epidermodysplasia verruciformis, dyskeratosis congenita, Huriez syndrome, Rothmund-Thomson syndrome, Bloom syndrome, etc.).[3] He declined HPV vaccination. Sexually transmitted infection history was negative, including HPV-associated genital pathology. Sexual partner history was positive for genital warts. Testing for hepatitis B and C, syphilis, chlamydia, gonorrhea, and HIV was negative.

DISCUSSION

Our patient developed 12 digital SCCis lesions, including 10 periungual lesions and two toe lesions (Table I). Only 8.1% and 12.6% of nail and digital SCC cases involve multiple tumors, respectively, and toe involvement occurs in just 12% of cases.[2] Only 1 case has reported a similar number of digital SCCs. Handisurya et al[4] described a 28 year-old male who developed verrucous proliferations on all fingernails and several toenails; however, this patient was immunosuppressed with HIV. Notably, the patient also had genital warts, perianal Bowenoid plaques, and anal cancer, all HPV-associated conditions.[4] A total of 27.4% of patients with digital SCC have a history of HPV-associated genital pathology or a sexual partner with similar history.[2] Thus, when treating patients with digital SCC, it is important to

Table I. Locations of digital and nail squamous cell carcinomas in our patient

Tumor	Age	Digit	Location	Therapy	HPV
SCCis	33	L1F	Nail apparatus	MMS	High-risk HPV
SCCis	33	L2F	Nail apparatus	Imiquimod, then MMS	High-risk HPV
SCCis	33	L3F	Nail apparatus	MMS	High-risk HPV
SCCis	33	L4F	Nail apparatus	Imiquimod, then MMS	High-risk HPV
SCCis	33	R2F	Nail apparatus	Imiquimod, then MMS	High-risk HPV
SCCis	33	R1T	Nail apparatus	MMS	High-risk HPV
SCCis	46	L1F	Distal tip of digit	MMS	HPV-16
SCCis	46	L1F	Nail apparatus	MMS	Not tested
SCCis	46	L2F	Nail apparatus	MMS	Not tested
SCCis	46	L3F	Nail apparatus	MMS	Not tested
SCCis	46	R3F	Overlying PIP joint	MMS	Not tested
SCCis	46	R1T	Nail apparatus	MMS	HPV-16

F, Finger; *HPV*, human papillomavirus; *MMS*, Mohs micrographic surgery; *PIP*, proximal interphalangeal; *SCCis*; squamous cell carcinoma in situ; *T*, toe.

ask about genital involvement, offer age-appropriate cancer screening, complete a thorough sexual history, and offer counseling/screening of sexual partners.

In our case, of the 8 cutaneous lesions tested, all were positive for high-risk HPV, including 2 positive for HPV-16, specifically. Previous studies have found 78% of periungual SCCs contain HPV-16 or HPV-16-related sequences.[5,6] Roughly 60% of US oropharyngeal cancers are HPV-16 positive.[7] Our case emphasizes the ability of HPV-16 to induce lesions at different body sites. To the best of our knowledge, this is the first reported case of HPV-16-associated oral and digital SCC in an immunocompetent patient. The development of digital and oral SCC has been reported in an immunocompromised patient; however, the digital SCCs in that case were not tested for HPV-16.[8] Genetic, biologic, and environmental factors likely influence susceptibility to HPV-associated cancers.[9] Although genetic changes have been associated with susceptibility to HPV-associated cancers, replication of findings has been limited; therefore, genetic testing was not pursued.[9]

Periungual SCC treatment options include excision, MMS, amputation, or radiotherapy.[10] Approximately 20% of digital SCC cases treated with MMS recur, compared to 3% for all cutaneous SCC.[2] Increased cellular proliferation may contribute, as HPV-associated digital SCC may have higher expression of tumor markers Ki-67 and $p16^{INK4a}$.[2] Both Ki-67 and p16 expression were markedly increased in our case. Additionally, recurrences may be due to persistent virus in adjacent tissue.[5]

We report the case of an immunocompetent male who developed cutaneous and oral HPV-16-associated SCCis, including 12 digital lesions, over a 17 year follow-up period. This case is unique both because of the number of digital SCCis lesions and the concurrent oral and digital HPV-16-associated SCCis in an immunocompetent patient.

Conflicts of interest

None disclosed.

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