Pediatric genital warts successfully treated with photodynamic therapy

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Abstract

Genital warts (GWs) are the most common sexually transmitted infections worldwide, caused by the human papillomavirus (HPV). In adults, the primary mode of transmission is through sexual contact, whereas in children, it can occur through skin-to-skin or skin-to-mucosa contact and be sexual or non-sexual. The increasing prevalence of GWs in children has renewed the interest in therapeutic management, which still presents a unique challenge, being influenced by many variables, including size, quantity, and location of warts, as well as the presence of comorbidities. Photodynamic therapy (PDT) has already shown encouraging results in treating viral warts in adult patients, but its use is still not standardized in the pediatric population. On this topic, we report the case of an otherwise healthy 5-year-old child affected by GWs, successfully treated with three sessions of PDT with 10% 5-aminolaevulinic acid (ALA) at one-month intervals. Our case is paradigmatic of the potential of PDT to treat difficult lesions in a pediatric setting.

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Key words: genital warts; photodynamic therapy; human papillomavirus; HPV; child sexual abuse.

Conflict of interest: the authors declare no potential conflict of interest.

Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Department because this article does not contain any studies with human participants or animals. Informed consent was obtained from the patient's parents.

Consent for publication: the authors certify that they have obtained all appropriate consent forms from parents. In these forms, parents consent to their child's images and other clinical information being reported in the journal. They acknowledge that the child's name and initials will not be published, and reasonable efforts will be made to protect their identity.

Availability of data and materials: all data underlying the findings are fully available.

Received: 29 February 2024.
Accepted: 24 August 2024.

Dermatology Reports 2025; 17:9979
doi:10.4081/dr.2024.9979

Introduction

Human papillomavirus (HPV) is considered the world's most common sexually transmitted disease. In adults, the primary mode of transmission is through sexual contact, whereas in children, it can occur through skin-to-skin or skin-to-mucosa contact and be sexual or non-sexual.[1] Autoinoculation or hetero-inoculation by parents or caregivers may account for horizontal transmission in female virgins or pediatric patients without a history of child sexual abuse (CSA).[1,2] Another explanation for non-sexually transmitted genital warts (GWs) in children is vertical transmission: during natural birth or cesarean section, the mother may directly transfer HPV to the newborn *via* contact with maternal genital mucosa or indirectly *via* contaminated objects or surfaces.[3] Theoretically, in-utero transmission may also occur both hematogenously, by semen at fertilization, or as a maternal ascendant infection.[4] Perinatal transmission combines vertical modes of transmission with horizontal transmission in the newborn period (kissing, diaper changing, and contaminated fomites).[1] Treatment is often difficult, especially in the pediatric setting. Several variables, including wart size, quantity, location, as well as the presence of comorbidities, influence treatment choices. No first-line therapy has been described in the pediatric population. Treatment choice should consider efficacy and tolerability equally.[5] Duress or pain related to therapeutic procedures should not overcome the advantages associated with the healing of the disease. The optimal approach for pediatric patients should be effective, painless, and easy to perform to ensure optimal compliance from both children and parents. Therapeutic options encompass medical (topical keratolytic, podophyllotoxin, and imiquimod) and physical treatments (electrosurgery, cryotherapy, laser ablation, and surgery).[5] However, these methods often present limitations such as local side effects (pain, scarring, hyper-/hypopigmentation), which adversely affect adherence to the treatment protocol. Additionally, many of them are effective only on visible lesions, not targeting subclinical ones, which increases the risk of recurrence. Furthermore, the risks of functional and psychological damage should not be underestimated in difficult-to-treat areas, including the genital area, especially in children.[6]

Photodynamic therapy (PDT) has demonstrated promising outcomes in treating viral warts in adults, achieving excellent aesthetic results with minimal side effects compared to other modalities.[7] However, its use in the pediatric population is still not standardized.

Case Report

We report the case of an otherwise healthy 5-year-old boy referred to our attention by the pediatric surgeon with a 13-month history of slowly growing brownish verrucous plaque localized in the perianal region.

The patient had been previously visited by many physicians (both pediatricians and dermatologists) with a diagnosis of GWs, already treated with several sessions of liquid nitrogen (cryotherapy), which was ineffective and poorly tolerated by the patient. At the time of our observation, asymptomatic brownish plaques with verrucous surfaces were visible in the perianal area (Figure 1A). The parents reported that the lesions made defecation difficult and painful for the child. No erythema, lacerations, scars, or signs of sexual abuse in the above-mentioned area were detected. Sexually transmitted infection (STI) laboratory diagnostic testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* cultures and serologic tests for human immunodeficiency virus (HIV), syphilis, hepatitis B, and cultures for other STIs were performed, with negative results. Maternal and paternal history of GWs or STIs was negative, while clinical examination did not reveal genital or non-genital warts. The same anamnestic and medical evaluation was conducted for the kindergarten teacher, who was, together with the parents, the only person to have routine contact with the child. As no physical and serologic abnormalities were detected in the child and given the possibility of non-sexual transmission of the GWs, the hypothesis of sexual abuse was ruled out. Due to the patient's poor compliance and the parent's unwillingness, surgical or physical treatments with laser abrasion were excluded. Off-label topical treatments with podophyllotoxin 0.5% solution and imiquimod 5% cream were not considered owing to their pro-inflammatory effects, especially contraindicated in pediatric patients. Furthermore, sinecatechins 15% ointment, an extract of green tea leaves containing a mixture of catechin compounds approved for the treatment of external and perianal warts, is not indicated in pediatric populations. Therefore, we scheduled three sessions of PDT at one-month intervals. After acquiring informed consent from both parents, 10% 5-aminolaevulinic acid (ALA) (Biosynth AG, Staad, Switzerland) in polyethylene glycol ointment was applied in occlusion for three hours. Irradiation was applied with diode red light at 630 nm in wavelength (S630, Alpha Strumenti, Milan, Italy). The light source was positioned at 50 mm from the affected area, which gave a skin irradiance of about 160 mW/cm^2. The light exposure period was 8 min, resulting in a total light dose of 75 J/cm^2. The procedure was quite tolerated by the patient, who complained of a moderate burning sensation during the light exposure. The patient was treated at home with an emollient cream and a non-alcoholic disinfection solution. After the third session, clinical examination revealed a significant reduction of the verrucous plaque (Figure 1B). Almost complete clearance was achieved at the three-month follow-up, with the persistence of only a few isolated papular elements (Figure 1C). At six months follow-up, complete healing was observed, with no sign of relapse. Subsequent follow-ups were scheduled at six months.

Discussion

PDT is a non-invasive therapeutic procedure that exploits the interaction between a photosensitizing agent, light exposure, and molecular oxygen to induce localized and selective cytotoxicity. Photosensitizers commonly used in dermatology are the prodrug ALA or its methylated ester (MAL), which are converted by the heme biosynthetic pathway to protoporphyrin IX (PpIX). After an incubation period, subsequent activation by light of an appropriate wavelength produces reactive oxygen species (ROS), destroying target cells and leading to an immune-inflammatory response.[8] Beyond its established applications in non-melanoma skin cancer, PDT has gained a level of evidence I and strength of recommendation B in an expanding range of inflammatory and infectious diseases, including HPV-related lesions, with excellent tissue selectivity and cosmetic outcomes.[7,8] PDT exerts antimicrobial effects on viruses, bacteria, fungi, and parasites, inducing rapid activation of specific immunity in the affected skin. HPV-infected cells, being highly proliferative and selectively producing more PpIX than surrounding non-infected cells, make ideal targets for PDT. In fact, PDT induces wart regression by producing ROS, which causes the apoptosis of infected keratinocytes. Simultaneously, PDT stimulates immune-specific responses, releasing various cytokines (interleukin-1β, interleukin-2, tumor necrosis factor-α).[9] Notably, interferon-α levels strongly correlate with PDT efficacy and clinical outcomes.[9] Antimicrobial PDT has been demonstrated to be effective not only on visible lesions but also on non-clinically visible ones since it selectively targets HPV-infected keratinocytes, thus reducing the viral load and, consequently, the recurrence rate at follow-ups.[10,11] Our therapeutic schedule was drawn from literature data and prior experience

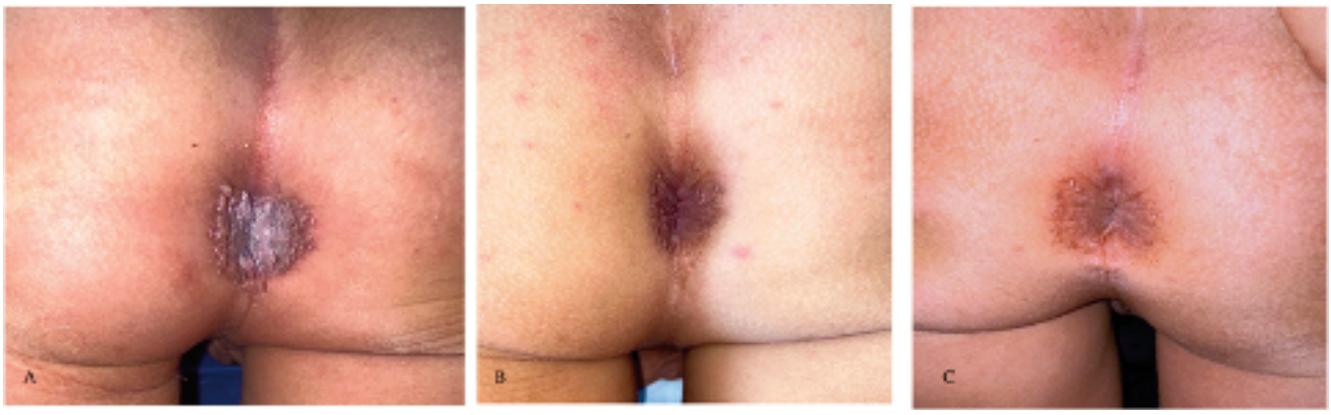

Figure 1. (**A**) Verrucous plaque in the perianal region before PDT; (**B**) reduction of the verrucous plaque after three sessions of ALA-PDT at one-month intervals; (**C**) almost complete resolution at three-month follow-up after the third session of ALA-PDT, with the persistence of only a few isolated papular elements.

treating viral warts, including genital ones, and other infectious diseases in children.[6,12-16] While various therapeutic modalities exist for GWs management, no single treatment has proven definitively effective. Medical therapies with topical podophyllotoxin, sinecatechins, or imiquimod often result in intense inflammatory reactions, leading to poor patient compliance. On the other hand, physical treatments are frequently painful and require prolonged daily regimens, with a high risk of superinfections in a humid environment like a genital one. Recently, several reports have highlighted recalcitrant warts' regression after the HPV 9-valent vaccine, which has been demonstrated to induce higher antibody titers than those produced by natural infection.[17] Based on these data, we recommended vaccination to our patient at the age of 9 years.

Conclusions

The remarkable outcome in our patient underscores PDT's effectiveness in the pediatric population, particularly for extremely delicate anatomical localization like the perianal one, where invasive treatments may lead to permanent anal stenosis and difficulty in defecation. PDT emerges as an intriguing strategy with a low recurrence rate, capable of treating HPV-infected cells in subclinical lesions.[18] Major limits are the potential onset of local side effects, such as pain, and the long incubation time that can bother young patients.[19] Nevertheless, they appear mild when compared to the other available therapeutic alternatives, making PDT a valuable option.[20]

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