

Intralesional Injection of Bleomycin Sulphate into Resistant Warts in Renal Transplant Recipients versus Non-transplant Warty Patients

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Sixteen adult renal transplant patients and 20 non-transplant patients with warts underwent intralesional therapy with bleomycin sulphate. One unit/ml bleomycin sulphate was injected in 93 warts in renal transplant recipients and 100 warts in non-transplant patients with proven resistance to conventional treatment for at least 6 months. The treatment was compared with a normal saline placebo injected into the paired warts in the same patient. Thirty-four out of 93 warts (37%) in renal transplant recipients vs. 59 out of 100 warts (59%) in non-transplant patients were completely cured after one to three injections. We found bleomycin completely ineffective in 56 warts (60%) in renal transplant recipients, but ineffective in only 17 warts (17%) in non-transplant warty patients. None of the patients treated experienced any side effects except for local pain which was well tolerated, especially by non-transplant patients.

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Warts are sites on the skin and contiguous mucous membranes infected by specific members of the papilloma virus group. Resistance to treatment may prove to be a property of the viral type (1) and it has been argued, based on the varying success rates of viral treatments, that the method of treatment is less important than the person who applies it (2). Susceptibility to infection with the wart virus and the rate of resolution of such infections depends on the immune response. In vitro assays have shown an increase in cell-mediated response at the time of resolution (3). The frankly immunodeficient or immunosuppressed individual presents a real therapeutic problem (4). Although sporadic verrucous lesions are common in normal individuals, warts may become so numerous as to be disfiguring in renal transplant recipients (5). Malignant transformation, especially in sun-exposed areas, may occur in rare instances (6).

Intralesional injection of warts with the anti-ne-

oplastic/antibiotic drug bleomycin sulphate is an alternative approach for the treatment of warts (4) as well as in other skin tumours (7, 8). In 1976, Hudson reported that bleomycin was effective in the treatment of 25 patients with plantar warts and resolution occurred within 6 months after a single injection (9). In another report, warts resolved in 18 out of 25 patients (10).

This study was performed to evaluate the efficacy of intralesional bleomycin sulphate injection as a way to treat resistant warts in renal transplant recipients, vis-à-vis non-transplant warty patients, as well as to document the relationship between the cure of warts and graft function, interval after renal transplantation, and types of immuno-suppressive drugs. To our knowledge, this is the first study of treatment resistant warts in renal transplant patients by means of intralesional bleomycin sulphate.

PATIENTS AND METHODS

Sixteen renal transplant recipients and 20 nontransplant warty patients were treated with intralesional injection of bleomycin sulphate. All patients had had warts for more than 6 months and had been refractory to chemical cautery (salicylic acid and lactic acid, 16.7% of each in flexible collodion) or electrodesiccation.

Group 1: Renal transplant patients

This group comprised 16 patients (13 males and 3 females), whose ages ranged from 25 to 40 years (mean age 31.8 ± 3.9). The duration after renal transplantation ranged between 8 and 120 months (mean 11.6 ± 2.7). All patients were receiving combinations of immunosuppressive agents, including prednisolone, azathioprine and cyclosporin, and were classified into three sub-groups:

- Triple immunosuppression group: Those who were receiving all three drugs simultaneously (6 patients).
- Azathioprine group: those who were receiving azathioprine and prednisolone (4 patients).
- Cyclosporin group: those who were receiving cyclosporin and prednisolone (6 patients).

Group 2: Non-transplant patients

Fourteen males and 6 females, who were not suffering from any systemic or skin disease other than warts and were not taking any immunomodulating drugs. Their ages ranged between 15 and 50 years (mean 25.2 ± 9.3 years).

We decided to select patients with two warts or more which were matched for site and size, so that the patients could serve as their own controls. Bleomycin sulphate (Bristol Laboratories, Syracuse, New York, U.S.A.) is marketed in vials, each containing 15 U of bleomycin as sterile lyophilized material. Bleomycin sulphate solution was prepared by dissolving 15 U of the powder in 15 ml of sterile standard saline. Standard saline was used as placebo, so that in each patient, treated lesions were injected with bleomycin and control warts with saline. Bleomycin sulphate solution and standard saline were injected with 1 ml disposable tuberculin syringes fitted with a 30-gauge needle with the bevelled edge upwards. Injection was made directly into the wart tissue. If the wart was large, a divided dose was injected into two sites to obtain an even distribution of the solution. A dose of 0.1 ml was injected into warts less than 5 mm in diameter, 0.2 ml into warts over 5 mm in diameter, and the injection sites were covered with surgical tape which was removed the next day by the patient. The syringes were freshly prepared on the day of use to avoid the loss of potency caused by storing the bleomycin solution in plastic (11).

Blanching of wart tissue indicated proper injection. At the 3rd and 6th weeks the warts were assessed and uncured warts were reinjected with the same solution (either bleomycin or saline) as previously. The treatment was considered a failure if a wart persisted after three injections. No patient received more than 2 ml of bleomycin sulphate. Final assessment was made at the end of the 12th week and the wart was considered to be cured when there was restoration of the normal epidermal texture including the epidermal ridge pattern. 'Incomplete response' means a partial decrease in the size of a wart.

Statistical analysis

The χ^2 -test was used for evaluation of the data. A p -value < 0.05 was considered significant.

RESULTS*Assessment of the outcome at 12 weeks*

In renal transplant recipients, out of 93 bleomycin-treated warts, 34 (37%) showed complete cure, 3 (3%) showed incomplete response and 56 (60%) warts found among 8 patients showed no response. By contrast, in 55 saline-injected warts, incomplete response was observed in 2 (4%), while none showed complete cure ($p < 0.0001$). The response to treatment was affected by the site of the lesion, being greatest in hand lesions and poorest in plantar lesions.

Of the 6 patients who received the triple immunosuppressive therapy, 5 showed complete cure, while

none of the patients treated with azathioprine plus prednisolone (4 patients) showed complete cure and of the 6 patient treated with cyclosporin plus prednisolone, only 2 showed complete cure. In non-transplant patients, out of 100 bleomycin-treated warts, 59 (60%) diagnosed in 12 patients, showed complete cure, 24 showed incomplete cure and 17 showed no change. In contrast, out of 40 saline-treated warts, only one (2.5%) showed complete resolution ($p < 0.001$), one (2.5%) showed incomplete cure and no change was observed in 38 (95%).

Description of response to intralesional bleomycin treatment

The day following treatment, the injected warts became red and painful, then they turned black. By one week a blue-black eschar was formed and found to separate after 3 weeks, resulting in complete healing. There were no significant side effects. Most patients experienced pain, especially in plantar and periungual warts, this being more manifest in transplant patients. In this study, there was no significant relationship between cure of warts and the presence of post-transplant hyperglycaemia, graft function, duration after renal transplantation, or cyclosporin whole blood trough level.

DISCUSSION

Bleomycin has both antibiotic and antineoplastic properties, by virtue of its ability to cause DNA strand scission, especially in dividing cells entering the mitotic phase (12). The mechanism by which bleomycin acts is not yet known but may be mediated by its cytotoxic or virucidal properties (4). Bleomycin is inactivated by an intracellular aminopeptidase enzyme called bleomycin hydrolase (13). Bone marrow red cells, liver and spleen are rich in this enzyme, which is why haemopoietic and hepatic or renal toxicity do not occur (14). The immunological system is unaffected (15). The most serious complication is interstitial fibrosis of the lungs. All the toxic effects are dose related, those in the skin (scleroderma-like changes) occur after the administration of 150 mg and those in the lungs occur when over 450 mg has been given. The paucity of bleomycin hydrolase in the skin results in firm and localized binding with the drug when injected intradermally, which is why the very small doses used in warts treatment are effective (4).

In 1988, Amer et al. (16) reported complete re-

duction in 97 out of 143 warts (67.8%) after one or two bleomycin injections, while 25 warts (17.5%) showed incomplete resolution and there was no therapeutic response in 21 (14.7%) warts.

In our study the objective was to use bleomycin to treat warts in renal transplant recipients and to compare the results with those observed in non-transplant warty patients. Size- and site-matched warts in the same patients were used as controls. In renal transplant patients, a complete response was achieved in 36.6% of warts injected with bleomycin, while only 2 out of 55 (3.6%) saline-injected warts showed complete resolution. In non-transplant patients, 59 out of 100 warts (59%) showed complete response.

The regional variation observed in the response to bleomycin therapy is probably due to difficulty in injecting certain areas, as well as the type of virus, which may differ from one site to another. In contrast, the experience of Munkvad et al. (17) was very disappointing. They found no difference between the group treated with bleomycin and the placebo group. This contradiction between our results and those of Amer et al. (16) on the one hand, and those of Munkvad et al. (17) might be attributable to racial or climatic differences, or to differences in the dose of bleomycin used. We and Amer et al. (16) used bleomycin sulphate in a dosage of 1 U/ml saline solution. Nevertheless, Munkvad et al. (17) used 1% solution bleomycin sulphate in saline or oil. Furthermore, Bunney et al. (4) reported results in non-transplant patients that tally more or less with those observed in our study and in that of Amer et al. (16).

In renal transplant patients there are several important features. First, the depressed cell-mediated immunity of these patients may increase their susceptibility to infection with human papilloma virus. Thus, the measures that can stimulate a cell-mediated immune response, such as D.N.C.B. (dinitrochlorobenzene), can be used to treat warts, but the graft may in such cases be endangered. Moreover these measures appear to be less effective and require weekly repeat treatment for varying periods (18). In contrast, bleomycin may act directly, and is therefore particularly valuable when the immune response is depressed or missing (4). Second, warts may be so numerous as to be disfiguring (5) and malignant transformation, particularly in sun-exposed areas, can occur (6). So, warts in such patients need an effective treatment.

In our study the results of cure in renal transplant

patients (36.6%) were less satisfactory than those observed in non-transplant warty patients (59%). This could be attributed to a suppressed cell-mediated immune response in renal transplant recipients. It may be of interest to mention that warts in a group with triple immunotherapy in our study showed a better response than the other two groups. This may be explained by the fact that these patients were given smaller doses of prednisolone, azathioprine and cyclosporin. Our results in non-transplant patients coincide more or less with those previously reported.

In conclusion, beside other measures, intralesional injection of bleomycin is a valuable line of therapy in non-transplant patients and is probably very valuable in some renal transplant recipients in whom warts have been resistant to other modalities of therapy.

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A Case of Prurigo Pigmentosa Considered to be Contact Allergy to Chromium in an Acupuncture Needle

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A 53-year-old male developed prurigo pigmentosa on his back, after undergoing acupuncture for 3 years. The eruptions were ceased on discontinuing the therapy but recurred with its resumption. The acupuncture needle contained 18.12% chromium. Erythema was induced by patch testing with potassium dichromate, and a flare-up was observed in the area of the patch test on resumption of acupuncture. We consider that the eruptions were induced by contact allergy to the chromium component of the acupuncture needles.

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Prurigo pigmentosa has frequently been reported in Japan (1) but is rare in the Western world (2). The disease is an inflammatory disorder of unknown etiology characterized by the paroxysmal development of pruritic reddish papules followed by pigmentation in a reticular pattern. Here we report a case of prurigo pigmentosa associated with the use of an acupuncture needle.

CASE REPORT

A 53-year-old male visited our Department in December

1987, complaining of pruritic erythema on his back. He had a history of dapsone allergy. He also had a 4-year history of lumbar pain and had undergone acupuncture therapy every 2 weeks for 3 years. Recently, he had developed pruritic eruptions on his back the day after acupuncture, with exacerbation and enlargement of the lesion observed with repetition of the therapy.

On physical examination, reticular pigmentation, reddish papules and wheals were observed on his back (Fig. 1). Clinical examination showed no abnormalities in the peripheral blood or urine, nor liver dysfunction, and IgE (RIST) was <500 U/ml. Histological examination of an excised biopsy specimen taken from a papule on his back disclosed hydropic degeneration of the basal layer and edema and lymphoid cell infiltration of the papillary dermis (Fig. 2).

Since the possibility of contact allergy due to environmental factors has been suggested as an etiologic mechanism of prurigo pigmentosa, patch tests were performed using European standard allergens. Erythema was observed in the patch test area of potassium dichromate after 7 days, and reactions to other allergens were negative. The erythema persisted for over 1 month and the pigmentation was still present after 2 months. The same results were obtained on repeating the patch test with potassium dichromate.

From these results, we concluded that the allergic reaction to the chromium component of the acupuncture needles had caused the prurigo pigmentosa. According to the manufacturer, the needles contained 18% chromium, 9% nickel, 70% iron and 1% manganese. Patch tests with iron and manganese proved negative. When acupuncture was suspended, and oral therapy of betamethasone (0.25 mg/day) and *d*-chlorpheniramine maleate (2 mg/day) was initiated, the eruptions gradually abated. Lumbar pain intensi-