

Potentiating Effect of Imiquimod in the Treatment of Verrucae Vulgares in Immunocompromised Patients

Sir,

Verruca vulgaris is a benign epithelial hyperplasia caused by human papilloma viruses that causes therapeutic problems, especially in immunocompromised patients. We report here 2 patients on continuous immunosuppressive medication with relapsing warts resistant to topical immunotherapy with diphenylcyclopropenone (DCP). As an alternative, occlusive treatment with 5% imiquimod cream was successfully tried. Imiquimod is a recently introduced immunomodifier intended for condylomata acuminata.

CASE REPORTS

Case 1

A 38-year-old man was admitted to our department with verrucae on the soles of both feet, the knees, forearms and several finger tips. He had had autoimmune hepatitis since 1980 and had received consecutive immunosuppressive therapy (prednisolone, azathioprine) for many years. His continuous immunosuppressive medication included prednisolone 10 mg daily; an intercurrent massive-dose treatment of prednisolone 100 mg daily had been given initially and then slowly reduced. Azathioprine had been continuously administered at a dosage of 50 mg daily but, as a result of hepatic status, the dosage had had to be increased to 50 mg twice daily at intervals. Since 1983 he had been suffering from multiple verrucae vulgares which had been treated with keratolytic topicals, cryotherapy and electrodesiccation without any success. Relapses occurred immediately after discontinuation of these treatments. At admission we started topical immunotherapy with DCP, which has been successfully used in uncontrolled studies of the treatment of refractory warts for many years (1–3). The initial challenge with 0.5 ml of 2% DCP in acetone was performed on the back of the right foot. Three days later the patient developed itching, erythema and a bullous reaction. After a 2-week interval DCP was applied on the affected site of the right sole at weekly intervals, starting at a concentration of 0.0001% and slowly increasing up to 1%. The only side-effect observed was itching. Interestingly, we saw a marked reduction at the treated site of the warts but none of the other locations of the verrucae vulgares responded. After 22 applications the DCP treatment was discontinued. As there was a strong need for therapy we decided to reduce all verrucae vulgares by means of CO₂ laser surgery as the patient had hyperkeratotic nodules and plaques, especially on the soles of the feet. Three days later we started occlusive, overnight dressings with 5% imiquimod cream (Aldara®) of all treated sites, initially daily for 4 weeks. Except for a slight erythema after the first application no side-effects were reported. Topical application of 5% imiquimod was continued 3 times a week for 10 months. The patient has now been free of relapse for 12 months since CO₂ laser surgery was performed.

Case 2

A 17-year-old boy had been suffering from therapy-resistant verrucae vulgares on the left sole of his foot and on several fingers for 2 years due to dilatative cardiomyopathy since birth. He had undergone heart transplantation in 1990. His continuous immunosuppressive medication included prednisolone 7.5 mg, azathioprine 50 mg and cyclosporin 5 mg/kg body weight daily. Owing to the widespread distribution of verrucae vulgares and the patient's desire for therapy CO₂ laser surgery was performed and we started topical immunotherapy with DCP in the same way as described above. Even at a concentration of 2% DCP he reported only minimal itching and

erythema within the pretreated sole of the left foot. As he developed a relapse of warts on all operation sites, including an additional filiforme verruca on the nose, we discontinued topical immunotherapy after 10 DCP applications. CO₂ laser surgery was repeated and 3 days later we started occlusive overnight dressings with 5% imiquimod cream (Aldara®) at the affected sites. Owing to the reduced compliance of the patient these occlusive dressings were applied 3 times a week for 3 months without any side-effects. So far, the patient has remained free of relapse for 9 months since CO₂ laser surgery was performed.

DISCUSSION

The case history of both these patients shows the lack of effective therapeutic options and the high relapse rate in the treatment of verrucae vulgares in immunocompromised patients. There are several reports in the literature on successful topical immunotherapy of verrucae vulgares (1, 2, 4–7) but none of these concern immunocompromised patients. We were recently able to confirm the efficacy of successful topical immunotherapy in a 14-year-old immunocompetent girl who had experienced therapy-resistant disseminated verrucae planae of the face (3). This encouraged us to apply topical immunotherapy in these 2 immunocompromised patients. The clinical course of patient 1, showing typical itching and erythema after the first weeks of DCP treatment, indicated a response but, after almost 5 months of therapy, neither the pretreated nor non-pretreated sites had responded. This suggests that DCP exerts a direct toxic effect, as opposed to the required effects of sensitization and efferent phase elicitation. Imiquimod is a local immune-response modifier which has been successfully introduced for the treatment of condylomata acuminata (8–11). It induces cytokines such as interferon- α , interleukin-1, -6 and -12 and tumor necrosis factor α *in vitro* or when applied topically (12). These cytokines induce and stimulate cellular immunity by acting on cytotoxic T cells and natural killer cells, stimulating a strong anti-viral response and a greater response to viral antigens.

It has been reported that imiquimod is capable of destroying warts, even of the large confluent verrucous condylomata type. However, owing to a possible lack of penetration through the verrucous callus in plantar warts it seems wise to first ablate the warts by CO₂ laser therapy and apply imiquimod thereafter in order to destroy residual virus DNA and prevent a relapse. By presenting these 2 difficult and previously therapy-resistant cases, which have now been successfully treated, we wish to highlight this novel therapeutic approach to the treatment of relapsing verrucae vulgares in immunocompromised patients. Furthermore, long-term treatment (8–10 months) did not interfere with other immunoparameters relating to the transplant situation of Case 2 or the continuous immunosuppressive medication.

REFERENCES

1. Lewis HM. Topical immunotherapy of refractory warts. *Cutis* 1973; 12: 863–865.

2. Wiesner-Mentzel L, Happle R. Rejection of plantar warts after treatment with diphencyprone. *Z Hautkr* 1984; 59: 1080–1083.
3. Weisshaar E, Neumann H-J, Gollnick H. Successful treatment of disseminated facial verrucae with contact immunotherapy. *Eur J Dermatol* 1998; 8: 488–491.
4. Greenberg JH, Smith TL, Katz RM. Verrucae vulgares rejection. A preliminary study on contact dermatitis and cellular immune response. *Arch Dermatol* 1973; 107: 580–582.
5. Larsen PO. Contact immunotherapy of resistant warts with diphenylcyclopropenone. *J Dermatol Treatment* 1995; 6: 81–83.
6. Orecchia G, Douville H, Santagostino L, Rabbiosi G. Treatment of multiple relapsing warts with diphencyprone. *Dermatologica* 1988; 177: 225–231.
7. Rampen FHJ, Steijlen PM. Diphencyprone in the management of refractory palmo-plantar and periungual warts: an open study. *Dermatology* 1996; 193: 236–238.
8. Edwards L, Ferenczy A, Eron L, Baker D, Owens ML, Fox TL, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. *Arch Dermatol* 1998; 134: 25–30.
9. Beutner KR, Spruance SL, Hougham AJ, Fox TL, Owens ML, Douglas JM. Treatment of genital warts with an immune-response modifier (imiquimod). *J Am Acad Dermatol* 1998; 38: 230–239.
10. Tying SK, Arany I, Stanley MA, Tomai MA, Miller RL, Smith MH, et al. A randomized, controlled, molecular study of condylomata acuminata clearance during treatment with imiquimod. *J Infect Dis* 1998; 178: 551–555.
11. Beutner KR, Tying SK, Trofatter KF, Douglas JM, Spruance S, Owens ML. Imiquimod, a patient-applied immune-response modifier for treatment of external genital warts. *Antimicrob Agents Chemother* 1998; 42: 789–794.
12. Testerman TL, Gerster JF, Imbertson LM, Reiter MJ, Miller RL, Gibson SJ, et al. Cytokine induction by the immunomodulators imiquimod and S-27609. *J Leukoc Biol* 1995; 58: 365–372.

Accepted April 28, 2000.

Elke Weisshaar and Harald Gollnick
Department of Dermatology and Venereology, Otto-von-Guericke-University, Leipziger Strasse 44, D-39120, Magdeburg, Germany.
E-mail: Elke.Weisshaar@medizin.uni-magdeburg.de

Electron Beam Therapy in Patients with Scleredema

Sir,

Scleredema is characterized by diffuse swelling and induration of the skin, which begins in the cervical region and spreads symmetrically over the upper part of the body (1). Three groups of scleredemic patients can be distinguished (2): one with abrupt onset after infection (Buschke), one with insidious onset and one with previous diabetes. Scleredema associated with infection has a self-limiting course but this is not the case when it is associated with diabetes (1). Many different treatments have been proposed for scleredema (1, 3–5), including electron beam therapy in isolated cases. We report here on 3 patients with diabetes-associated persistent scleredema, in whom substantial clinical improvements were noted after electron beam therapy.

CASE REPORTS

Case 1

A 40-year-old man presented with a 7-month history of progressive induration and thickness of the skin of his posterior neck and upper back. He had had non-insulin-dependent diabetes mellitus for 1 year, for which he had been administered oral hypoglycemics. Physical examination revealed extensive erythematous non-pitting edema of the posterior neck and upper back, with concomitant limitation of rotation of the neck. A biopsy specimen showed a thickened dermis with thick collagen bundles separated by clear spaces with alcian blue-staining mucin lying between them. He was treated with localized electron beam therapy to the lesion. He received a total of 24 Gy in 12 fractions (2 Gy per fraction) for 14 days. He tolerated the treatment well without adverse reactions. At 3-month follow-up, clinical examination showed a marked improvement with decreased induration of the lesion, accompanied by a decrease in the degree of the erythema, and an improvement in the range of movement of the neck. Further evaluation at 7 months revealed no aggravation of the skin lesion.

Case 2

A 41-year-old man presented with a 6-year history of hard, woody plaque on the posterior neck. He had suffered from diabetes mellitus for 14 years, which had been controlled by oral medication. A biopsy finding was consistent with scleredema. He was treated with 10 doses of localized electron beam therapy for 2 weeks (total 20 Gy in 10 fractions). At 2-month follow-up, clinical improvement was seen with a reduction in the degree of sclerosis of the skin. The improvement was sustained at 5-month follow-up.

Case 3

A 53-year-old man with a 15-year history of non-insulin-dependent diabetes mellitus and neuropathy presented with an 8-year history of painful hard waxy plaque on the posterior neck and shoulders. A biopsy specimen confirmed the diagnosis of scleredema. He received localized electron beam therapy (total 24 Gy in 12 fractions). His symptoms, including pain and stiffness of the lesion, were markedly improved.

DISCUSSION

Scleredema is a rare disorder whose etiology remains unclear. It is characterized by non-pitting edema and hardening of the skin around the neck, shoulder and trunk (1). Evidence of systemic involvement in scleredema is rare, but various extracutaneous manifestations, including involvement of the tongue, muscles, heart, esophagus and lung, have been described (1). Scleredema may be associated with infections, paraproteinemia, multiple myeloma and poorly controlled diabetes mellitus (1, 6). On microscopic examination, the epidermis is usually unaffected. The major alteration noted is a marked thickening of the reticular dermis, possibly 2–3 times that of normal (1). The collagen fibers appear to be