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## RESEARCH ARTICLE

# Local hyperthermia treatment of extensive viral warts in Darier disease: A case report and literature review

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### Abstract

**Background:** Darier disease is an autosomal dominant hereditary skin disease that is susceptible to secondary bacterial or fungal infections, but rarely to human papillomavirus (HPV) infections. Multiple or extensive warts from HPV remain a therapeutic challenge, but local hyperthermia is effective. We treated a patient with Darier disease who had superimposed warts in the genital and neck regions.

**Materials and methods:** The patient was treated with tolerable local hyperthermia with infrared light from a halogen lamp (surface temperature, 40°C) to a single target lesion on the genitalia (30 min daily) for 3 consecutive days.

**Results:** Within 2 weeks, the target lesion cleared and synchronous regression of untreated lesions on the neck was observed.

**Conclusions:** In Darier disease, local hyperthermia treatment of HPV warts in 1 region was effective in treating multiple lesions, including lesions at a remote site, possibly by promoting an immune response against HPV.

**Keywords:** skin, human papillomavirus, temperature, verruca vulgaris

### Introduction

Human papillomavirus (HPV) infection of the skin causes proliferative lesions known as verruca vulgaris or warts. Conventional treatment of warts usually consists of repeated topical application of immunomodulatory and cytotoxic agents, cryotherapy, laser ablation, and surgery. These treatments may be complicated by pain, limited efficacy, long healing time, secondary bacterial infection, or scarring. Extensive or large warty lesions are a major therapeutic challenge to dermatologists.

Elevated body temperature is a defensive mechanism by which the human body may fight against microbial infection and neoplasms [1]. Artificial systemic or local hyperthermia has been used to treat cancers and infectious diseases, with varied efficacy [2]. Warts may be effectively treated with local hyperthermia [3–10]. Heat sources for

treatment of warts have included the neodymium-doped yttrium aluminium garnet (Nd:YAG) laser [3, 6], hot water bath [10], radiofrequency [5], infrared radiation [4, 9], and a self-applied heat patch [7]. Different protocols for treatment of warts have included different temperature (40°C to 50°C), treatment duration (30 s to 30 min), and timing (successive or intermittent treatment with intervals from several days to weeks) [3–10].

Infrared radiation may be absorbed by normal human skin. Absorbance percentage may vary with wavelength and skin level, including epidermis and dermis (absorbance at 1000 nm: epidermis, 35% and dermis, 48%; absorbance at 1400 nm: epidermis, 72% and dermis, 20%), with the remaining infrared radiation absorbed by subcutaneous fat [8]. More heat may be absorbed in an epidermal wart lesion than normal skin because of the hypertrophic

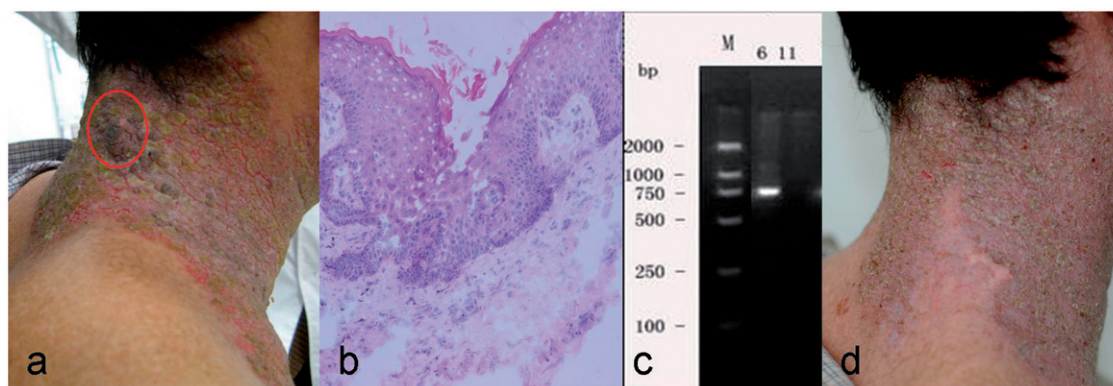


Figure 1. Clinical and histologic appearance of neck lesions in a 35-year-old man with warts and Darier disease. (a) Warts (circled) superimposed on lesions of Darier disease. (b) Diffuse vacuolated keratinocytes in the upper epidermis were characteristic of HPV-infected skin; epidermal invagination and suprabasal lacunae with dyskeratotic acantholytic cells were characteristic of Darier disease (hematoxylin-eosin, frozen section of neck lesion, original magnification  $\times 200$ ). (c) DNA segment specific for HPV type 6. (d) At 15 days after hyperthermia treatment, all papules and plaques in the neck disappeared completely, but Darier disease persisted.

character of the epidermis in HPV-infected skin. The amount of heat absorption by the tissue is quantified by the thermal dose ( $D$ ), which is a function of temperature ( $T$ ), duration of treatment ( $t$ ), and a factor  $R$ , according to the equation  $D = t \times R^{T-43}$  ( $R = 2$  when  $T \geq 43^\circ\text{C}$ ;  $R = 4$  when  $T \leq 43^\circ\text{C}$ ;  $43^\circ\text{C}$  is the critical temperature above which heated cells are more susceptible to apoptosis) [11]. We previously showed that infrared local hyperthermia ( $44^\circ\text{C}$  for 30 min, given once daily for 3 consecutive days and then for 2 more days, 2 weeks later) resolved plantar warts in  $>50\%$  of patients within 3 months [4].

Darier disease is an autosomal dominant disorder that may present with multiple keratotic papules or plaques in seborrheic regions. Characteristic histopathological findings include dyskeratosis of keratinocytes with formation of corps ronds (characteristic of apoptosis) and acantholysis (focal areas of separation between suprabasal epidermal cells). A mutation in the ATP2A2 gene, which encodes a calcium pump (type 2) sarco-endoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase (SERCA2) highly expressed in epidermal keratinocytes, is responsible for Darier disease [12]. As a result of perturbed calcium ion signalling in Darier disease, the function of junctional complexes in keratinocytes are adversely affected, leading to acantholysis, a distinct histological feature of the disease. Topical steroids, or topical or oral retinoids, may improve the symptoms of Darier disease [13]. However, Darier disease may be associated with bacterial or fungal infections because of small wounds in the skin. Darier disease lesions are rarely infected by HPV [14–16], possibly because the HPV life cycle is intimately linked to epithelial differentiation [17]. In Darier disease, there is perturbed differentiation and a loss of cell to cell adhesion, which might be an unfavorable condition

for HPV genome replication [18]. Initial cutaneous infection by HPV is through a microscopic wound.

We report a case of a patient recently treated for extensive warts from HPV infection associated with longstanding Darier disease. Treatment included hyperthermia at  $40^\circ\text{C}$  for 30 min, for 3 consecutive days, and the warty lesions were resolved by 15 days after treatment, much sooner than expected. Furthermore, both treated and untreated lesions at remote sites were resolved.

### Case history

A 35-year-old Chinese man was referred to the outpatient clinic with a 2-month history of warty lesions in the genital and posterior neck regions that had not resolved with occasional wet dressings with nitrofurazone (1:5000) solution (Figures 1 and 2). He had a 27-year history of pruritic, malodorous red patches on his trunk, worse during the summer. He was single, heterosexual, and sexually active with a regular partner, and he denied sexual promiscuity. Family history was notable for similar skin disorders in his maternal grandmother, mother, sister, and sister's daughter. A diagnosis of Darier disease had been made based on clinical appearance and histopathological findings (Figure 1). He had been treated with oral retinoic ethylester (0.03 mg, once daily) for the past 6 years, with control of the lesions except for frequent exacerbation during the summer.

Physical examination showed irregularly shaped, slightly reddish, hyperkeratotic or crusted, malodorous patches or plaques on his face, neck, axilla, trunk, suprapubic region, and groin. There were brownish, warty papules and plaques on his scrotum. There also were warty plaques superimposed on the reddish patches on right side of the neck (Figures 1



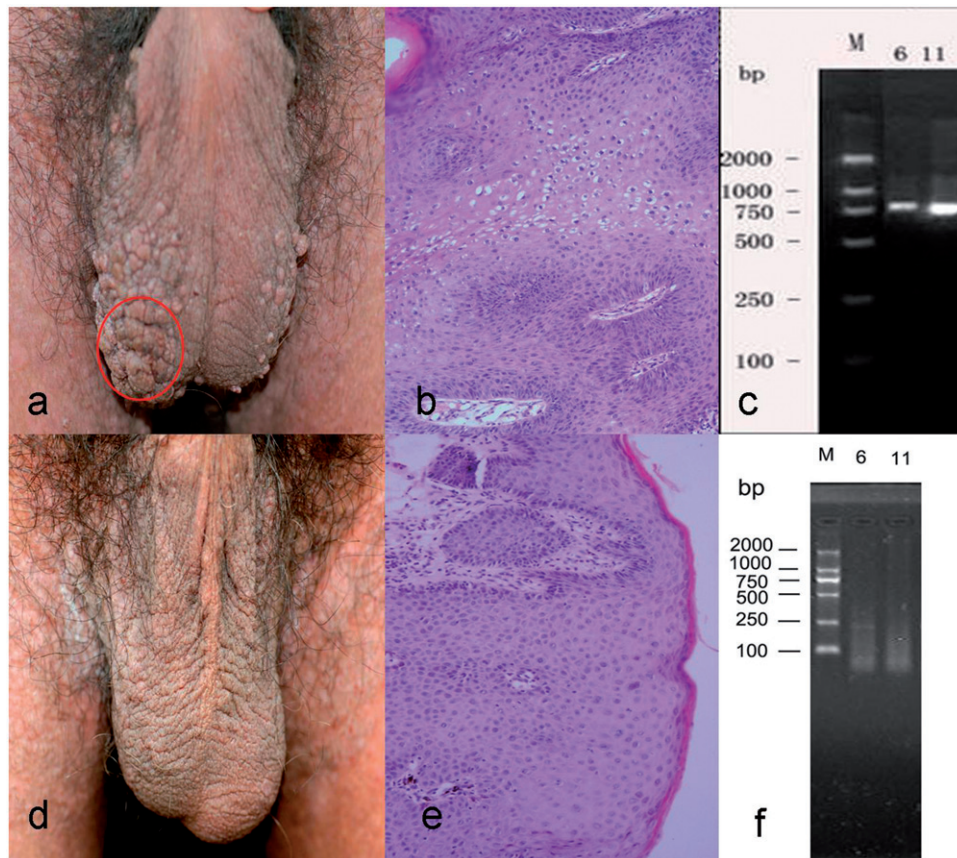


Figure 2. Clinical and histologic appearance of scrotal lesions in a 35-year-old man with warts and Darier disease. (a) Papillary and cauliflower-shaped papules and plaques in the scrotum. (b) Patches of vacuolated keratinocytes in thickened epidermis were characteristic of HPV-infected skin (hematoxylin-eosin, original magnification  $\times 200$ ). (c) DNA segments specific for HPV types 6 and 11. (d, e) Clinical and histologic findings after 2 months hyperthermia treatment, showing resolution of the warty lesions. (f) No HPV-specific DNA was detected after 2 months treatment.

and 2). Laboratory tests including complete blood count, urinalysis, and hepatic and renal function tests were normal. Serologic tests for syphilis, HIV, and hepatitis B were negative. Chest radiography and ultrasonography of the abdomen and lymph nodes were normal.

Biopsy of the warty lesions of the scrotum and neck showed features of viral warts, and the neck lesion also had features of Darier disease (Figures 1 and 2). Polymerase chain reaction showed DNA segments specific for HPV types 6 and 11 in the scrotal lesions and HPV type 6 in the neck lesions (Figures 1 and 2), confirming the diagnosis of HPV viral warts and Darier disease [19].

### Method and result

The patient was treated with a patented local hyperthermia generator (patent no. ZL 200720185403.3, China Medical University) after informed consent was obtained from the patient and approval was

obtained from the Ethics Committee of China Medical University (2009, no. 22). The device had been installed with an energy source of infrared light from a halogen lamp (most (>90%) wavelengths from 760 to 2300 nm; peak wavelength, 1200 nm) (dichroic reflector halogen lamp, MR16, 50 W, Hua Xu Lighting, Lianyungang, China). The heat was concentrated and delivered through a metal tube to the skin surface without direct skin contact, the end of the tube being 2 to 3 cm from the skin surface. A confluent plaque on the scrotum was selected as the target lesion (Figure 2), and the lesion (1.77 cm<sup>2</sup>) was heated to 40°C for 30 min, once daily for 3 consecutive days. By 15 days after the 3-day treatment, all of the papules and plaques in the scrotum and neck had disappeared completely, with residual areas of hyperpigmentation (Figures 1 and 2). No adverse effects were observed except for a slight burning sensation during the treatment that was well tolerated.

A biopsy from the scrotum at 2 months after complete clearance of the warty lesions showed

no residual features of the wart (Figure 2), and polymerase chain reaction showed no further HPV-specific DNA detected (Figure 2). Follow-up evaluation 2 years later showed no recurrence of the warty lesions.

## Discussion

The patient had resolution of warty lesions with hyperthermia treatment. Previous reports of hyperthermia treatment of HPV-infected skin lesions have shown that hyperthermia is effective, but there is no consensus about methodology because of variation between studies in the clinical profile of patients, type of heat generating devices, hyperthermia parameters, and protocols [3–10]. In the present patient, there were extensive warty lesions associated with erosive Darier disease plaques of the neck and with scrotal skin that was not affected by Darier disease.

A placebo-controlled trial of hyperthermia treatment of 29 cases of hand warts with a radiofrequency device (surface temperature, 50°C;  $\leq 4$  treatments, each 30 to 60s, every 4 to 6 weeks) showed that treatment was effective (clearance frequency: treatment, 86%; control, 41%); the method was slightly ablative, because anaesthesia was required to relieve pain and some patients had scarring [5]. Recalcitrant common warts have been successfully treated with Nd:YAG laser hyperthermia (surface temperature, 40°C; treatment duration, 30 s; treatment repeated after 6 weeks) [6], and this method may result in 100% clearance of HPV DNA in the treated lesion, even when clinical improvement is not clearly documented [3]. A randomised placebo-controlled trial of plantar wart treatment also showed that infrared hyperthermia (surface temperature, 44°C; treatment duration, 30 min, once daily for 3 consecutive days plus 2 more treatments after 2 weeks) was effective (frequency of cure at 3 months: treatment, 54%; control, 12%), with tolerable burning sensation but no severe side effects [4].

In the present patient the warty lesion was quite extensive, especially in the genital region (Figures 1 and 2), and a destructive option for viral warts was not appropriate. Hyperthermia treatment resulted in clearance of lesions at both the treated and remote sites, which may be explained by the development of an immune response against HPV infection [4]. Cell mediated immunity may be important for elimination of HPV infection, but the molecular and cellular mechanisms are not fully characterised [20]. Hyperthermia may promote the release of heat shock proteins from damaged cells, resulting in stimulation of antigen-presenting cells, cytokine release and expression of cell surface molecules,

presentation of heat shock protein-bound peptide antigens to major histocompatibility complex class I molecules in dendritic cells, and induction of antigen-specific cytotoxic T lymphocytes [21]. Furthermore, hyperthermia at 40°C may increase antigen uptake and phagocytosis by dendritic cells and macrophages, increase migration of dendritic cells to regional lymph nodes, and promote lymphocyte movement to lymphoid and tumour tissue [22]. Whole body hyperthermia (39.5°C to 40°C for 6 h) may affect the severity of murine contact hypersensitivity, an established model of T cell mediated immune response in the skin [1]. Local hyperthermia at 42°C and 45°C for 30 min promotes migratory maturation of Langerhans cells in HPV-infected skin [23]. The migration of Langerhans cells may be coupled with decreased expression of CCL-20, which is a potent chemokine for recruitment of Langerhans cells to the skin [24]. In condyloma acuminata, local hyperthermia could modulate antiviral activity by an endogenous interferon-dependent pathway [25, 26]. In addition, hyperthermia at 42°C and 45°C for 30 min may promote apoptosis in both HPV-infected and normal keratinocytes, even though there may be different apoptosis signalling pathways in HPV-infected and normal skin [27]. Warts that respond to photodynamic therapy have dense CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes in the lesion [28], confirming participation of immune cells in the clearance of the lesions. We recently observed that in condyloma acuminata, which may regress after local hyperthermia treatment, dense CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytic infiltration was noted in lesions (unpublished observation).

Other factors may account for the rapid clearance of distant lesions in the present case. Spontaneous resolution may have occurred, because HPV-infected lesions may have a self-limiting course, with 30% warts regressing spontaneously within 3 months [29]. The rare occurrence of HPV infection with Darier disease may imply a skin condition in Darier disease unfavourable for HPV infection [18]. The patient had been on long-term use of oral retinoic ethyl ester for Darier disease, and retinoid may be effective in eliminating warty lesions [15]. Hyperthermia may stimulate cytotoxic and apoptotic effects, which may help eliminate HPV-infected tissue [30–32]. Furthermore, the virus or viral replication may be inhibited directly by heat; copies of HPV E6 and E7 transcripts in HPV-infected tissue may be decreased after hyperthermia treatment (unpublished observation). Despite incomplete understanding of the mechanism, the present case shows that heat therapy may be another option to treat warts when other therapies fail or are not applicable.

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