Immunotherapy with Diphenylcyclopropenone of Recalcitrant Warts: A Retrospective Analysis

Sir,

Recalcitrant warts remains a major therapeutic challenge for patients as well as for dermatologists, and an effective, painless, atraumatic treatment modality is needed world-wide. Topical immunotherapy has for years been used with some success in the treatment of resistant warts (1). Dinitrochlorobenzene (DNCB) was the first contact sensitizer to be used but diphenylcyclopropenone (DCP) is today the preferred sensitizer because DCP is non-mutagenic in contrast to DNCB and long-term carcinogenesis is not expected (1, 2). We here present a retrospective analysis of DCP treatment of recalcitrant warts.

PATIENTS AND METHODS

The response to DCP treatment was evaluated in 25 patients referred to the department of dermatology with recalcitrant warts (11 females and 14 males, age 12 to 66 years). In addition, 14 other patients were treated with DCP but withdrawn from this analysis for various reasons such as immunosuppression (3 patients, of whom 2 patients had a transplant), side effects (3 patients), personal reasons (2 patients), lost to follow-up (3 patients), still receiving DCP treatment at the time of registration (2 patients) and response considered a spontaneous regression, although a therapeutic effect of DCP cannot be excluded (1 patient cured after 1 treatment). The diagnoses of the warts were made clinically. The treated warts included solitary, multiple, plane, hyperkeratotic, deep plantar and mosaic warts. The warts were located on hands and feet. The patients were referred from private dermatology practice (91%) and from general practitioner (9%) with a diagnosis of "treatment-resistant warts". All patients had, prior to referral to the clinic, been treated with a variety of treatment modalities including keratolytics, curettage, freezing with liquid nitrogen, podophyllin and cantharone. The estimated duration of warts at entry ranged from 1 to 20 years.

The patients were sensitized by a single application of 1% DCP in petrolatum on the dorsum of the foot using a Finn-chamber. The area was occluded with impermeable tape (Sleek) and left for 8 h. The patients were then instructed to remove tape, Finn-chamber, and DCP ointment and to wash the area with soap and water. Sensitization was defined as a transient eczematous reaction, developed on the dorsal aspect of the foot, within 48 h. Approximately 3 weeks after sensitization, the warts were treated with DCP in petrolatum. The treatments took place approximately every third week. The first treatment was performed with DCP 1%. For the subsequent treatments concentrations of 0.5%, 1%, 2% or 5% were used, depending on the severity of the local reaction at the treatment site. The most frequent concentration used was 1%. Prior to each DCP treatment hyperkeratoses were removed with a scalpel. The treated site(s) was covered with Sleek tape and the DCP ointment removed by the patient after approximately 8 h. The treatment stopped i) with total clearance of warts, ii) if the treatment was considered ineffective, or iii) if systemic or severe local side effects developed. All treatments were performed in the department. Response to treatment was registered as cleared if all DCP-treated warts were cleared and as not cleared if all DCP-treated warts were not cleared. The assessment of treatment response was performed during the routine visits to the clinic and the patients were discharged from the outpatient clinic when no visible wart tissue was left. The patients that were cleared of wart tissue were subsequently contacted by telephone interviews for evaluation of recurrences.

RESULTS

Of the 25 patients who fulfilled the DCP treatment, 14 patients (56 %) were registered as cleared and 11 patients (44 %) as not cleared. The patients cleared of wart tissue received a similar number of treatments (median 4, range 2–11) as the patients who were not cleared (median 4, range 2–7). Recurrences were estimated from telephone interviews: of the 14 patients cleared of wart tissue, 3 were lost to follow-up, 3 reported that warts had returned, and 8 patients reported that no recurrences were observed. For these 8 patients, the interviews were carried out a median of 19 months after the patients were registered as cleared (the interval ranged from 1 to 31 months). DCP treatment was also performed in 2 patients who had a transplant and were being treated with immunosuppressive agents. Warts failed to clear in both patients.

Three patients stopped DCP treatment because of side-effects: one patient experienced bullous dermatitis at the treatment site. One patient with atopic dermatitis developed severe local dermatitis at the treatment site and spreading to other skin areas. One patient experienced widespread urticaria, which was treated with antihistamines and local steroids and was still present 4 months after the last DCP treatment.

DISCUSSION

Uncontrolled studies, half-side comparison studies and case reports have reported cure rates between 50% and 85% from DCP treatment of resistant warts (3–11). The most extensive study was designed as a prospective, open study based on 241 patients and a cure rate of 85% was reported (average 7.8 treatments per patient) (7). In the retrospective analysis presented here, we found a cure rate of 56% of patients with recalcitrant warts (median of 4 treatments per patient). However, if a higher number of treatments had been applied, the cure rate may have been higher.

In the literature, side effects have been reported such as local and widespread dermatitis, generalized exanthema, erythema multiforme, urticaria and vitiligo (3–7, 11, 12). In the presented study, 3 patients stopped treatment because of side-effects, the most severe being widespread urticaria still present 4 months after the last DCP treatment. Therefore, close supervision is essential during DCP treatment due to the risk of cutaneous side effects.

Based on the literature and the retrospective analysis presented here, it is our impression that DCP sensitization and treatment may be a useful alternative when routine treatment modalities have failed. Nevertheless, the true efficacy of DCP treatment remains unknown. To clarify this true efficacy it may be a possibility to carry out randomized, half-side comparison studies based on large groups of patients and blinded response evaluations. However, this set-up theoretically may introduce bias due to a systemic effect on non-DCP treated warts.

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Accepted January 10, 2000.

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Classic Kaposi's Sarcoma and Vascular Endothelial Growth Factor

Sir,

Kaposi's sarcoma (KS) is a highly invasive and intensely angiogenic neoplasm of unknown cellular origin. Angiogenesis and capillary permeability can play a central role in the development and progression of KS. The principal features of KS are abnormal vascularization and the proliferation of endothelial cells and spindle cells. KS cells appear to be of smooth muscle origin but secrete a potent inducer of endothelial cell chemotaxis and invasiveness which could be responsible for angiogenesis and the resulting highly vascularized lesions. This inducer could be vascular endothelial growth factor (VEGF). VEGF has been reported to be a predominant angiogenic factor expressed in KS cells (1), although basic-fibroblast growth factor (bFGF) also acts synergistically with VEGF in the induction of angiogenic KS-like lesions in a mouse model *in vivo* (2).

Data *in vitro* support the hypothesis that abnormal vascularization in the KS lesions may be, at least in part, the result of the secretion of VEGF. Here we report, for the first time, *in vivo*, an increased amount (3- and 2.5-fold, respectively) of VEGF in sera of 2 patients with classic KS, as compared with 5 control sera from age and sex-matched healthy subjects (95 ± 33 pg/ml). VEGF levels were determined in duplicate using a commercial enzyme-linked immunosorbent assay (R&D Systems, Abingdon, United Kingdom). The level of VEGF was calculated using a standard curve obtained with human recombinant VEGF (from 7.8 to 1000 pg/ml).

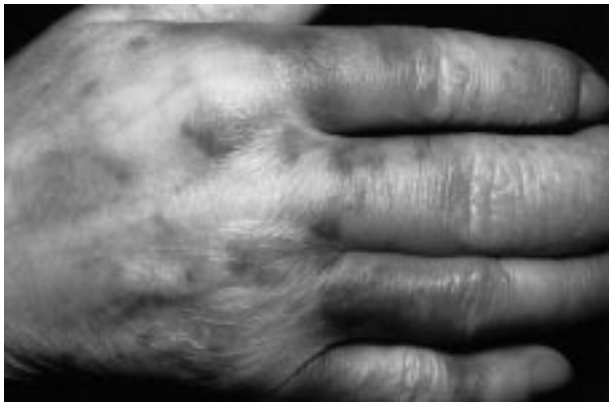

Fig. 1. Red-purple macules and plaques on the hand, patient 1.

CASE REPORTS

Case 1

A 77-year-old Spanish man, without any significant personal or family history, had asymptomatic cutaneous lesions in the form of reddish-blue plaques on the legs which gradually enlarged over the previous 2 years. He reported that they had gradually increased in number and size, extending to other areas of the body. He did not receive any specific treatment. Physical examination revealed macules, plaques and red-purple nodules on his hands, left wrist, forearms, abdomen, feet and legs (Fig. 1). The lymphoedema of his hands and forearms were so severe as to hinder function. Complete blood cell count and blood chemistry were normal. HIV test was negative. A biopsy specimen from the left foot confirmed the diagnosis of KS. A computed tomographic scan of the thorax and abdomen showed no visceral extension of KS. Serum VEGF was 316 ± 45 pg/ml. Treatment with interferon-α2b was started. The patient did not come to follow-up and continued the same treatment in another centre.

Case 2

A 72-year-old Spanish man presented in 1996 with a 1-year history of purplish plaques and nodules, starting on the toe of the left foot and gradually spreading to involve the left leg. Medical history included non-insulin dependent diabetes. HIV test was negative. A diagnosis of classic KS was confirmed by a biopsy specimen from the foot. Endoscopy and colonoscopy were normal. Abdominal images from computed tomography scan and X-ray examination of the chest were normal. Results of a complete blood cell count and serum chemistry