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Case Report

Concurrent tinea pedis HPV-associated squamous cell carcinoma of the ventral toes treated with Mohs micrographic surgery

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Abstract

We present a case of human papillomavirus-associated squamous cell carcinoma arising between the ventral toes. A 60-year-old man presented with a 6-year history of a growth between the right fourth and fifth toes that had previously been thought to be secondary to hammertoe deformity. Initial biopsy favored verruca vulgaris with associated fungal hyphae and he was treated accordingly. Subsequent biopsy showed squamous cell carcinoma in situ with positive for high-risk human papillomavirus subtypes 16 and 18. He was successfully treated with Mohs surgery. This is the first published case of human papillomavirus 18-associated interdigital squamous cell carcinoma of the toes treated with Mohs surgery.

Introduction

Human papillomavirus (HPV)-associated squamous cell carcinoma (SCC) of the digits is rare, with fewer than 200 cases reported in the literature.^{1,2} We present a case of HPV-associated SCC on the ventral toes of two adjacent web spaces, successfully treated with Mohs surgery, which was originally diagnosed as a verruca vulgaris with concurrent tinea pedis.

Case Synopsis

A 60-year-old man without a history of immunosuppression, prior skin cancers, or genital warts presented with a 6-year history of a nonhealing growth between the right fourth and fifth toes. He was previously seen by a podiatrist who attributed his interdigital changes to his hammertoe deformity and surgically resected the in-

volved area on the proximal phalanx of the right fifth toe. Pathology examination showed bone and normal skin findings. However, the lesion continued to enlarge, and the patient was subsequently seen in the dermatology clinic. Physical examination showed a hyperkeratotic yellow plaque with maceration between the right fourth and fifth toes, along with thickened yellow toenails and subungual debris. There were no other concerning lesions on the fingers, genitals, or remaining toes. A shave biopsy favored verruca vulgaris with fungal hyphae. The suspected verruca was treated with cryotherapy and his tinea pedis was treated with oral fluconazole and ketoconazole cream. One month later, terbinafine cream was given for persistent tinea pedis. The patient returned to clinic two years later, stating that although the lesion initially improved, it recurred and now extended onto the third and fourth toes. A repeat shave biopsy of the right toe fourth and fifth webspace was diagnostic for squamous cell carcinoma in situ ([Figure 1](#)). In situ hybridization performed on the skin biopsy was positive for high-risk HPV subtypes 16 and 18 and the patient was referred for Mohs surgery ([Figure 2](#)).

At the time of his Mohs surgery consultation, two large and clinically distinct yellow-brown hyperkeratotic plaques at least 2cm in diameter, were noted on the ventral toes between the right fourth and fifth and right third and fourth digits ([Figure 3](#)). Mohs surgery for the carcinoma between the fourth and fifth toes was notable for invasive SCC with peripheral SCC is on stage 1 ([Figure 4](#)). The tumor was cleared after two stages. A subsequent biopsy of the discontinuous plaque between the third and fourth toes showed SCC in situ for which he also had Mohs surgery. The tumor was cleared in three stages. Repair with a full thickness skin graft was performed by the plastic surgery consultant ([Figure 5](#)).

Given the HPV-positivity of his tumor, multiple avenues for obtaining the three-series 9 valent HPV vaccine were attempted, but coverage was denied by insurance. His only option was to pay out of pocket for the cost

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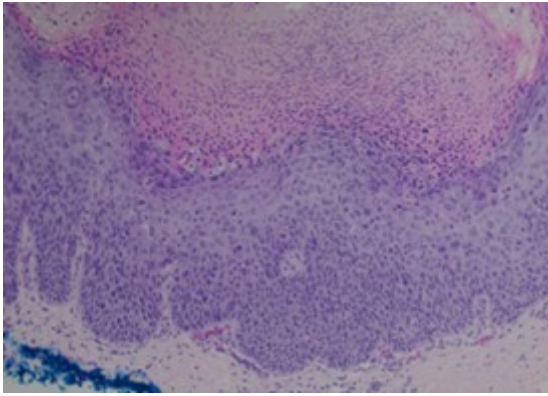


Figure 1. Biopsy showing atypical squamous cells confined to the epidermis without invasion into the underlying stroma consistent with squamous cell carcinoma in situ. There is full-thickness keratinocyte dysmaturation with loss of cellular polarity, nuclear pleomorphism, hyperchromasia, and increased mitotic activity (hematoxylin-eosin stain, 100X).

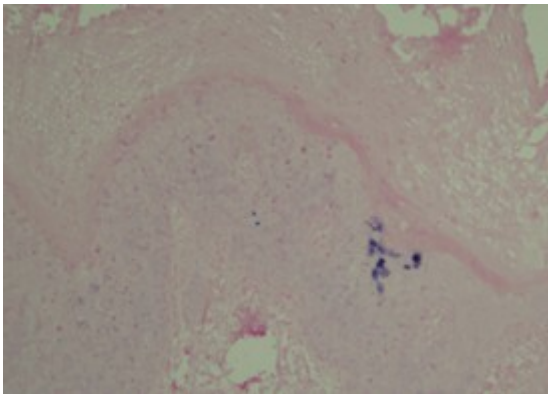


Figure 2. In situ hybridization for human papillomavirus positive for high-risk subtypes 16 and 18, 100X.



Figure 3. Initial presentation on and between the right third to fifth digit prior to Mohs surgery.

of the vaccine, which he declined. The site remains well-healed and without evidence of recurrence at 6-month follow-up (Figure 6). Routine 6-month skin exams were recommended to ensure adequate longitudinal surveillance.

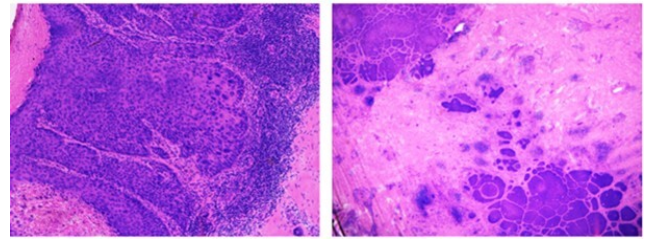


Figure 4. Mohs sections showing squamous cell carcinoma in situ (left) and invasive squamous cell carcinoma (right).

Case Discussion

Cutaneous squamous cell carcinoma arising from chronic interdigital maceration of the foot is exceedingly rare. Chronic inflammation, infection, and irritation have been suggested to contribute to carcinoma development.^{2,3} However, cutaneous SCC can be difficult to diagnose as it can share clinical and pathological features of verruca vulgaris both with and without HPV infection. Prior report of SCC clinically coexisting with verruca have been described.⁴ Cohen et al reported a 63-year-old man who developed a nonhealing nodule on the left dorsal hand that appeared after known trauma. Although the initial punch biopsy was consistent with verruca vulgaris, the lesion continued to grow, and a repeat punch biopsy confirmed verruca on the edges and invasive SCC centrally.⁴ The authors postulated that the verruca may have been etiologically related to the development of SCC.⁴

Impaired immunity and antecedent trauma are also thought to be risk factors for digital SCC.⁵ Basal keratinocytes can be exposed to HPV virions with epithelial trauma.⁶ We suspect this might have been the case in our patient, with HPV virions infecting two adjacent interdigital webspaces and ventral toes owing to chronic maceration of the webspace and chronic friction on the ventral toes. This would explain the development of two clinically and histopathologically distinct SCC/SCCs. Although ventral digit SCC is less common than SCC of the dorsal hands, they have also been associated with additional risk factors such as arsenic ingestion, chronic scars or ulcers, ultraviolet light, and other radiation exposure.³ Cohen et al described a 62-year-old man with a clinically appearing verruca on the left fourth finger distal pad unresponsive to treatment. Biopsy confirmed a SCC.³ The tumor was cleared after 5 stages of Mohs surgery, which highlights the challenges of treating these tumors with deeper and wider subclinical extension and adjacent tumor invasion. At the time of this submission, HPV-related SCC of the hand webspace has not been reported.

HPV-associated digital SCC is also associated with higher risk of recurrence. The rate of tumor recurrence after excision has been reported to be 43%, compared to 13% to 26% after Mohs micrographic surgery.¹ This may be attributed to residual HPV infection at the margins in the absence of microscopic cellular atypia. For skin cancers in this area, Mohs surgery offers complete margin analysis compared to traditional excision with per-



Figure 5. Postoperative defect after two stages of Mohs surgery on the right fourth and fifth toes and webspace (left) and after full-thickness skin graft repair (right).



Figure 6. Postoperative 6-month follow-up.

manent sectioning and the evaluation of representative section edges. Further, tissue preservation with minimal margins for tumor clearance is crucial for preserving function and form compared to wide excision or amputation.

There was one prior case report of HPV 16-induced SCC in situ of the fourth interdigital webspace of the toes treated with excision with 5mm margins.⁶ There was another report of HPV 58-associated SCC in situ on the fourth interdigital space on the left foot with concurrent cervical carcinoma.⁷ More recently, Snoussi et al described a case of ventral toe SCC in the fourth interdigital webspace in a patient with a three-year history of macerated skin between his toes, also treated with surgical excision. However, HPV subtyping was not reported.⁸ Our case is the first to report SCC associated with HPV 16 and 18 coinfection and arising from chronic interdigital maceration related to tinea pedis. Our case is also the first case, to our knowledge, treated with Mohs micrographic surgery and involving more than one webspace.

HPV 16 is the leading cause of all HPV-attributable cancers.⁹ Around 90% of digital SCCs are HPV-related and there is evidence to suggest an association between digital and periungual SCC and HPV 16.^{1,6} On the nail, 50% of SCC in situ, and 73% of invasive SCC have been attributed to HPV 16.¹⁰ Anogenital-digital spread has been suggested in the pathogenesis of digital SCC^{1,5,6} and nail SCC.¹¹ In one case series, 7 out of 51 patients with digital SCC had a concurrent or prior history of genital HPV-re-

lated pathology. Of the 7 patients, 6 of them had identical HPV subtype of their digital tumor and genital lesions.¹ A review of 45 cases of polydactylous SCC showed an average of 3.9 digits affected, often on contiguous digits and was seen more frequently on the fingers than the toes.¹² HPV 16 was associated with 25.8% of all cases of polydactylous SCC and more likely to be diagnosed at an earlier age in immunosuppressed patients.

HPV vaccination has been found to reduce the development of keratinocyte carcinomas even in immunocompetent patients without known HPV infection and may be a cost-effective way to mitigate risk.¹³ The 9-valent Gardasil 9 (HPVs 6,11,16,18,31,33,45,52,58) vaccine is one of three licensed HPV vaccines in the United States. There is one prior report of a 15-year-old girl who had disease resolution of polydactylous disease associated with HPV 16 after cryotherapy and Gardasil HPV vaccine.¹⁴ Bossart et al did a retrospective study evaluating the number of dermatological procedures before and after vaccination with Gardasil-9 vaccine in immunocompromised patients.¹⁵ In their study, the mean age of patients was 62 years, and they found a reduction in the number of interventions after vaccination. Although there are concerns of waning immunity and immune response to HPV vaccines in patients over the age of 40, patients may still be able to develop immunity after vaccination and benefit both from a therapeutic and preventative perspective. Thus, HPV vaccines may be beneficial for patients, even those beyond the age of 45 years, which is the cur-

rent approved maximum age for administration. Reducing the burden of HPV-associated disease such as verrucae, HPV-associated SCC on the skin, anogenital region, or oropharynx would greatly reduce the burden of disease on patients and the health care system.

Conclusion

Squamous cell carcinoma rarely arises from locations such as the toes, fingers, or nail unit. Diagnosis can be challenging as SCC can mimic benign conditions such as corns, seborrheic keratosis, or verruca vulgaris.³ SCC arising from concurrent tinea pedis and verruca is exceedingly rare.⁶⁻⁸ Several HPV subtypes have been impli-

cated in the development of SCC, most commonly HPV 16. Treatment of underlying HPV and longitudinal surveillance following surgery is warranted.^{1,5} Future studies may help evaluate the utility of HPV vaccine in its preventative and therapeutic role in HPV-associated cutaneous SCC

Potential conflicts of interest

The authors declare no conflicts of interest.

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