Archives of Clinical & Experimental Dermatology

Yumed Text
OPEN ACCESS JOURNALS

Case Report | Vol 5 Iss 2
ISSN: 2583-6374
https://dx.doi.org/10.46527/2583-6374.149

Off-Label Human Papillomavirus Vaccination and Shortened, Low-Dose Topical Imiquimod in an Elderly Patient with Multiple Actinic Keratoses

Anna Hastrup[1], Emily Wenande[1*], Niels Bech-Thomsen[3] and Merete Haedersdal[1,2]

[1]Department of Dermatology, Copenhagen University Hospital - Bispebjerg, Denmark
[2]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[3]Clinic of Dermatology, Naestved, Denmark

[*]**Corresponding author:** Emily Wenande, Department of Dermatology, Copenhagen University Hospital Bispebjerg Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark, Tel: +45 38 63 61 73; E-mail: emily.cathrine.wenande@regionh.dk

Received: October 15, 2023; **Accepted:** October 31, 2023; **Published:** November 08, 2023

Abstract

Human papillomavirus (HPV) is associated with skin dysplasia development. This case report describes a clinical response observed following combined HPV vaccination and low-dose topical imiquimod in an elderly patient with multiple actinic keratoses (AK). A 95-year-old immunocompetent man was evaluated for AK at an office-based dermatological practice. Due to the patient's age and disease burden, prolonged or invasive treatments were deemed inappropriate. Consequently, the patient was offered off-label 9-valent HPV vaccination at 0- and 2 months as a potential adjunct to low-dose imiquimod. Short, low dose imiquimod therapy consisted of 3,75% cream applied 3 x weekly for two weeks. Over three months later, a significant lesional reduction was noted. Local skin reactions were uncharacteristically marked, with oozing erosions in treated skin areas. No systemic side effects were observed. Our case may reflect a particularly strong response to imiquimod alone despite shortened and low-dose therapy or alternatively, a combined effect with HPV vaccination. Given the case findings' limited generalizability, larger controlled trials are warranted to investigate the utility of HPV vaccination and difficult-to-treat AK patients.

Keywords: ***Actinic keratosis; Case report; HPV; Keratinocyte carcinoma; Skin cancer***

1. Abbreviations

AK: actinic keratosis; BCC: basal cell carcinoma; PDT: photodynamic therapy; HPV: human papillomavirus; i.m.: intramuscular; KC: keratinocyte carcinoma; SCC: squamous cell carcinoma

Citation: Hastrup A, Wenande E, Bech-Thomsen N, et al. Off-Label Human Papillomavirus Vaccination and Shortened, Low-Dose Topical Imiquimod in an Elderly Patient with Multiple Actinic Keratoses. Arc Clin Exp Dermatol. 2023;5(2):149.

2. Introduction

Human papillomavirus (HPV) has previously been implicated as a factor associated with development of skin dysplasia [1]. Not infrequently, presence of viral DNA is reported in keratinocyte carcinoma (KC) and the precursor lesion, actinic keratosis (AK), particularly in the setting of immunosuppression [1]. These observations raise the question as to whether HPV vaccines, given alone or with conventional therapy, might be offered to difficult-to-treat patients who are unable to undergo invasive or prolonged standard of care therapies. In the following case report, we describe off-label HPV vaccination offered as a potential adjuvant therapy to low-dose topical imiquimod in an elderly patient with a high AK burden.

3. Case Report

A 95-year-old immunocompetent Caucasian man with extensive sun damage attended a private dermatology clinic in Naestved, Denmark. In the period between 2005-2019, the patient had undergone a total of 14 surgical excisions of basal cell carcinomas (BCC). During this period, the patient also began presenting with multiple AKs. Due to his high burden of disease and advanced age, the patient had since requested not to undergo further invasive or prolonged treatments. Despite repeated subsequent sessions with photodynamic therapy (PDT), his AK burden remained consistently high. As an exploratory approach, the patient was therefore offered low-dose topical imiquimod combined with HPV vaccination by his dermatologist. Prior to the first vaccination, the patient provided informed verbal and written consent to this off-label therapy.

At day 0 and two months later, the patient received an intramuscular (i.m.) injection of a commercially available 9-valent HPV vaccine (*GARDASIL®9, Merck, Kenilworth, NJ, USA*). One month after the first vaccination, the patient's at-home nurses were instructed to apply 3,75 % imiquimod cream (*Zyclara 3,75%, Valeant Pharmaceuticals, Bridgewater, NJ, USA*) on skin areas with red scaly spots on the patient's trunk, upper arms, or head and neck area three times weekly in a shortened off-label, two-week regimen (two sachets per session (0.5 g)), consisting of six applications in total. During the two-week regimen, a total of twelve sachets of imiquimod were used with complete compliance. The patient had not previously been treated with imiquimod.

Clinical response, consisting of AK disease severity, was evaluated pretreatment and at follow-up visits by the same experienced dermatologist. Accordingly, all clinical AKs (Olsen grade I-III) on the trunk, upper extremities, or head and neck were counted. Local skin reactions and adverse events were monitored during the follow-up period, as was the patient's subjective experience during treatment.

TABLE 1 presents clinical AK counts documented at each visit in treated skin areas. Prior to vaccination, the patient presented with a total of 75 AKs. One month after the first vaccination, limited change in AK counts had occurred (71 AK). At 2-months, (two weeks following cessation of low-dose imiquimod therapy), an increase in AK number was seen (96 AK). By 3½ months however, the number of clinical AKs had dropped to a total of 16 lesions, with only a single AK observed in the head and neck area at the final visit.

TABLE 1. **Clinical actinic keratosis (AK) counts in treated skin areas over 3,5 months.**

	Day 0	Month 1 IQM start	Month 2	Month 3,5
Scalp and forehead	10	10	20	0
Ears	6	6	6	0
Face and neck	15	10	20	1
Body and upper arms	44	45	50	15
Total AK count	**75**	**71**	**96**	**16**

IQM: topical application of imiquimod 3,75% (Zyclara) three times weekly for two weeks.

No systemic side-effects were observed following each HPV vaccination. At the 2-month visit, multiple, deep oozing erosions were noted in topically treated areas (FIG. 1). This surprisingly exaggerated inflammatory response had not previously been observed with conventional PDT. At the 3 ½ month visit however, the patient reported marked satisfaction with the improvement in his skin. Unfortunately, the patient succumbed to an unrelated hospital-acquired infection following routine pacemaker implantation shortly after the 3½ month visit, precluding longer follow-up.

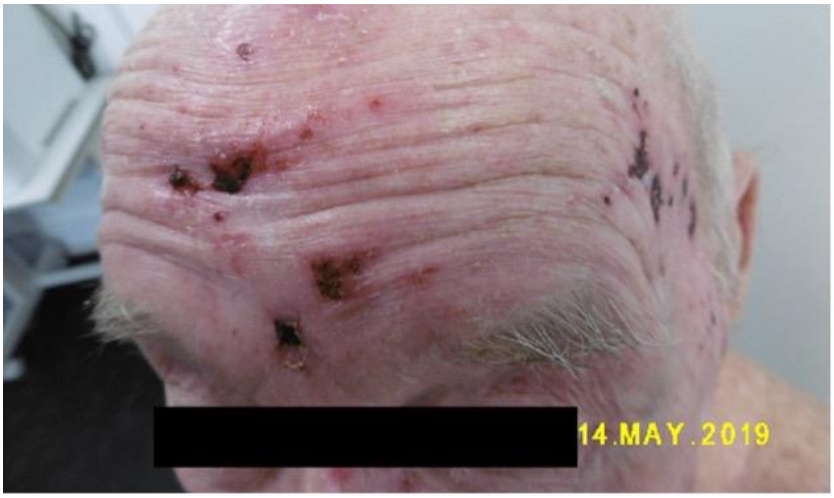

FIG. 1. **Marked local skin reactions including hemorrhagic erosions on the face of an elderly patient seen two weeks after cessation of off-label, shortened topical imiquimod therapy.**

4. Discussion

Approved for treatment of AKs and superficial BCCs, imiquimod is a toll-like receptor 7 agonist which stimulates the innate and adaptive immune response [2]. For AK, the standard topical regimen for imiquimod 3,75% consists of daily application in a ‘two week on/two weeks off/two weeks on’ schedule. Using this regimen, lesional clearance rates are a reported 81,8 %, with inflammatory responses correlated with superior AK clearance 8 weeks post treatment [3,4]. In our case, a low 3,75% dose (as opposed to 5% formulation) and shortened two-week treatment duration were used to provide a more tolerable, convenient treatment in our elderly patient. Despite these conservative measures, the patient achieved a 79% lesional clearance after presenting with a brisk and unprecedented local inflammatory response in combination treated areas (FIG. 1). Though it remains

plausible that the observed results stem from the imiquimod treatment alone, our patient's clinical response could reflect a combined systemic effect of vaccination + imiquimod. At least in some instances a systemic effect appears possible, given that previous treatment studies of β-HPV-associated recalcitrant cutaneous warts report that intramuscular α-HPV vaccination can lead to clearance of distant warts [5]. However, there is also the possibility that our patient is merely particularly responsive to imiquimod despite low dose shortened therapy.

Imiquimod clears both visible and subclinical dysplastic skin lesions within 3 months of treatment initiation [3,4]. Observed at the patient's 2-month visit, the apparent increase in AK lesion count represents a clinically well-known phenomenon of pharmacological AK treatment, where induction of inflammation (i.e., erythema) causes subclinical lesions to become visible thereby easing their clinical detection [3,4]. This response occurs rapidly, as early as 4-7 days after treatment initiation, and is also described in patients undergoing systemic chemotherapy for other malignancies [6].

The HPV vaccine has previously shown potential as an off-label treatment for KC and precursors in a handful of case reports [7]. Multiple case studies have examined the effect of combining intramuscular and intratumoral 9-valent HPV vaccination in squamous cell carcinomas (SCCs) of elderly patients unsuitable for surgical excision. Thus, in three immunocompetent patients with SCCs and one immunosuppressed patient with a SCC in situ, complete tumor clearance was observed after a follow-up ranging between 3 and 11 months [8-11]. Quadrivalent HPV vaccination as a preventative strategy for KC has also been reported by Nichols et al.. A reduction in development of new SCCs and BCCs was shown in two immunocompetent patients after administering the quadrivalent HPV vaccine and two immunocompromised patients after administering the 9-valent HPV vaccine [12,13]. We previously noted a similarly therapeutic effect on AKs, observed in thirteen immunocompetent patients with high lesional burden following 9-valent HPV vaccination [14,15]. Interestingly, a 2023 cohort study reported that following 9-valent HPV vaccination, 32 immunosuppressed patients with a history of SCC, SCC in situ and AK underwent significantly fewer dermatologic interventions (i.e. biopsies, curettages, excisions) versus pre-vaccination (HR 0.27; CI 0.14-0.51, $p<0.001$) [16]. At present however, no larger randomized controlled trials have examined HPV vaccination for the aforementioned indications.

The presence of β-HPV DNA is commonly reported in AK and KC lesions, but a possible etiological role remains controversial [1]. Occasional isolation of β-HPV DNA does not prove causality and the classic histological findings associated with α-HPV are not described in AK [17]. Rather than a causal relationship between β-HPV and AK, the association may have an immunological explanation. In a seminal paper by Strickley et al., authors showed that T-cell immunity against commensal papillomaviruses suppresses UV-induced skin cancer development in mice. Viral immunity following natural infection, vaccine or T-cell transfer was proposed to increase targeting of atypical keratinocytes by resident CD8+ T-cells, thereby reducing both wart and dysplasia development [18]. Accordingly, the herein observed clinical response may reflect a dual nonspecific action of imiquimod and boosted immunity against commensal HPV in our patient's skin.

HPV vaccination and imiquimod have previously been combined with the aim to enhance antiviral and antitumoral effects. One preclinical study of a different HPV DNA vaccine and topical imiquimod significantly increased antitumor immunity induced by vaccination [19]. The approach has also been explored in clinical settings to treat HPV-related skin cancer. In a case

of acquired epidermodysplasia verruciformis, complete lesional clearance was shown following standard i.m. quadrivalent HPV vaccination and topical imiquimod [20].

This report describes the case of a single patient evaluated with short-term follow up, limiting its generalizability. It is unclear whether the robust clinical response is a result of imiquimod alone or the combination treatment. Randomized controlled trials are necessary to assess the utility of HPV vaccination with shortened low dose imiquimod as a convenient treatment option in patients with extensive disease, advanced age, or individuals unwilling or unable to undergo more invasive and extended therapies.

5. Conflict of Interest

The authors have no conflicts of interest to declare. The manuscript's contents have not previously been presented elsewhere.

6. Funding

None

7. Ethical Approval

Not applicable to case reports.

8. Data Availability Statement

The data that support the findings of this study are available upon reasonable request from the corresponding author, [E.W.]. The data are not publicly available due to their containing information that could compromise the privacy of the patient.

REFERENCES

1. Weissenborn SJ, Nindl I, Purdie K, et al. Human papillomavirus-DNA loads in actinic keratoses exceed those in non-melanoma skin cancers. J Invest Dermatol. 2005;125(1):93-7.
2. Hanna E, Abadi R, Abbas O. Imiquimod in dermatology: an overview. Int J Dermatol. 2016;55(8):831-44.
3. Gupta G. Lmax and imiquimod 3.75% in daily clinical practice. J Eur Acad Dermatol Venereol. 2015;29 Suppl 1:15-8.
4. Swanson N, Abramovits W, Berman B, et al. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. J Am Acad Dermatol. 2010;62(4):582-90.
5. Nofal A, Marei A, Ibrahim AM, et al. Intralesional versus intramuscular bivalent human papillomavirus vaccine in the treatment of recalcitrant common warts. J Am Acad Dermatol. 2020;82(1):94-100.
6. Johnson TM, Rapini RP, Duviv M. Inflammation of actinic keratoses from systemic chemotherapy. J Am Acad Dermatol. 1987;17(2 Pt 1):192-7.

7. Neagu N, Dianzani C, Venuti A, et al. The role of HPV in keratinocyte skin cancer development: A systematic review. J Eur Acad Dermatol Venereol. 2023;37(1):40-6.
8. Nichols AJ, Gonzalez A, Clark ES, et al. Combined Systemic and Intratumoral Administration of Human Papillomavirus Vaccine to Treat Multiple Cutaneous Basaloid Squamous Cell Carcinomas. JAMA Dermatol. 2018;154(8):927-30.
9. Wilson A, Cowan TL, Marucci D, et al. Intralesional 9-valent human papillomavirus as a treatment for facial squamous cell carcinoma. J Eur Acad Dermatol Venereol. 2022;36(12):e1064-e5.
10. Nichols AJ, De Bedout V, Fayne RA, et al. Systemic and intratumoral 9-valent human papillomavirus vaccine treatment for squamous cell carcinoma in situ in a renal transplant recipient. JAAD Case Rep. 2020;6(4):289-91.
11. Geizhals S, Lebwohl M. The Successful Treatment of Multiple Cutaneous Malignancies with HPV Vaccination: Case Report. SKIN. 2020;4(2):148-51.
12. Nichols AJ, Allen AH, Shareef S, et al. Association of Human Papillomavirus Vaccine With the Development of Keratinocyte Carcinomas. JAMA Dermatol. 2017;153(6):571-4.
13. Nichols A, Nahm W, Rabinovitz H, et al. Keratinocyte Carcinomas in Immunocompromised Patients Are Reduced After Administration of the Nonavalent Human Papillomavirus Vaccine. J Drugs Dermatol. 2022;21(5):526-8.
14. Wenande E, Bech-Thomsen N, Haedersdal M. Reduction in actinic keratoses following 9-valent human papilloma virus vaccination. Dermatol Ther. 2020;33(4):e13454.
15. Wenande E, Bech-Thomsen N, Togsverd-Bo K, et al. Off-Label 9-Valent Human Papillomavirus Vaccination for Actinic Keratosis: A Case Series. Case Rep Dermatol. 2021;13(3):457-63.
16. Bossart S, Daneluzzi C, Moor MB, et al. HPV Vaccination in Immunosuppressed Patients with Established Skin Warts and Non-Melanoma Skin Cancer: A Single-Institutional Cohort Study. Vaccines. 2023;11(9):1490.
17. Doorbar J. Model systems of human papillomavirus-associated disease. J Pathol. 2016;238(2):166-79.
18. Strickley JD, Messerschmidt JL, Awad ME, et al. Immunity to commensal papillomaviruses protects against skin cancer. Nature. 2019;575(7783):519-22.
19. Chuang CM, Monie A, Hung CF, et al. Treatment with imiquimod enhances antitumor immunity induced by therapeutic HPV DNA vaccination. J Biomed Sci. 2010;17(1):32.
20. Maor D, Brennand S, Goh MS, et al. A case of acquired epidermodysplasia verruciformis in a renal transplant recipient clearing with multimodal treatment including HPV (Gardasil) vaccination. Australas J Dermatol. 2018;59(2):147-8.