Received: 21 December 2023 | Accepted: 14 January 2024

DOI: 10.1002/jmv.29431

RESEARCH ARTICLE

JOURNAL OF MEDICAL VIROLOGY WILEY

Strengthening the relationship between intractable plantar keratosis and human papillomavirus

Luis Alou[1] | Ricardo Becerro-de-Bengoa-Vallejo[2] | Marta E. Losa-Iglesias[3] | Juan Moreno[4] | Rubén Sánchez-Gómez[2] | Natalia González[1] | David Sevillano[1]

[1]Medicine Department, Microbiology Area, School of Medicine, Complutense University of Madrid, Madrid, Spain

[2]Nursing Department, Faculty of Nursing, Physiotherapy and Podiatry, Universidad Complutense de Madrid, Madrid, Spain

[3]Department of Nursing and Stomatology, Faculty of Health Sciences, King Juan Carlos University, Madrid, Spain

[4]Clínica del Pie Juan Moreno, Segovia, Spain

Correspondence
Luis Alou, Medicine Department, Microbiology Area, School of Medicine, Complutense University of Madrid, Madrid, Spain.
Email: luisalou@ucm.es

Abstract

The aim of the study was to determine the presence of human papillomavirus (HPV) in patients with intractable plantar keratosis (IPK) by comparing the histopathological findings of biopsies. A prospective, observational, and concordance study was carried out. Three different specimens were taken from each IPK. A first punch was sent for histopathological examination, and a second punch and a superficial skin scraping were both sent for HPV polymerase chain reaction (PCR) and type determination. A total of 51 patients were included. From the histopathological examination, it was determined that 35 (68.6%) samples were diagnosed as warts and 16 (31.3%) as keratosis. However, the presence of HPV was confirmed by PCR in 49 (96.1%) and in 42 (82.4%) samples obtained by punch and superficial scraping, respectively. In the 49 PCR-positive samples, the most common HPV types were HPV1, HPV2, HPV27, HPV57, and HPV65, accounting for 81.6% of the samples. In conclusion, this study demonstrates that HPV infection and IPK lesions are very closely related. Although we cannot confirm that HPV is the cause of the development of IPK, the high prevalence of HPV observed in these lesions calls for a change to the procedures for managing IPK.

KEYWORDS

histopathology, human papillomavirus, intractable plantar keratosis, PCR, punch, scraping

1 | INTRODUCTION

Intractable plantar keratosis (IPK) is a deep lesion in a callous region, usually on the plantar surface of the metatarsal heads, causing severe pain and discomfort in the forefoot.[1] An IPK can arise due to irregular foot posture and will continue unless an orthosis is used to support the abnormality or the abnormality is corrected surgically.[2] Smoking has been suggested as a significant risk factor for the development of IPK lesions, in addition to prolonged pressure on the affected area. The vasoconstrictive effect of nicotine on peripheral vessels causes the subcutaneous tissue to atrophy, which may increase bone–skin contact and result in callus formation.[3,4]

Increasing skin thickness and concentrated keratin areas are associated with painful corns and skin infection by human papillomavirus (HPV). Plantar warts, caused by active intraepidermal HPV, appear as excessive growths on pressure points of the sole of the foot.[5]

Most individuals are asymptomatic carriers of HPV; the estimated prevalence of HPV in normal human skin is within the range of 70%–80%, where it can persist for several years.[6,7] Although numerous HPV types have been described, a study indicated that five HPV types (HPV1a, 2a, 27, 57, and 65) cause 98% of plantar warts.[8]

The diagnosis of plantar wart-associated HPV is mainly based on clinical inspection. Histopathological examination and HPV typing by polymerase chain reaction (PCR) assay are recommended in cases where the diagnosis is uncertain.[9] Biopsies of the lesions are the gold standard for HPV detection and typing. However, less invasive samples such as superficial scraping are equally reliable, showing similar sensitivity for HPV detection and typing as biopsy.[10,11]

Diagnosis of IPKs usually relies on symptomatology and clinical presentation,[12,13] so histopathological analyses of IPK are seldom conducted. Although some professionals feel confident in their ability to differentiate between plantar warts and IPK, such distinctions can prove to be inaccurate.[12,13] A recent study examining 43 cases of surgically excised IPKs, revealed more than 50% of cases as plantar wart after histopathology analysis. Moreover, the authors reported a 6-month recurrence rate of 53.5% of which 53% and 43% were diagnosed as plantar warts and keratosis, respectively, in the postsurgery histopathological examination.[12] One reasonable explanation for the ineffectiveness of IPK treatment is that many of these IPKs are viral in origin, rather than mechanical as has been hypothesized in a recent scoping review.[14] Therefore, predicting the outcome based on clinical examination remains challenging without validation from other analytical methods.[13,14]

Our hypothesis is that IPK is a clinical manifestation of HPV infection and, therefore, these lesions require an analytical diagnosis guided specifically by the identification of the viral etiology. For this purpose, we aimed to investigate the prevalence of HPV in biopsies from recurrent IPK lesions using histopathological examination and PCR. A secondary objective was to determine whether the viral DNA found in the deeper portions of IPK was also detectable in superficial hyperkeratotic samples obtained by scraping.

2 | MATERIAL AND METHODS

2.1 | Design

A prospective, observational, and concordance study was conducted in a podiatric center (Clínica del Pie Juan Moreno) in Segovia, Spain, between October 2021 and March 2022. The study used a nonprobability consecutive sampling technique. The Ethics Committee of the Universidad Rey Juan Carlos, Madrid, Spain (code: 0703201905919) approved this research, and all subjects signed the informed consent form before the start of the study.

2.2 | Patients

Participants were individuals over 18 years of age, immunocompetent, and without systemic disease who at the time of admission presented a recurrent IPK lesion in the plantar region of the foot for at least 3 months, treated exclusively by periodic delamination (Figure 1).

Patients with resolution of plantar skin continuity, presenting ulcers and/or vesicles, patients who had undergone surgery on the affected foot, and pregnant patients were excluded.

Baseline measurements included general questions related to demographic variables, that is, sex, age, weight (kg), height (m), body mass index (kg/cm^2), the number of cigarettes smoked per day, and description of the lesion: location and time of evolution (years).

This work was reported according to the Strengthening The Reporting Of Cohort Studies in Surgery criteria.[15]

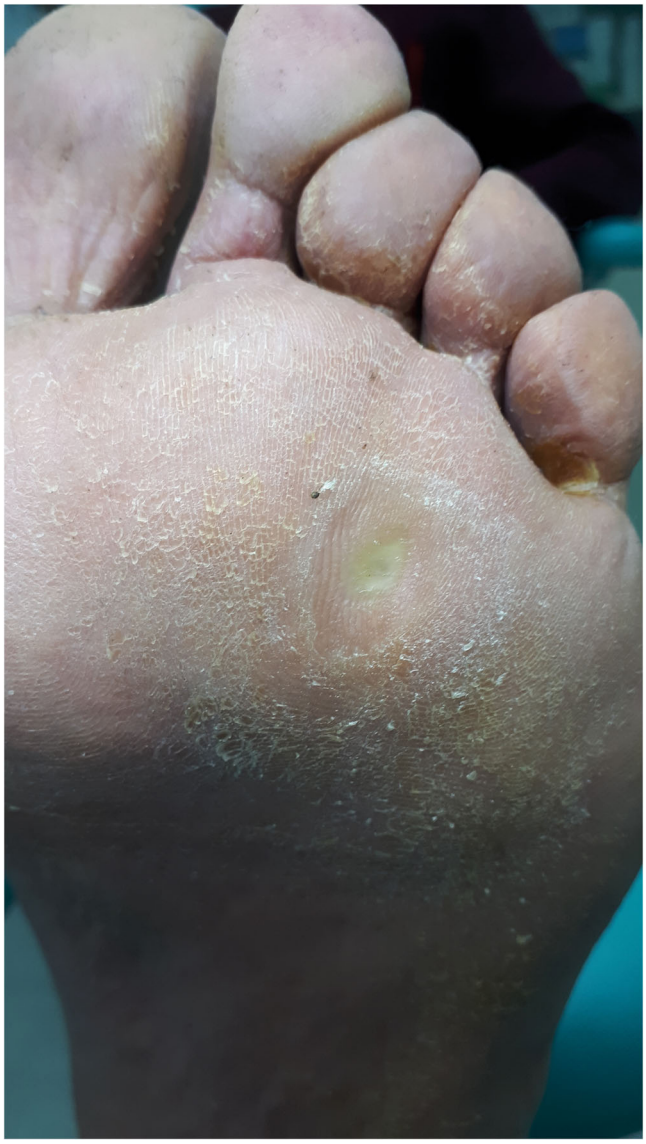

FIGURE 1 Plantar aspect of foot with an intractable plantar keratosis in the fourth metatarsal (M4).

2.3 | Samples

Three different specimens were collected from each IPK lesion. The first specimen was a skin-scraping sample obtained from the hyperkeratotic surface of the lesions using a scalpel. The second and third specimens were deep portions of the lesion obtained by punch biopsy (2 mm diameter punch). One biopsy specimen was intended for histopathological examination. The other biopsy sample and the superficial skin scraping were processed in parallel for HPV detection and typing by PCR.

2.4 | Histopathological study

The samples were immersed in 10% formalin and sent to a histopathology laboratory (Echevarne Laboratories). The specimens were embedded in paraffin and underwent hematoxylin and eosin staining. The dyed preparations were then examined under a microscope.

2.5 | HPV detection and typing

All of the samples were processed within 24 h of collection, as previously described.[10] Briefly, genomic DNA was extracted from the tissue obtained by punch and the superficial skin scraping using the NZY Tissue gDNA Isolation kit (NZYTech). Multiplex PCR was used to detect the four HPV types that are more commonly associated with plantar warts (HPV-1, −2, −27, and −57) using the specific primers and conditions suggested by Lei et al.[16] Negative samples for the multiplex PCR were subsequently analyzed using a nested PCR method, following the protocol described by Forslund et al.[17] to detect any additional HPV types. The resulting PCR products were then purified using a NZYGelpure PCR purification kit (NZYTech) and sequenced using the Sanger sequencing method with a BigDye terminator v3.1 cycle sequencing kit (Applied Biosystems). The nested PCR primers and an ABI 3730 XL genetic analyzer (Applied Biosystems) were employed for the sequencing process. The sequencing analysis was performed using software v.5.1 (Applied Biosystems), and the HPV sequence alignment was established by comparing the sequences with those in the GenBank database using BLASTn software (https://blast.ncbi.nlm.nih.gov/).

2.6 | Statistical analysis

The sample size ($n = 51$) was estimated for a statical power of 0.80 and an alpha of 0.05 using Medcalc® version 20.001 software (www.medcalc.org). Significant differences between the two qualitative and quantitative variables were analyzed using Fisher's exact test and the Mann–Whitney U test. A $p < 0.05$ was considered statistically significant. The sensitivity, specificity, positive predictive value, negative predictive value and agreement (Cohen's kappa) of the PCR for the detection of HPV from punch and superficial scrapings of IPK lesions were determined by comparing them with the histopathological results. Statistical analyses were performed using GraphPad Prism version 8.0.1 (GraphPad Software).

3 | RESULTS

The study included 51 patients with a mean age of 52 years (range 18–76) and 62.7% (32 of 31) of the participants were female (Table 1). All data from the study is summarized in Supporting Information S1: Table S1. The mean time of evolution was 9.9 years. All cases presented as a solitary IPK lesion, which in most cases developed on the weight-bearing areas of the foot and was tender in all cases. Fourteen patients (27.5%) exhibited an IPK in their third metatarsal (M3), which was the most common lesion, followed by the M2, M4, and M5, for 11 (21.6%), nine (17.6%), and eight (15.7%) patients, respectively.

The analytical results of histopathological examination and PCR tests are detailed in Table 2. Histopathological examination revealed 35 (68.6%) warts and 16 (31.3%) cases of keratosis. However, HPV was detected in 49 (96.1%; $p = 0.0004$) samples obtained by biopsy and 42 (82,4%; $p = 0.1665$) samples obtained by superficial scraping, including 14 of 16 lesions determined as keratosis by histopathology. PCR of superficial scrapings, not biopsies, failed to detect plantar wart in seven cases. Two lesions were consistently considered as keratosis by histopathology and were negative for HPV PCR in both samples (biopsy and scraping).

Among the smokers, 18 (35.3%) IPKs were diagnosed as plantar wart and nine (17.6%) as keratosis. In the nonsmokers, 17 (33.3%)

TABLE 1 Patient characteristics ($n = 51$).

Gender	
Female; *n* (%)	32 (62.7)
Male; *n* (%)	19 (37.3)
Age (years); mean ± SD	52.2 ± 13.4
Time to develop of IPK (years); mean ± SD	9.9 ± 9.5
Nonsmoker; *n* (%)	24 (47.1)
Smoker; *n* (%)	27 (52.9)
IPK location; *n* (%)	
M1	5 (9.8)
M2	11 (21.6)
M3	14 (27.5)
M4	9 (17.6)
M5	8 (15.7)
IPJH	2 (3.9)
Heel	2 (3.9)

Abbreviations: IPJH, interphalangeal joint of the hallux; IPK, intractable plantar keratosis; M, metatarsal; SD, standard deviation.

TABLE 2 Analysis of correlation between histopathology and PCR tests for IPK diagnosis.

Histopathology (biopsy)	HPV PCR Biopsy* Positive *n* (%)	HPV PCR Biopsy* Negative *n* (%)	HPV PCR Superficial scrapping** Positive *n* (%)	HPV PCR Superficial scrapping** Negative *n* (%)
Plantar wart *n* = 35 (68.6%)	35 (68.6%)	0 (0.0%)	28 (54.9%)	7 (13.7%)
Keratosis *n* = 16 (31.3%)	14 (27.5%)	2 (3.9%)	14 (27.5%)	2 (3.9%)
Total	49 (96.1%)	2 (3.9%)	42 (82.4%)	9 (17.6%)

Abbreviations: HPV, human papillomavirus; IPK, intractable plantar keratosis; PCR, polymerase chain reaction.

*p = 0.0004; **p = 0.1665 versus histopathological diagnosis (Fisher's Exact Test).

TABLE 3 Prevalence of HPV types determined by PCR of biopsy samples and correspondence with positive cases detected by PCR of scraping samples or by histological analysis.

HPV types	PCR Biopsy HPV -positive *N* = 49 (%)	PCR Superficial scraping HPV-positive *N* = 42 (%)	PCR Superficial scraping HPV-negative* *N* = 7 (%)	Histopathological analysis Biopsy* Plantar wart *N* = 35 (%)	Histopathological analysis Biopsy* Keratosis *N* = 14 (%)
HPV1	6 (12.5)	6 (14.3)	0 (0.0)	4 (11.8)	2 (14.3)
HPV2	8 (16.7)	7 (16.7)	1 (14.3)	5 (14.7)	3 (21.4)
HPV4	3 (6.3)	2 (4.8)	1 (14.3)	2 (5.9)	1 (7.1)
HPV9	1 (2.1)	1 (2.4)	0 (0.0)	0 (0.0)	1 (7.1)
HPV19	1 (2.1)	1 (2.4)	0 (0.0)	0 (0.0)	1 (7.1)
HPV27	9 (18.8)	9 (21.4)	0 (0.0)	6 (17.6)	3 (21.4)
HPV57	12 (25.0)	8 (19.0)	4 (57.1)	10 (29.4)	2 (14.3)
HPV63	2 (4.2)	2 (4.8)	0 (0.0)	2 (5.9)	0 (0.0)
HPV65	5 (10.4)	5 (11.9)	0 (0.0)	4 (8.3)	1 (7.1)
HPV111	1 (2.1)	1 (2.4)	0 (0.0)	1 (2.9)	0 (0.0)
HPV209	1 (2.1)	0 (0.0)	1 (14.3)	1 (2.9)	0 (0.0)

Note: Percentage (%) represents the relative percentage of HPV types versus the number of column cases.

Abbreviations: HPV, human papillomavirus; PCR, polymerase chain reaction.

*HPV types detected from PCR-positive biopsies.

were diagnosed as plantar warts and seven (13.7%) as keratosis (Supporting Information S1: Table S2). The histopathological (p = 0.7724) and PCR findings (p = 0.2165) were not significant different according to smoking status of patients. Plantar warts and keratosis were diagnosed homogeneously in smoker and nonsmoker subjects, regardless of technique.

The result of the histopathological analysis was independent of the time of evolution. Median evolution time for keratosis was 7.5 years compared to 7 years for plantar wart (p = 0.6104). Nevertheless, lesions with superficial HPV detection (n = 42, median 5.0 years) had a significantly shorter evolution time (p = 0.0214) compared to superficial HPV-negative samples (n = 7, median 20.0 years). The two HPV-negative lesions (biopsy and scraping) diagnosed as keratosis had a time of evolution of 5 and 10 years, respectively. For keratosis diagnosed by histopathology, no preferred location was observed (Supporting Information S1: Table S3).

Table 3 shows the prevalence of HPV types in the IPK lesions detected in the biopsy samples. The most common HPV types detected were HPV1, HPV2, HPV27, HPV57, and HPV65, which accounted for 81.6% of the IPKs. The types identified in the HPV-positive scraping samples matched those found in the biopsy samples. Furthermore, the distribution of HPV types in false negatives (HPV-negative scraping samples or keratosis determined by histopathology) showed heterogeneity that is consistent with the prevalence of types detected in cases confirmed by all three methods.

The diagnostic accuracy of HPV PCR of punch and surface scraping samples for IPK compared to histopathological study is

TABLE 4 Diagnostic accuracy of HPV PCR from biopsy and superficial scraping of IPK compared to the histopathological study.

	HPV PCR Biopsy Value (95% CI)	HPV PCR Superficial scraping Value (95% CI)
Sensitivity	100.0 (90.1–100.0)	80.0 (63.0–91.5)
Specificity	12.5 (2.2–36.0)	12.5 (1.5–38.3)
Positive predictive value	71.4 (57.5–82.1)	66.6 (60.9–71.9)
Negative predictive value	100.0 (17.7–100.0)	22.2 (6.2–55.0)
Kappa test	0.16 (−0.04 to 0.36)	−0.08 (−0.32 to 0.15)

Abbreviations: CI, confidence interval; HPV, human papillomavirus; IPK, intractable plantar keratosis; PCR, polymerase chain reaction.

shown in Table 4. HPV PCR of biopsy samples showed a high sensitivity (100%) for the detection of HPV and slight agreement (Kappa: 0.16) with the histopathological study when plantar wart was diagnosed. HPV PCR of superficial scraping samples showed lower sensitivity (80%) for the detection of HPV and no agreement (Kappa: −0.08) was found between superficial scraping for IPK and the histopathological examination.

4 | DISCUSSION

This study has been conducted to determine the role of HPV in IPK, demonstrating that the association between these lesions and HPV is much more prevalent than reported in scientific literature. To our knowledge, this is the first study to determine the presence of HPV in IPK by PCR and histopathology.

An IPK is a painful cystic degeneration that occurs in a calloused area due to excessive shearing forces on a sharp bony projection or a focalized area. This is usually caused by abnormal biomechanics and structural deformities in the foot. The distinctive clinical presentation of IPK informs the diagnosis and guides the therapeutic management of the lesion. The treatment is limited to removing the pressure areas that respond to the origin of the pain, either through conservative methods or corrective surgical interventions.[18]

The identification of a deep core, that is, visible after the removal of surface calluses and connects with a bony projection or pressure zone during clinical examination, with or without the support of noninvasive diagnostic microscopic techniques, is considered sufficient to establish the diagnosis of IPK, although several studies warn of the need for complementary analytical techniques to differentiate IPK from other entities that mimic it, such as plantar warts.[1,13,18–20]

Although it is universally accepted that IPK's etiology is mechanically influenced, histopathological examination of central core removal after surgery has revealed that 50% of IPKs are really plantar warts.[12] Our histopathological findings confirm this, demonstrating that 68.6% (35 out of 51) of IPKs in our series were plantar warts.

However, the PCR diagnosis targeting HPV revealed that an alarming 96.1% of IPKs (49 out of 51 suspected) concealed a plantar wart, including the majority (14 out of 16) of keratosis diagnosed by histopathological examination. Eighty percent of the HPV detected belong to the five most common types causing plantar warts (HPV1, HPV2, HPV27, HPV57, and HPV65). The majority of the remaining HPV types identified in our series have previously been reported to cause plantar or skin warts[8,21] and, with the exception of HPV types 9 and 19 (one case of each), all cases were confirmed as plantar warts by the histopathological analysis.

IPK is a frequently recurring injury, even following corrective surgery for the presumed foot deformity.[12,19,22] After surgical excision of the corns, Lopez et al.[12] reported IPK recurrences at 6-month follow-up in approximately 50% of the lesions, regardless of whether they were diagnosed as plantar wart (53%) or keratosis (43%) by histopathology. Koltaj et al.[19] found a lower recurrence rate of 23% at 1 year of follow-up compared to Lopez's study, which was achieved using the Er:YAG laser for tissue lesion ablation. Clinical examination of all the recurrent lesions indicated the signs of plantar warts and they were therefore treated with Nd:YAG laser therapy for plantar warts, which uses a deep penetrating photothermal effect to eradicate viruses under the lesions. The author assumed that these lesions had concurrent IPK and plantar wart at baseline and that HPV is responsible for the recurrence of IPK. It is probable that the reduced recurrence rate observed in this study is connected to an improved therapeutic approach for eliminating the virus located under the IPK.

According to the aforementioned studies, the inefficacy of IPK treatment may be attributed to the skin lesion not being caused by mechanical keratosis, but rather by a viral infection or a combination of both aetiologies. This fact confirms the need for an analytical diagnosis to complement the clinical examination of IPKs, which in any case, given the false negatives found in our series with histological examination, should be targeted specifically to detect HPV.

One potential explanation for the false positives found in the histopathology study is that the histopathological technique would be virtually insensitive compared to biopsy PCR when the active virus is located in deep tissues or underneath exceptionally keratotic lesions.

The power of detection by histological examination is not reliant on the evolution time of the lesion, as the duration of symptoms of lesions diagnosed as both keratosis and plantar warts was similar in our study (7.5 vs. 7 years, respectively). However, the time of evolution may be a variable that conditions the proportion of potentially detectable plantar warts. The histological identification of plantar warts in our study was comparatively higher than that observed in Lopez's study for lesions with a much shorter duration of symptoms (5.5 years), so it is possible that the infection progresses by contiguity with more superficial tissues or that the infection reduces the migration of cells that thicken the keratosis as the duration of symptoms increases, favoring the histological identification of plantar warts.

Biopsy is widely considered the gold standard sampling method for HPV diagnosis by PCR. However, recent studies have reported

excellent sensitivity (100%) of the technique when using scrapes or swabs from superficial skin samples for detecting cutaneous warts.[10,11,23]

Our findings demonstrate that PCR is a highly sensitive technique for detecting plantar warts in IPK lesions obtained from biopsies, but less so (80%) from superficial scrapings. Nonetheless, using scrape sampling, PCR detected HPV in 42 of 49 lesions with HPV-positive biopsies, which included the 14 keratoses identified by histology, with only seven false negatives. Scraping samples yielded identical HPV types to the biopsy counterpart. On the other hand, it is noteworthy that lesions associated with false negatives from scrapings showed a significantly longer duration of symptomatology (median 20 years) than that of lesions correctly diagnosed as plantar warts using this sampling method (median 5 years). Therefore, it seems that for these long-lasting lesions, is recommended the detection of HPV from deep tissues. From a pathological viewpoint, HPV inoculation into a keratinocyte requires prior epidermal abrasion or mechanical trauma and a transiently impaired immune system.[24] Given the extraordinarily high prevalence of HPV as a transient microorganism in normal skin in the general population,[6,7] it is not surprising that many cases of plantar warts in IPK lesions are caused by activation of pre-existing HPV rather than direct contact transmission.

The negative effects of smoking on skin health and healing have been described in the dermatological and surgical literature for many years,[25] and there is speculation that it may be a risk factor for the development of IPK.[3] However, using histopathological examination as a diagnostic reference, our study did not show a higher incidence of keratosis in smokers. Similar findings were reported by Lopez et al.[12]

Our study is limited by its single-institution nature, in which the clinical examination relies on the assessment of a single observer.

In conclusion, this study demonstrates that HPV infection and IPK lesions are more closely related than suggested by the scientific literature. Although we cannot confirm that HPV is the cause of the onset and development of IPK, the high prevalence of HPV observed in these lesions calls for a change in the procedures for managing IPK, both diagnostically and therapeutically. It is currently unclear whether eradicating the HPV would effectively treat the pathology without the support of complementary measures to alleviate the problem of mechanical plantar pressure, especially if the patient is an HPV carrier.

AUTHOR CONTRIBUTIONS

Luis Alou: Writing—review and editing; formal analysis. **Ricardo Becerro-de-Bengoa-Vallejo**: Conceptualization; supervision; project administration. **Marta E. Losa-Iglesias**: Writing—original draft. **Juan Moreno**: Investigation; data curation; visualization; resources. **Rubén Sánchez-Gómez**: Writing—original draft. **Natalia González**: Investigation. **David Sevillano**: Writing—review and editing; formal analysis.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ETHICS STATEMENT

The Ethics Committee of the Universidad Rey Juan Carlos, Madrid, Spain (code: 0703201905919) approved this research, and all subjects signed the informed consent form before the start of the study.

ORCID

Luis Alou http://orcid.org/0000-0002-0859-008X
Ricardo Becerro-de-Bengoa-Vallejo http://orcid.org/0000-0003-1568-7602
Marta E. Losa-Iglesias http://orcid.org/0000-0001-7588-2069
Juan Moreno http://orcid.org/0009-0004-1925-7508
Rubén Sánchez-Gómez http://orcid.org/0000-0001-7071-9860
Natalia González http://orcid.org/0000-0002-6874-954X
David Sevillano http://orcid.org/0000-0003-0212-2194

REFERENCES

1. Pontious J, Lane GD, Moritz JC, Martin W. Lesser metatarsal V-osteotomy for chronic intractable plantar keratosis. Retrospective analysis of 40 procedures. *J Am Podiatr Med Assoc*. 1998;88:323-331.
2. Mann RA, Mann JA. Keratotic disorders of the plantar skin.*J Bone Jt Surg*. 2004;85:938-955.
3. Ahn C, Mulligan P, Salcido R. Smoking-the bane of wound healing: biomedical interventions and social influences. *Adv Skin Wound Care*. 2008;12:227-236.
4. Guo S, Dipietro LA. Factors affecting wound healing. *J Dent Res*. 2010;89:219-229.
5. Watkins P. Identifying and treating plantar warts. *Nurs Stand*. 2006;20:50-54.
6. Antonsson A, Forslund O, Ekberg H, Sterner G, Hansson B. The ubiquity and impressive genomic diversity of human skin papillomaviruses suggest a commensalic nature of these viruses. *J Virol*. 2000;74:11636-11641.
7. Hazard K, Karlsson A, Andersson K, Ekberg H, Dillner J, Forslund O. Cutaneous human papillomaviruses persist on healthy skin. *J Invest Dermatol*. 2007;127:116-119.
8. de Planell-Mas E, Martínez-Garriga B, Zalacain AJ, Vinuesa T, Viñas M. Human papillomaviruses genotyping in plantar warts. *J Med Virol*. 2017;89:902-907.
9. Zhu P, Qi RQ, Yang Y, et al. Clinical guideline for the diagnosis and treatment of cutaneous warts (2022). *J Evid Based Med*. 2022;15:284-301.
10. García-Oreja S, Álvaro-Afonso FJ, Sevillano-Fernández D, Tardáguila-García A, López-Moral M, Lázaro-Martínez JL. A non-invasive method for diagnosing plantar warts caused by human papillomavirus (HPV). *J Med Virol*. 2022;94:2897-2901.
11. de Koning MNC, Khoe LV, Eekhof JAH, et al. Lesional HPV types of cutaneous warts can be reliably identified by surface swabs. *J Clin Virol*. 2011;52:84-87.
12. Lopez FM, Kilmartin TE. Corn cutting in the 21st century. *Podriatr Now*. 2016;19:24-27.
13. Tollafield DR. Clinical photographic observation of plantar corns and callus associated with a nominal scale classification and inter-observer reliability study in a student population. *J Foot Ankle Res*. 2017;10:45.

14. Reilly IN, Longhurst B, Vlahovic TC. Surgical excision of intractable plantar keratoses (Corns) of the foot: a scoping review. *J Am Podiatr Med Assoc*. 2023;113:22-044.
15. Agha R, Abdall-Razak A, Crossley E, et al. STROCSS 2019 guideline: strengthening the reporting of cohort studies in surgery. *Int J Surg*. 2019;72:156-165.
16. Lei YJ, Gao C, An R, et al. Development of a multiplex PCR method for detecting and typing human papillomaviruses in verrucae vulgaris. *J Virol Methods*. 2008;147:72-77.
17. Forslund O, Ly H, Higgins G. Improved detection of cutaneous human papillomavirus DNA by single tube nested 'hanging droplet' PCR. *J Virol Methods*. 2003;110:129-136.
18. Mann RA. Intractable plantar keratosis. *Instr Course Lect*. 1984;33:287-301.
19. Koltaj S. Er:YAG laser treatment of Intractable Plantar Keratosis (IPK). *LA&HA - J Laser Health Acad*. 2013;2013:32-35
20. Bae JM, Kang H, Kim HO, Park YM. Differential diagnosis of plantar wart from corn, callus and healed wart with the aid of dermoscopy. *Br J Dermatol*. 2009;160:220-222.
21. Kuriyama Y, Kosaka M, Kaneko A, et al. Skin surface material for detecting human papillomavirus infection of skin warts. *J Dermatol*. 2023;50:1450-1458.
22. Finney SM, Kilmartin TE, Flintham C. The modified Schwartz procedure in the management of intractable plantar keratoses: a retrospective review. *Foot*. 2003;13:108-113.
23. Bruggink SC, de Koning MNC, Gussekloo J, et al. Cutaneous wart-associated HPV types: prevalence and relation with patient characteristics. *J Clin Virol*. 2012;55:250-255.
24. Vlahovic TC, Khan MT. The human papillomavirus and its role in plantar warts. *Clin Podiatr Med Surg*. 2016;33:337-353.
25. Thomas J, Merrill VV, Rodriguez LA. Relationship between smoking and plantar callus formation of the foot. The podiatry institute. *Inc*. 2012;38:196-199.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Alou L, Becerro-de-Bengoa-Vallejo R, Losa-Iglesias ME, et al. Strengthening the relationship between intractable plantar keratosis and human papillomavirus. *J Med Virol*. 2024;96:e29431. doi:10.1002/jmv.29431