Topical medication as an initial therapeutic option for protruding and non-protruding condylomata acuminata of the distal urethra

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SUMMARY

Genital warts (also known as condylomata acuminata) caused by the human papillomavirus (HPV) represent one of the most common sexually transmitted infections. Although they are usually found in the outer genital region, a small proportion of men can present with (often unrecognised) intraurethral warts, generally limited to the distal urethra and urethral meatus. This poses a treatment challenge not adequately addressed by the current guidelines. Here, we present two cases of low-risk HPV-positive patients with protruding and non-protruding condylomata acuminata of the distal urethra, which were treated successfully by using two different topical regimens (ie, a combination of policresulen and imiquimod for one patient and 5-fluorouracil monotherapy for the other). Although this type of management results in lower rates of tissue destruction and complications and may be given preference as an initial therapeutic option, additional prospective comparative clinical studies are needed to elucidate its potential in similar cases.

BACKGROUND

Human papillomavirus (HPV) represents the most common sexually transmitted infection in the world, with more than 40 sexually transmitted viral genotypes that have been characterised and sequenced.[1] Based on their oncogenic potential, genital HPVs can be classified into high-risk types responsible for cervical cancer and other types of malignancies and low-risk (LR) types responsible for anogenital and cutaneous warts.[1]

In the latter group, genotypes 6 and 11 are the most frequent causes of such benign lesions—particularly genital warts (also known as condylomata acuminata), which affect millions of people around the world every year. More specifically, although a wide array of HPV types can cause genital warts, HPV 6 and 11 together account for approximately 90% of all cases.[2 3] The lesions can vary in shape, size and colour, appearing as smaller, flesh-coloured bumps or demonstrating a cauliflower-like appearance. In addition, they are highly infectious, showing transmission rates that exceed 60%.[4]

Previous studies have already established that HPV is more frequently demonstrated in the outer genital area when compared with the urethra.[5] Conversely, intraurethral warts are a rare presentation of anogenital warts, with valid epidemiological data lacking. They are often unrecognised and usually limited to the distal 2–3 cm of the urethra, most frequently in the urethral meatus.[6 7] This localisation can be associated with a plethora of complications, such as voiding difficulties, urethral bleeding, obstruction and fistula formation.[5]

The pertinent clinical question is what to choose as the optimal therapeutic modality for intraurethral condylomas from our available treatment armamentarium. Cryotherapy and/or electrocautery are still widely used and are often the method of choice for practitioners in treating intraurethral genital warts; however, they are considered rather invasive.[8 9] A recent systematic review showed that 5-aminolaevulinic acid photodynamic therapy is effective in terms of wart clearance and recurrences, although with a certain risk of adverse events.[10] In contrast, laser therapy has a lower rate of complications, but with the potential for severe adverse events such as urethral fibrosis and strictures.[6] Can topical treatment protocol then be considered an ideal initial approach?

Here, we present two cases of patients with protruding and non-protruding condylomata acuminata of the distal urethra that were successfully treated with two different topical treatment regimens (as a monotherapy and as a combination therapy), without disease recurrence after the follow-up period of 6 months.

CASE PRESENTATION

Two patients (aged 27 and 31) visited an outpatient clinic on separate occasions, primarily due to voiding difficulties. Patient 1 was a 27-year-old Caucasian heterosexual male individual with no medical or surgical history, no family history of autoimmune or chronic diseases and no previous hospitalisations. He reported smoking 20 cigarettes/day, and he denied taking any regular medication, alcohol consumption or recent travel. He reported voiding difficulties that had been present for 1 month, manifesting as weak urine stream in the absence of pain or visible haematuria.

Patient 2 was a 31-year-old Caucasian heterosexual male individual with a prior case of chlamydial urethritis in his medical history, but without any surgeries, previous hospitalisations or significant family history of autoimmune/chronic diseases. He denied smoking, alcohol intake, regular medications or recent travel. He reported slight voiding difficulties in the form of weak urine stream, but his primary concern was a visible papillomatous lesion protruding from the urethral orifice that was present for 2 weeks before he decided to pursue a

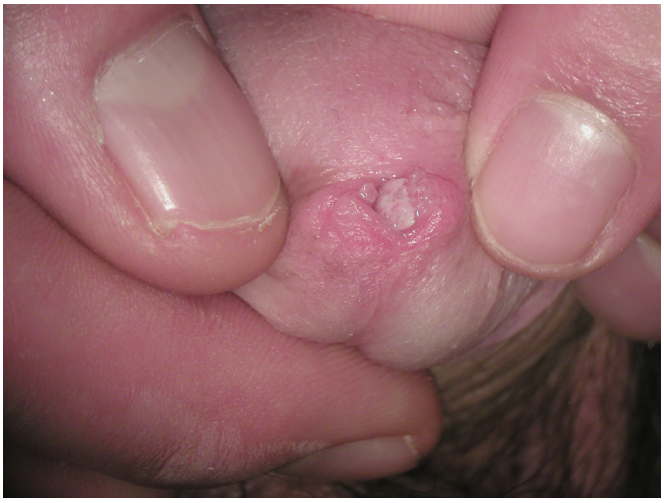

Figure 1 Non-protruding intraurethral condyloma (patient 1).

detailed medical check-up. There was no pain or visible haematuria present.

INVESTIGATIONS

Direct visualisation at magnification by using a photocolposcope (Olympus OCS 500 with a mounted Olympus C-4040ZOOM 4.1. megapixels camera) was pursued for both patients (by means of meatal eversion for patient 2 and without any intervention for patient 1), resulting in the clear visualisation of suspected condylomata acuminata of meatal/distal urethra (figures 1 and 2). As both patients refused biopsy of the lesions, in order to exclude potential coinfection with high-risk HPV serotypes, urethral swabs were tested with the hc2 HPV DNA Test using Hybrid Capture 2 technology (Digene Corporation Gaithersburg, USA), which is a signal amplified hybridisation antibody capture assay that uses microplate chemiluminescent detection. This showed the presence of LR HPV monoinfection in both patients (HPV type 6 in patient 1, and HPV type 42 in patient 2).

A complete anogenital and oral examination was performed for both patients, without any findings. Additional urological examination concentrating on the palpation and measurement of the testes and the identification of palpable varicoceles were uneventful in both patients. Doppler ultrasonography was used to exclude the possible presence of varicocele or testicular tumours, and suprapubic ultrasound was used to evaluate the prostate gland, which was normal in both patients. All ultrasonographic examinations were done with the use of a Philips ClearVue V.650 ultrasound machine with active array technology.

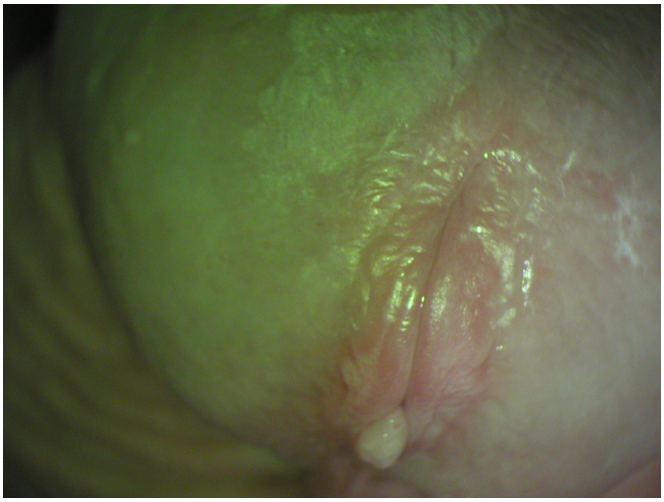

Figure 2 Protruding intraurethral condyloma (patient 2).

Moreover, taking into account the sexual history of both patients, a detailed microbiological assessment (using molecular approaches and culture techniques depending on the pathogen tested) of other common sexually transmitted infections was pursued, with negative findings for *Chlamydia trachomatis*, *Ureaplasma* sp, *Mycoplasma hominis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, other pathogenic aerobic bacteria and fungi in both patients. Rapid HIV tests, HBsAg, anti-HBC, anti-HCV and *Treponema pallidum* hemagglutination assay tests were negative in both cases. There were no inflammatory cells in the urine sediment of patient 1, while patient 2 had 10–15 erythrocytes per high-power field (centrifugal urine). Hence, the diagnosis of intraurethral condylomata acuminata was established.

TREATMENT

Patient 1 (ie, a 27-year-old with non-protruding intraurethral condylomas) was treated with an alternating or intermittent combined treatment approach using 36% policresulen solution (Albothyl) (Takeda GmbH, Singen, Germany) and 5% imiquimod cream (Aldara) (Meda AB, Solna, Sweden) intraurethrally. Such a combined, intermittent approach was introduced with a rationale of improving the long-term clinical outcome, that is, not only to minimise the risk of recurrence but also to decrease the possibility of imiquimod-associated adverse effects at application and non-application sites. These topical preparations were used intermittently three times per week for a total of 6 weeks, never concurrently (ie, on the same day) during the same treatment session. A shortened catheter was used for intraurethral instillation of 1.5 mL of policresulen solution, whereas a cotton swab was employed for intraurethral application of 100 mg of the imiquimod cream. Since this is considered an off-label use of the aforementioned products, the patient gave his informed consent after detailed explanation of the procedure and potential side effects/adverse reactions. The medication was applied by the treating physician, who was always the same person for the purpose of consistency. No adverse events were observed during the treatment course.

Patient 2 (ie, a 31-year-old with protruding intraurethral condyloma) was treated with topical 5% 5-fluorouracil cream (Efudix) (MEDA Pharma GmbH & Co. KG, Hamburg, Germany) intraurethrally as a monotherapy, three times per week for a total of 6 weeks. A cotton swab was used for intraurethral application of 100 mg of the cream. Since this is considered an off-label use of this product, the patient gave his informed consent after a detailed explanation of the procedure and potential side effects/adverse reactions. The medication was applied by the treating physician, who was always the same person for purposes of consistency. A mild dysuria was observed as an adverse event after the first two cream applications, but was not noted by the patient during the remaining treatment period.

OUTCOME AND FOLLOW-UP

The afore-described topical protocol resulted in complete resolution of lesions within the treatment period; more specifically, the lesions disappeared after 4 and 6 weeks of treatment for patient 1 and patient 2, respectively. A control visualisation of urethral meatus at magnification was conducted with the use of a photocolposcope (as described above) for both patients, showing a complete disappearance of lesions. Urine stream improved

for both patients, and microscopic erythrocyturia in patient 2 subsided as well. There were no recurrences during the follow-up period of 6 months. Further urological assessment (most notably urethroscopy) was recommended for both patients, which they declined.

DISCUSSION

Although condylomata acuminata are usually seen on the external genitalia, the urethra can uncommonly be affected as well, with lesions usually located in its distal part or in the urethral meatus[6 7]; this localisation of warts represents a true therapeutic conundrum for both physicians and the affected individuals. Consequently, our description of two patients represents a first literature report of combined intermittent topical treatment with 36% policresulen and 5% imiquimod for patient 1, showing a comparable effect in the regression of lesions and the lack of recurrences during the follow-up period when compared with the monotherapy with 5% 5-fluorouracil in patient 2.

What is specific for these two patients is a sole presence of condylomas in the urethra, which is rarely reported in the medical literature. For example, Olsen *et al* described condyloma acuminatum of the prostatic urethra and urethral meatus, without finding any lesions on the external genitalia.[11] Furthermore, in their study of biopsy-verified HPV infection, Fralick *et al* described 14 lesions confined solely to the urethra; of those, 8 manifested as a single lesion and six as multiple lesions.[12] More recently, Zayko *et al* described a patient with isolated papillary growth in the prostatic urethra without the presence of any lesions on external genitalia,[13] while Takahashi *et al* reported a patient presenting with a large number of genital warts at the urethral meatus following genital piercing, harbouring HPV types 6 and 66.[14]

Many treatment modalities have been tried for intraurethral condylomas, but none of them has been completely satisfactory. Surgical excision, fulguration and laser treatment carry a significant risk for stricture development; furthermore, podophyllum resin is effective for external lesions, but overly cytotoxic and irritating for intraurethral use.[6] Conversely, the use of 5-fluorouracil is well tolerated with occasional irritation, which corresponds to the initial wart burden, and certain authors have combined it with 2% lidocaine in the same syringe for instillation purposes.[6] In one of our patients, we showed that it can be applied successfully as a cream and in monotherapy.

There is ample literature on adverse effects of imiquimod that can be linked not only to local inflammatory reactions at the application site but also to adverse events in non-application sites (most notably fever); moreover, there have been anecdotal reports of distant inflammatory mucosal reaction.[15] We did not observe any type of adverse reaction in patient 1, who received imiquimod, possibly due to the planned intermittent treatment approach with the addition of policresulen, which enabled a more interspersed exposure to the cream and longer time periods between two applications when compared with more frequently used monotherapy regimens.

One limitation of our report is that the patients declined urethroscopy/cystoscopy procedures prior to treatment, which could have been used to appraise the whole urethra (not just the distal/meatal part) for the potential presence of condylomas as well as to use biopsy procedures for pursuing additional histopathological examination. This is a recommended procedure to exclude the potential presence of urothelial papillary carcinoma, and it enables ancillary studies such as HPV in situ hybridisation and p16 immunohistochemistry to support further the histological impression, as was recently done by Meliti *et al* in their case of condyloma acuminatum in the male urethra.[16] Still, patient reluctance in such instances is not uncommon and has been observed in cases akin to ours.[17]

Hence, following detailed consultation procedures with both patients and exhaustive clinical/microbiological investigations, we started directly with topical treatment. As already mentioned, some prior studies have already demonstrated the efficacy of topical application of certain chemotherapeutics in managing HPV-related changes of the urethra.[6 10] This is valid not only for 5-fluorouracil (which has been used most frequently alone or in combination with interferon-alpha 2a)[18] but also for cidofovir and BCG.[19 20] More recently, the use of 5-aminolevulinic acid photodynamic therapy was shown to be successful and safe in the treatment of condylomata acuminata of urethral meatus[21] and the whole anterior urethra.[22]

Extended condylomata acuminata can also be observed in the urethra of immunocompromised transplant patients, which then pose a particular therapeutic challenge. Consequently, Florin *et al* showed that a combination of surgical transurethral resection or the use of holmium-YAG (Yttrium Aluminium Garnet) laser with adjuvant intraurethral cidofovir instillations may be a salient treatment option in such cases without any evident side effects, circumventing in turn the need for more radical surgical approaches.[19] Nonetheless, recurrences are commonly observed in patients with immunosuppression, which means longer treatment courses may be required in such instances.[19 23] This is why reports of new topical combinations that are potentially effective are of increasing importance.

Official guidelines are starting to recognise the importance of implementing specific recommendations regarding intraurethral lesions, which are frequently approached on a case-to-case basis. Current guidelines state that treatment approaches should be individualised based not only on the location, number, morphology, size and keratinisation of warts but also on whether they are new or recurrent lesions[9 23 24]; furthermore, 2019 IUSTI Europe guidelines on anogenital warts recommend surgical treatment of intrameatal lesions—including excision, electrosurgery or laser ablation.[23] This is in line with a recent German guideline that provides a detailed section on the treatment of intrameatal and intraurethral genital warts, endorsing surgical/ablative methods as a treatment of choice.[25] A Cochrane systematic review has shown that 5-flurouracil is more effective for verrucae when compared with placebo,[26] while immunomodulatory therapies (such as imiquimod) are emphasised as having higher cure rates (despite lower initial clearance rates) and subsequently lower recurrence rates.[24] In our study, the combined approach of imiquimod with policresulen was pursued in order to further lower the possibility of disease recurrence. Portuguese guidelines also highlight a combination of treatments to increase effectiveness (ie, a proactive sequential treatment).[9] Croatian diagnostic–therapeutic guidelines for men with HPV-positive partners also do not address the specificities of intraurethral (or even meatal) localisation, which may have to be included in future iterations.[27]

For now, all intraurethral topical applications of chemotherapeutics and immunomodulatory preparations are off-label therapeutic modalities; therefore, this should always be explained to the patient. There is definitely a need for more prospective and comparative clinical studies, and potentially even clinical trials with enough power precisely to gauge the effectiveness and safety traits of specific topical preparations (as well as their combinations). In the future, dynamic monitoring of HPV viral loads (as already evidenced by Xie *et al*)[22] during the treatment

of intraurethral condylomata acuminata can also be used to demonstrate the effectiveness of the chosen approach objectively and to guide the local treatment methodically.

Learning points

- Intraurethral condylomata acuminata represent a rare but under-recognised manifestation of infection with human papilloma virus, usually affecting the distal part of the urethra in protruding and non-protruding fashion and resulting in a substantial treatment challenge.
- Modalities with less tissue destruction may be given preference as an initial therapeutic option; a novel approach of intermittent topical treatment with 36% policresulen and 5% imiquimod may be comparable to topical approaches already tried, such as monotherapy with 5% 5-fluorouracil.
- At the moment, all intraurethral topical applications of chemotherapeutics and immunomodulatory compounds are off-label therapeutic approaches, which should be clarified with the patient.
- Prospective comparative clinical studies will be needed to answer the question of what represents an optimal initial treatment regimen and subsequently inform guideline development.

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