Acta Dermatovener (Stockholm) 56: 155–158, 1976

CUTANEOUS SIDE EFFECTS OF BLEOMYCIN THERAPY

Y. Werner and B. Törnberg

From the Department of Dermatology and the Department of Pathology, Södersjukhuset, Stockholm, Sweden

Abstract. In a series of eight patients with malignant lesions treated with bleomycin, the morphology of the erythematous skin areas was studied in punch biopsies. The main changes were found in the squamous cells of the epidermis, varying from slight cell degeneration, to complete lysis.

Key words: Bleomycin; Dermatitis medicamentosa; Histopathology

Bleomycin is an antibiotic, derived from *Streptomyces verticillus* and isolated by Umezawa in Japan in 1963. It has a cytostatic effect, effected in low concentrations by inhibiting the mitosis, in high concentrations by blocking the incorporation of thymidine into DNA in the S-phase and by splitting up the DNA into smaller fractions.

Many reports have described the beneficial therapeutic effect of bleomycin, especially on squamous cell carcinoma of the head, neck and genital region (1, 2, 8, 9), but also in the treatment of mycosis fungoides (10) and basal cell carcinoma (7, 9, 11).

Umezawa et al. (4, 5, 12) have shown that following daily intraperitoneal instillation of bleomycin into mice, the highest concentrations are attained in skin and lung, with only trace or no demonstrable drug in kidney, brain and liver. Many authors (1, 3, 6, 9, 11) have reported that the most significant side effects of bleomycin are lung fibrosis and skin changes. Skin complications are correlated to the total dose administered and occur at doses exceeding 200 mg.

Kiefer (6) reported a cutaneous toxicity frequency of 88% in 18 patients, occurring at total doses between 200 and 300 mg. Alopecia and exanthema are the most frequent symptoms, but hyperkeratosis and erythema of the hands, stomatitis and ulceration on the knees have also been described. Blum et al. (1) reported a skin affectation incidence of 70% at total doses exceeding 500 mg, including stomatitis, hyperpigmentations of the pressure areas of the skin, oedema and erythema of the extremities, especially hands and feet. These types of skin reaction are described in many reports. In two investigations the skin changes were also examined histologically (3, 6). Kiefer found hyperkeratosis and slight acanthosis but otherwise no significant changes in epidermis or dermis. Cohen described epidermal acanthosis with focal atypia and a few cells with individual cell keratinization, and dense collagen with areas of homogenization of the dermis. In our material we found quite remarkable microscopical changes, especially in the epidermis. The intention of this report is to illustrate the morphology.

MATERIAL

The series consisted of 8 patients, 7 with squamous cell carcinoma and one patient with mycosis fungoides who

Fig. 1. Blue-red painful nodules on the buttocks after 210 mg bleomycin (patient no. VIII).

Table I. *Symptoms after Bleomycin therapy in eight patients*

Patients		Diagnosis	Bleomycin dosage at first appearance of symptoms	Total dose Bleomycin (mg)	Symptoms
I	72 yrs ♂	SCC[a] of the mouth	30	60	Painful red infiltrations on elbows and neck
II	64 yrs ♂	SCC of the tongue	240	300	Erythema and painful infiltrations on elbows
III	71 yrs ♂	SCC of lung	180	300	Painful red infiltrations on elbows, swelling and erythema of palms with vesicules
IV	75 yrs ♀	SCC of mouth	105	105	Erythema and infiltrations on knees and elbows, swelling of palms and face
V	63 yrs ♂	Metastasis of SCC	285	315	Erythema and infiltrations on elbows, neck and face
VI	46 yrs ♀	Mycosis fung.	105	240	Pustulation on the back, ulceration around eyes, mouth and genital region
VII	50 yrs ♀	SCC of skin	150	300	Erythema and painful infiltrations on elbows; swelling of fingerjoints
VIII	58 yrs ♂	SCC of esophagus	210	300	Painful, blue-red infiltrations on the buttocks and swelling of palms

[a] SCC=squamous cell carcinoma.

developed skin reactions during the therapy. They were given 15 mg bleomycin i.m. 5 days a week, with an intended total dose of 300 mg.

The side effects were seen at doses between 30 and 205 mg, consisting of erythema and painful infiltrations in the skin on the elbows and knees (in 2 patients also on the neck and face), swelling of the palms with vesiculation, and in one patient painful blue-red nodules on the buttocks (Fig. 1). One patient developed ulcerations around the eyes, mouth and genital region, pustulation on the skin of the back, and high fever (Table I). In 3 of the patients the therapy was discontinued because of the skin complications. In all cases the skin reactions disappeared completely within 2 months.

Fig. 2. Punch biopsy of erythematous skin lesion on the elbow after 150 mg bleomycin. Increasing degeneration of epidermal cells with an area of complete necrosis and ulceration. Moderate lymphocytic infiltration of the dermis (patient no. VII).

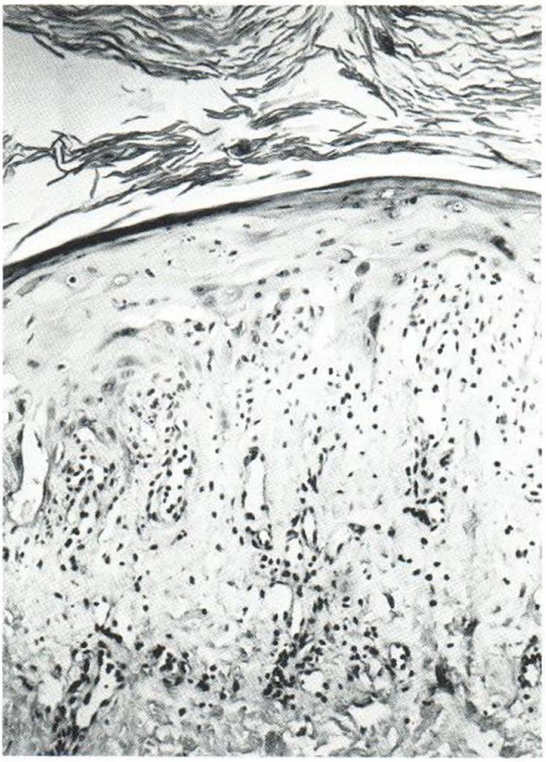

Fig. 3. Degenerative changes of the epidermal cells of all layers and hyperkeratosis. In contrast, the dermal changes are non-conspicuous with only scattered lymphocytes and dilated capillaries (patient no. VIII).

Histopathological study

Punch biopsies were taken from central and peripheral areas of skin lesions for fixation in neutral formaldehyde solution and staining with H & E.

The main changes were found in the epidermis, varying from slight cell degeneration, to complete lysis resulting in central necrosis and ulceration (Figs. 2, 3, 4). These findings were not directly correlated to the dermal changes of oedema, perivascular infiltration of lymphocytes, and increased number of capillaries. Total necrosis of the epidermal cells could be found even where the dermis failed to show any considerable damage. Thus, morphologically, the epithelial cells of the epidermis seemed to be the target cells, the stromal changes being mainly secondary to the epidermal changes.

DISCUSSION

In experimental studies, bleomycin has been found to concentrate in the skin. The best cytostatic effect is found in squamous cell carcinoma of the skin and mucous membranes. The highest incidence of side effects is also reported to involve the skin, where a great variety of skin changes are seen. In our material the skin changes were all of the same type, namely painful red infiltrations on the elbows and swelling and erythema of the palms but mostly also on the knees. Remarkably enough, we saw no ulcerations, even when the biopsy showed degeneration of the epidermal cells until complete necrosis. The morphological changes are essentially the same as those encountered in areas having been irradiated with "tumour dosages". These typical epidermal changes have not been described before. No explanation can be given as to why especially the elbows, knees and palms are affected. There was nothing remarkable in biopsies from grossly unaffected skin. In this series there was no correlation between the degree and extent of the skin lesions and the effect of the drug on the malignant lesions.

REFERENCES

1. Blum, R., Carter, S. & Agre, K.: A clinical review of bleomycin, a new antineoplastic agent. Cancer *31*: 903, 1973.

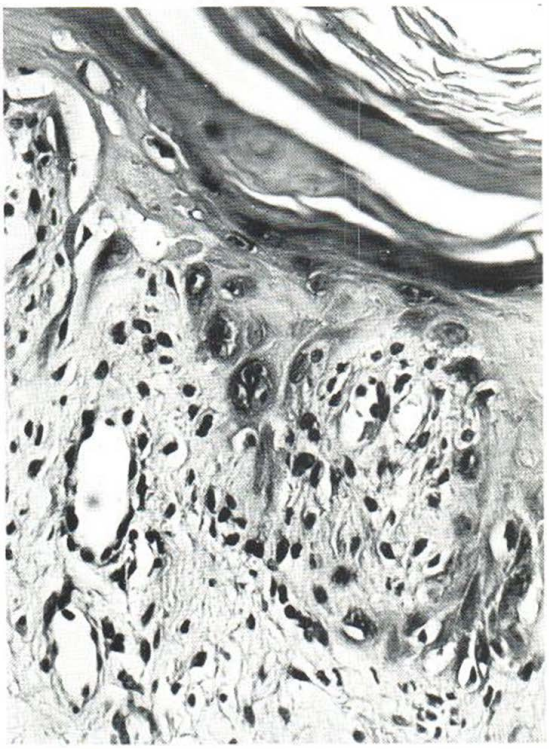

Fig. 4. Detail of epidermis showing advanced degeneration of the epithelial cells, some of which are in complete lysis. The hyperkeratosis is obvious (patient no. VII).

2. Christensen, L.: Bleomycin, ein neues Antitumor-Antibiotikum zur Behandlung neoplastischer Krankheiten. Wien Klin Wschr *84:* 737, 1972.
3. Cohen, I., Mosher, M., O'Keefe, E., Klaus, S. & De Conti, R.: Cutaneous toxicity of bleomycin therapy. Arch Dermatol *107*: 553, 1973.
4. Ichikawa, T., Matsuda, A., Miyamoto, K., Masatoshi, T., Kaihara, T., Sakamoto, K. & Umezawa, H.: Biological studies on bleomycin A. J Antibiot (ser A) *20*: 149, 1967.
5. Ishizuka, M., Takayama, H. Takeuchi, T. & Umezawa, H.: Activity and toxicity of bleomycin. J Antibiot (ser A) *20*: 15, 1967.
6. Kiefer, O.: Über die Nebenwirkungen der Bleomycintherapie auf der Haut. Dermatologica *146:* 229, 1973.
7. Mishima, Y. & Matunaka, M.: Effect of bleomycin on benign and malignant cutaneous tumors. Acta Dermatovener (Stockholm) *52*: 211, 1972.
8. Pfister, R., Theissing, G. & Völter, D.: Die antibiotische Behandlung maligner epithelialer Tumoren der Haut mit Bleomycin. Fortschr Med *89:* 583, 1971.
9. Sachidananda, S., Slayton, R., Wolter, J., Perlia, C. & Taylor, S.: Clinical study with bleomycin. Cancer *28*: 1142, 1971.
10. Spigel, S. & Coltman, C.: Therapy of mycosis fungoides with bleomycin. Cancer *32*: 767, 1973.
11. Takeda, K., Sagawa, Y. & Arakawa, T.: Therapeutic effect of bleomycin for skin tumors. Gann *61*: 207, 1970.
12. Umezawa, H., Ishizuki, M., Maeda, K. & Takeuchi, T.: Studies on bleomycin. Cancer *20*: 891, 1967.

Received May 15, 1975

Y. Werner, M.D.
Department of Dermatology
Södersjukhuset
S-100 65 Stockholm
Sweden