Clinical Letter

Complete resolution of disseminated cutaneous warts after repetitive partial treatment with ALA PDT – indication of a PDT-induced systemic immune response

Dear Editors,

Cutaneous warts are caused by infection of keratinocytes by human papillomaviruses. They occur most often in childhood, with a prevalence of up to 33 % among children between six and twelve years of age [1]. Spontaneous regression is common and a clearance rate of 50 % has been reported in 333 schoolchildren within an observation period of one year [2]. Apart from watchful waiting, treatment options include chemical (e.g. salicylic acid, 5-fluorouracil), physical (cryotherapy, cautery) or surgical removal and immunological therapy (imiquimod) [3, 4]. In recent years photodynamic therapy (PDT) has been used as a new therapeutic approach for viral warts, with remission rates ranging between 28 % and 95 % [5–8]. A 24-year-old Caucasian man presented at our department with a 16-year history of multiple recalcitrant cutaneous warts. On clinical examination the patient had more than 60 warts that were distributed on his face, trunk, suprapubic region, arms, hands and subungually. Apart from bronchial asthma, the patient's medical history was completely negative without any indication of an underlying immune disorder. His family history was also negative.

Various therapies including cryotherapy, laser treatment, curretage and prolonged topical application of a wart tincture (a mixture of salicylic acid, lactic acid and glacial acetic acid) were unsuccessful. Histological examinations of biopsies taken from the face and neck showed acanthosis, compact orthokeratosis, focal parakeratosis, papillomatosis, elongated rete ridges and increased vascularity with some thrombosed vessels in the papillary dermis compatible with a diagnosis of viral warts. Human papillomavirus testing with PCR (low- and high-risk) was negative. The results of additional blood tests (complete blood count, blood chemistry including HIV and hepatitis serology, electrophoresis and total immunoglobulins) were within the normal range.

Based on previous studies that provided promising results with photodynamic therapy (PDT) for treatment-resistant warts, we decided to try PDT for two small circumscribed areas that contained a total of six warts. One area was located on the right middle finger and the other on the back of the left hand, both measuring approximately 2 × 2 cm. The warts were pretreated over five days with daily use of a wart solution (10 % salicylic acid, 10 % glacial acetic acid and 10 % lactic acid each in collodion elasticum). After an application period of 24 hours each, the skin was soaked in a lukewarm hand bath where the superficial layers of the warts were removed by the patient himself with a callus shaver. This treatment was stopped one day before and resumed one day after each PDT session. PDT was carried out with a 20 % 5-aminolaevulinic acid (ALA) cream that was applied on the target areas at an approximate thickness of 1 mm and covered with an adhesive dressing (Suprasorb® F, Lohmann & Rauscher, Austria). After four hours all remnants of the ALA cream were removed and the target areas were illuminated with red light (BF-RhodolLED®, 635 nm; Biofrontera AG, Leverkusen, Germany) at an intended dose of 37 J/cm² and an irradiance of 68 mW/cm². Due to severe pain during illumination, the dose and intensity of the red light were decreased by 75 % during the first and second session and by 50 % during the third PDT session, respectively. In addition, the skin was cooled during illumination with a cold air blower (CRIOJet Air Mini, Linde Gas Therapeutics GmbH, Niefern-Öchselbronn, Germany). A total of four PDT sessions were performed at weekly intervals. After the second PDT session the warts within the treated areas already showed a marked reduction in size, whereas the untreated warts remained unchanged. At two months after the last PDT session, the patient not only presented with clearance of the treated warts but also, for the first time after more than one and a half decades, with complete resolution of all warts (Figure 1a–d). No further relapse occurred during a follow-up period of two years.

The mechanism of action of PDT involves the formation of singlet oxygen causing cell necrosis and apoptosis [9] as well as a diffuse inflammatory reaction [10]. Cell destruction leads to expression and secretion of damage-associated molecular patterns, cytokine release, mobilization of neutrophils and maturation of dendritic cells, with subsequent activation of the adaptive immune system [10]. Apart from local effects, PDT can also elicit a systemic immune response. In mice bearing both subcutaneous and lung EMT6 tumors, local PDT treatment not only resulted in almost complete ablation of the subcutaneous tumor but also significantly reduced the number of distant lung tumors at ten days after PDT. This inhibition was tumor-specific and dependent on the presence of CD8+ T cells [11]. Another study by the same group of authors investigated the effects of local PDT on the systemic immune response in patients with basal cell carcinoma. By measuring lymphocyte reactivity to the BCC-associated tumor antigen Hip1 the authors demonstrated that systemic immune recognition was increased in patients following local tumor PDT.
This effect was inversely related to the light dose and area treated [12]. In a study that employed repeated ALA PDT exposures at 10-day-intervals for recalcitrant genital and perianal condylomata acuminata, biopsies were performed at different time points for immunohistochemical evaluation. Nine out of 15 patients showed complete remission after five PDT sessions. Predominance of a dense infiltrate of CD4+ T lymphocytes was seen after one and three PDT sessions. Interestingly, CD8+ T cells also increased significantly in responders during the first month of treatment. Finally, a marked increase in CD1a+ dendritic cells was observed up to the fifth PDT exposure. These data indicate that rapid activation of a specific immune response might be a crucial step in mediating the therapeutic effect of PDT in HPV infections of the skin [13]. Accordingly, clearance of both treated and untreated warts has been reported after intralesional

Figure 1 Left hand before PDT (a) and two months after PDT (b); right hand before PDT (c) and two months after PDT (d). Only the warts within the black circles were treated with PDT. Note the complete resolution of all warts after PDT. Some atrophic scars from previous treatments are seen on the back of the right hand.
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immunotherapy with mumps, measles and rubella vaccine, which also suggests the induction of an enhanced immunoreactivity against HPV as the underlying mode of action [14].

To the best of our knowledge this is the first report to provide evidence that topical PDT might lead to resolution of distant warts via induction of a specific systemic immune response. Given the anecdotal nature of this evidence our observation needs to be confirmed by future studies on larger number of patients.

Conflict of interest
None.

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