Case Reports in Dermatology

Case Rep Dermatol 2022;14:275–282
DOI: 10.1159/000525896
Received: May 20, 2022
Accepted: June 30, 2022
Published online: October 4, 2022

Single Case

Treatment of Condylomata Acuminata Using a New Non-Vapor-Generating Focused Ultrasound Method following Imiquimod 5% Cream

Jacek Calik[a] Tomasz Zawada[b] Torsten Bove[b]

[a]Old Town Clinic, Wroclaw, Poland; [b]TOOsonix A/S, Hoersholm, Denmark

Keywords
Human papillomavirus · Condylomata acuminata · Genital warts · Anogenital warts · High-intensity focused ultrasound · Focused ultrasound

Abstract
Condylomata acuminata is the most common sexually transmitted disease in the world. Physical treatments include excision, cryotherapy, electrocautery and ablative CO_2, and Nd:YAG laser ablation, while topical treatments include imiquimod immunotherapy and antimitotic podophyllotoxin or sinecatechins. Efficacies of all methods are low, and recurrences are very common. A new combined method is presented as a single case in a 25-year-old male patient diagnosed with numerous condylomas on the penis, scrotum, and lower abdomen. The treatment consisted of a 7-week topical monotherapy using 5% imiquimod cream followed by local treatment with 20 MHz high-intensity focused ultrasound on remaining recalcitrant lesions. Results showed resolution of approximately 70% of the condylomas after imiquimod treatment, and full resolution of all recalcitrant condylomas treated subsequently with high-intensity focused ultrasound. The method is concluded to be safe and effective and, furthermore, presents a new physical method that does not generate airborne infectious human papillomavirus particles that pose a health risk for the medical team performing therapy. Further studies in larger populations are recommended to confirm the combined efficacy of the proposed method.

Correspondence to:
Torsten Bove, torsten.bove@toosonix.com

Case Rep Dermatol 2022;14:275–282
DOI: 10.1159/000525896

Introduction

Condylomata acuminata, also referred to as genital warts, anogenital warts, or condylomas, is the most common sexually transmitted disease in the world. The disease is caused by human papillomavirus (HPV), most often of subtype 6 and 11, but includes more than 30 other subtypes [1]. The HPV infection will often result in development of benign skin and mucosal tumors including genital warts but, in some cases, may develop into malignant cancers. HPV 6 and 11 are highly infectious, and approximately 65% of individuals with an infected sexual partner contract the virus within 3 weeks and 8 months. Active treatment should therefore be prioritized directly upon diagnosis in order to stop further spread of the disease. Furthermore, the presence of HPV virus in sexually active adults may be indicative for the presence of other sexually or contact transmitted diseases and a full diagnosis for both HPV and other active or latent diseases, e.g., HIV, hepatitis, syphilis, etc., may therefore be relevant [1–3].

Guidelines for diagnosis and therapy have been published and updated on a regular basis [4–8]. Recommended physical treatments typically include excision, cryotherapy, electrocautery and ablative CO_2, and Nd:YAG laser ablation, while topical treatments include imiquimod immunotherapy and antimitotic podophyllotoxin or sinecatechins. In all cases, efficacy is relatively low and recurrences are very common, and while larger systematic investigations are not available, combination treatments are reported as necessary to obtain full resolution [1, 2]. In this study, we show the case of a patient treated with a combination of conventional topical therapy followed by a new physical focused ultrasound method to optimize the therapeutic effect and improve the overall safety profile of the treatment for both patient and medical team.

Case Presentation

A 25-year-old patient came to the Old Town Clinic concerned about the presence of skin lesions in the lower abdomen area. The man first noticed the lesions on the skin 2 months before the described visit (November 2021). After clinical and dermoscopic evaluation, the lesions were identified as condylomata acuminata in the form of white papules arranged in clusters with the presence of centered vessels. The lesions were multiple (several dozen) but did not give the patient discomfort except for the awareness of having them. A macro-photo of the condition as presented at the initial visit is shown in Figure 1.

During the medical interview, it was established that the man was sexually active with various partners. He could not identify from whom he could have contracted the infection. The patient was advised to avoid sexual contact until the lesions were cured, and gynecological examination of the patient's sexual partners was advised.

According to internationally accepted guidelines for treatment [4–7], large-field immunotherapy with topical 5% imiquimod cream (Aldara®; MEDA Pharma GmbH & Co. KG, Bad Homburg, Germany) applied externally to the general affected area covering the genitals and lower abdomen was initiated immediately. Initially, imiquimod cream applied once every second day was prescribed to assess tolerability and efficacy. At the first clinical evaluation after 7 days, neither adverse response nor activity of the drug in the form of inflammation in the lesions was observed. Due to the extent of the lesions and the lack of the early clinical effect, an intensified therapy using imiquimod cream daily for 5 consecutive days with a 2-day break before next clinical evaluation was therefore prescribed. At the following clinical evaluation, the expected inflammation had started, and the treatment regime was therefore continued for further 2 weeks. In this period, a clearly intensified inflammatory process

Case Rep Dermatol 2022;14:275–282
DOI: 10.1159/000525896

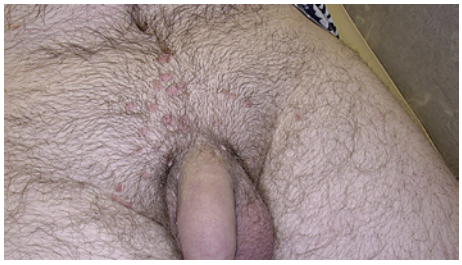

Fig. 1. Macro-photo at initial visitation. The subject has widespread condylomata acuminata around the genital area and lower abdomen.

affecting most of the condyloma lesions was observed. The therapy was continued for further 3 weeks until dry scabs were spontaneously released. The total duration of therapy with 5% imiquimod was thus 7 weeks. In the opinion of the practitioner, the maximum therapeutic effect using this treatment was achieved at that point, and no further improvements could be expected.

A complete regression of viral infection was observed in most of the treated lesions, but several active condylomas could still be identified, mainly in the central part of the lower abdomen. Together with the patient, a decision was made to radicalize treatment using physical methods. The following options were taken into account: cryotherapy, laser therapy, electrocautery, and high-intensity focused ultrasound (HIFU). Due to the small size of individual lesions and a low pain threshold of the patient, it was agreed to use high-frequency HIFU. The method was furthermore favored by the patient as it is not damaging to, or influenced by, the presence of hair in the area.

Treatments were performed using a medical 20 MHz HIFU system (System ONE-M®; TOOsonix A/S, Hoersholm, Denmark). This device can be used to target features near the surface of the skin, and reproducibly deliver a clinically efficient thermal and mechanical insult with localized heating to approximately 60–65°C that will spontaneously kill cells and denaturate fibrous tissue. The system has earlier been demonstrated to provide safe and efficient treatment of other dermatological indications, including basal cell carcinoma and Kaposi sarcoma [9], actinic keratosis [9, 10], seborrheic keratosis [11], superficial vascular tumors [12], and verruca vulgaris [13].

With very superficial location of lesions, a HIFU handpiece with nominal focal depth (NFD) of 0.8 mm is preferred for the treatment, thus utilizing the most superficial focal depth available from the standard range delivered with the system. With this superficial treatment modality, an ablative method is obtained, whereby the HIFU by intention produces a superficial necrotic volume that will convert to a thin external wound scab that heals over the following few weeks. Handpieces with deeper focal depths for nonablative treatments without scab formation are available but were not relevant for this case.

Results from prior treatments indicate that virus infected cells are removed directly in the wound crust, and that the healing process furthermore may induce a wider beneficial immune response in the directly adjacent/deeper nontreated tissue [9, 13]. Sequelae have been very limited, and only sporadic cases with further fibrous change of an already damaged dermis have been observed [9–13].

Prior to treatment, the handpiece goes through a standard preparation procedure, whereby a cross-hair observed on a high-resolution video feed on the system's computer user interface is manually placed at the exact location of the focal zone, thereby securing accuracy of treatment within some ±100 μm in the horizontal plane.

Using the video feed from the integrated dermoscope in the handpiece, remaining persistent lesions after imiquimod treatment can be identified, and focal zones can be centered in the upper part of each lesion without damaging deeper skin structures. "Shoulder-by-shoulder"

Case Rep Dermatol 2022;14:275–282
DOI: 10.1159/000525896

Fig. 2. Dermoscope picture of a recalcitrant condyloma. **a** Condyloma after completed 5% imiquimod treatment regime. **b** Condyloma directly after HIFU treatment; a whitening effect can be observed where HIFU dosing has caused light edema. **c** Treated field 5 weeks after a single HIFU treatment; a light increased vessel network and light fibrotic changes to the skin structure can be observed, but condyloma is no longer visible.

HIFU doses of 1.1 J/dose at durations of 150 ms/dose are administered with a distance of approximately 1 mm between each dose to fully cover each lesion, including a small circumferential margin of approximately 1 mm. Repetition of each dose is approximately 1–2 s. Progress and status of treatments is monitored in real-time via the video feed from the dermoscope in the handpiece, which clearly shows treated areas as raised lighter points where the epidermis is lifted or partly separated. Standard ultrasound gel (Aquasonic 100®; Parker Laboratories Inc., Fairfield, NJ, USA) is used to provide acoustic coupling between the handpiece and skin.

An initial test treatment session using the above method was started at the 7-week clinical evaluation visit, where topical imiquimod therapy was considered complete. Due to the pain that appeared immediately after the start of the procedure, scored at severity 5 on a 0–10 point VAS scale, the procedure was stopped with a plan to perform it later after applying appropriate premedication. Six days later, the test treatment was resumed. About 60 min before the procedure, the patient received an analgesic pain relief, 2 tablets each containing 37.5 mg tramadol + 325 mg paracetamol (Doreta®; KRKA, Novo Mesto, Slovenia). Treatment on selected visible persistent viral lesions on the lower abdomen, the base of the penis, and on the scrotum was administered. In this case, the procedure could be carried out without complications, and the patient scored average pain at 2 on a 0–10 point VAS scale.

A second full HIFU procedure on all remaining active lesions, and using the same premedication protocol, was performed 2 weeks after the first session. Lesions on the penis and scrotal sac were treated with the assistance of skin eversion by the operator's finger in order to minimize pain and increase the precision of the procedure by stabilizing flaccid skin in the genital area.

HIFU-treated lesions were evaluated 5 weeks after the first session. A full therapeutic effect was achieved, with complete elimination of all treated condylomas. A structure of repair vessels and slight scarring could be observed in the treated fields after the procedure by dermoscope but without signs of recurrence of the disease. Figure 2 shows dermoscopic pictures (Fotofinder Medicam 1000®; FotoFinder Systems GmbH, Bad Birnbach, Germany) of a recalcitrant condyloma before and after HIFU treatment and after 5 weeks of healing. The immediate whitening effect following each HIFU dosing of ultrasonic energy to the target can be observed. Five weeks after treatment the field is almost fully normalized and only very small fibrotic and vascular changes can be observed.

A careful dermoscopic assessment of the entire potentially infected area of the skin using the integrated dermoscope camera in the handpiece of the HIFU device was performed at the 5-week visit. Here, 6 additional minor lesions with a diameter of about 1–2 mm were noticed, which corresponded to persistent condylomas. These lesions were not noticed in the previous visits due to the densely growing hair and the assessment of lesions before the procedure using a manual dermoscope with ×10 magnification only. A final HIFU treatment of these

Case Rep Dermatol 2022;14:275–282
DOI: 10.1159/000525896

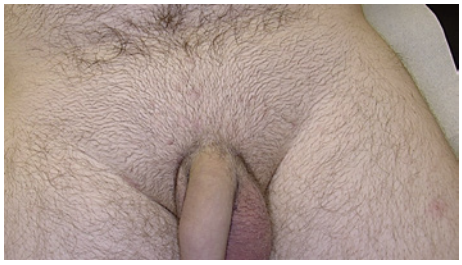

Fig. 3. Macro-photo of subject after completed treatment for 7 weeks of 5% imiquimod cream followed by HIFU treatment. The total healing period after the first test HIFU treatment was 64 days, 50 days after the "main" treatment, and 22 days after a treatment of 6 very small additional elements not observed in the first visits. A full resolution has been confirmed by dermoscopic examination. Note: Patient performed shaving of genital hair during healing period. No damage to hair follicles could be observed.

6 omitted condylomas was performed 7 weeks after the first treatment. Figure 3 shows a macro-photo of the general affected area 118 days (approximately 17 weeks or 4 months) after the treatment was started with imiquimod and subsequent HIFU treatment. To consolidate the response to treatment, the patient was vaccinated with the first dose of HPV vaccine (Gardasil 9®; MSD/Merck and Co., Inc., Kenilworth, NJ, USA) with a plan for subsequent dosing given at the prescribed periods of 2 and 6 months after the first injection.

Clinical Post-Note

One of the patient's sexual partners came to the Old Town Clinic, where she was gynecologically examined and a Pap smear was performed for the presence of 14 types of HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68. The examination was performed to assess whether there had been infection during sexual contact with potentially oncogenic strains of the virus. Genetic testing did not confirm the presence of genetic material of the above-mentioned viruses, nor were lesions of the nature of condylomas observed. The patient was offered anti-HPV vaccination. The patient and his partner are currently under clinical observation.

Discussion/Conclusion

The current case of treatment of condylomata acuminata in a young man shows a complete resolution of lesions with good treatment tolerance after large-field 5% imiquimod immunotherapy followed by targeted HIFU therapy on recalcitrant lesions.

The partial resolution of about 70% of the lesions after topical treatment matches data from literature, where a very wide range of efficacies ranging from 35% to 95% is reported [1–8]. The case therefore also confirms that topical treatment cannot be relied upon as an efficient monotreatment but must be combined with adjuvant therapy in order to secure full resolution.

It should be noted that among the physical methods that can give high efficacy rates, when performed by experienced practitioners, ablative lasers, and electrocautery presents a secondary safety issue for both practitioners and patients. Fumes and aerosols generated during such procedures may transfer genetic material of the HPV virus, which can be absorbed by the medical team despite the use of appropriate protection in the form of masks, glasses, and smoke extraction. Most often, the genetic material of the virus is deposited in the nose, throat, or larynx, which may eventually cause cancer [1–7].

Case Rep Dermatol 2022;14:275–282
DOI: 10.1159/000525896

During use of System ONE-M, the target skin area is covered by liquid ultrasound gel, and dosing induces a fully controllable thermal effect that is confined in very small volumes inside the superficial layers of the skin. Each HIFU dose typically induce an immediate whitening effect with mild edema approximately 1 mm around each target, followed by a mild general urticarial flare-response in the surrounding 3–10 mm. There are no fumes, bleeding, or liquid discharges from the treated volume, which gradually converts into a dry scab over the following 1–3 days.

The method thus strongly minimizes any risk of airborne spreading of viral infections. Moreover, the only physical contact of the handpiece with the patient is covered by a single-use protective film. Risk of contact transfer of virus can thus be effectively managed by simple good clinical practices of wearing medical gloves, cleaning devices with alcohol, and changing the protective film between patients.

An additional advantage of using the HIFU system is the ability to carry out the procedure with extremely high precision (about 0.1 mm accuracy) due to the integrated dermoscope camera in the handpiece providing real-time observation of the area under treatment. In this context, it is worth mentioning that the integrated dermoscope of System ONE-M enabled visualization of the six very small lesions that were neither visible on a manual dermoscope (×10 magnification) nor on a FotoFinder video dermoscope at ×20 magnification.

The only adverse event noted during the procedure was acute pain during HIFU dosing to areas, which are known to have a high density of sensory nerves. This could however be mitigated by appropriate premedication with analgesic tablets. Treatment could thereby be completed with very low pain score and without subsequent down-time for the patient.

Finally, in contrast to, e.g., laser or electrocautery treatments, the absence of open wounds following HIFU treatment reduces the risks for pain and other complications during the healing phase significantly. Patients in general do not experience any pain or discomfort during the 5–8 week healing period.

In conclusion, the TOOsonix System ONE-M is found to be a promising modality for safe and efficient treatment of condylomata acuminata when used in combination with initial topical therapy. HIFU treatment in this study was spread over 3 individual sessions but could potentially be condensed significantly after clinical routine and optimized treatment protocols have been established.

As a single case-based study, the presented results are by nature not statistically significant or representative for a general population affected by the condition. The positive results however suggest and encourage that further studies with larger participant numbers of both sexes should be conducted.

Statement of Ethics

This study was conducted ethically and in accordance with the World Medical Association Declaration of Helsinki. The subject signed a written informed consent regarding participation in treatment and publication of the case including anonymized photographs. Ethical approval was not required for this study in accordance with local/national guidelines.

Conflict of Interest Statement

Torsten Bove and Tomasz Zawada are shareholders in TOOsonix A/S, a medical device manufacturer of dermatological HIFU systems including the System ONE-M used in this case. Jacek Calik is shareholder of The Old Town Clinic, a private multispecialist medical clinic.

There are no employment, bonuses, consultancies, honoraria, stock ownership, options, grants, patents, or any other relevant relationships between the two companies or its employees.

Funding Sources

The treatment presented in this study was performed on equipment funded by TOOsonix A/S.

Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of the manuscript. The authors contributed to the work with the following:

Jacek Calik: conception of treatment (only), clinical diagnosis (only), obtaining written consent (only), treatment of patient (only), patient follow-up (only), data acquisition and analysis (equal), and drafting and writing (equal). Tomasz Zawada and Torsten Bove: conception of technology (lead), data acquisition and analysis (equal), and drafting and writing (equal). Jacek Calik, Tomasz Zawada, and Torsten Bove take responsibility for the integrity of the work as a whole and grant final approval of the final publication.

Data Availability Statement

All data generated or analyzed during this study is included in this article. Further inquiries can be directed to the corresponding author.

References

1 James WD, Berger TG, Elston DM, editors. Andrews diseases of the skin. 12th ed. Philadelphia: Elsevier; 2016.
2 Yanofsky VR, Patel RV, Goldenberg G. Genital warts: a comprehensive review. J Clin Aesthet Dermatol. 2012 Jun;5(6):25–36.
3 Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. BMC Infect Dis. 2013;13:39.
4 Lacey CJN, Woodhall SC, Wikstrom A, Ross J. 2012 European guideline for the management of anogenital warts. J Eur Acad Dermatol Venereol. 2013 Mar;27(3):e263–70.
5 Workowski KA, Bolan GA. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep. 2015 June 5;64(RR3):1–137.
6 O'Mahony C, Gomberg M, Skerlev M, Alraddadi A, de Las Heras-Alonso ME, Majewski S, et al. Position statement for the diagnosis and management of anogenital warts. J Eur Acad Dermatol Venereol. 2019 Jun;33(6):1006–19.
7 Gilson R, Nugent D, Werner RN, Ballesteros J, Ross J. 2019 IUSTI-Europe guideline for the management of anogenital warts. J Eur Acad Dermatol Venereol. 2020 Aug;34(8):1644–53.
8 Grillo-Ardila CF, Angel-Müller E, Salazar-Díaz LC, Gaitán HG, Ruiz-Parra AI, Lethaby A. Imiquimod for anogenital warts in non-immunocompromised adults. Cochrane Database Syst Rev. 2014 Nov 1;(11):CD010389.
9 Serup J, Bove T, Zawada T, Jessen A, Poli M. High-frequency (20 MHz) high-intensity focused ultrasound: new treatment of actinic keratosis, basal cell carcinoma, and Kaposi sarcoma. An open-label exploratory study. Skin Res Technol. 2020;26(6):824–31.
10 Seyed Jafari SM, Cazzaniga S, Bossart S, Feldmeyer L, Pelloni L, van Rhyn M, et al. Efficacy assessment of the high-frequency high-intensity focused ultrasound as a new treatment for actinic keratosis. Dermatology. 2022;238(4):662–7.
11 Calik J, Migdal M, Zawada T, Bove T. Treatment of seborrheic keratosis by high frequency focused ultrasound: an early experience with 11 consecutive cases. Clin Cosmet Investig Dermatol. 2022 Jan 28;15:145–56.

Case Rep Dermatol 2022;14:275–282
DOI: 10.1159/000525896

12 Calik J, Zawada T, Bove T. Treatment of superficial benign vascular tumors by high intensity focused ultrasound: observations in two illustrative cases. J Cosmet Dermatol. 2021. Epub ahead of print.
13 Bove T, Zawada T, Jessen A, Poli M, Serup J. Removal of common warts by high-intensity focused ultrasound: an introductory observation. Case Rep Dermatol. 2021;13(2):340–6.