CASE REPORT

Bleomycin-induced flagellate dermatitis

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SUMMARY

Flagellate dermatitis shows very characteristic lesions: linear erythema or hyperpigmentation in various areas of the skin. It is a side effect of bleomycin, an immunosuppressive drug used for several types of cancers. All physicians must be aware of this disease so they can make a rapid diagnosis and interrupt the causative agent. Our patient presented during chemotherapy for a Hodgkin's lymphoma pruritic, erythematous lesions on the lower limbs and the back diagnosed as flagellate dermatitis due to bleomycin.

BACKGROUND

Flagellate dermatitis, erythema or hyperpigmentation is a cutaneous side effect of bleomycin or its derivative peplomycin. The term 'flagellate' derives from the Latin *flagellum*, referring to the characteristic whip-like appearance. It is also rarely associated with ingestion of shiitake mushrooms, dermatomyositis and adult-onset Still's disease.

Bleomycin sulfate is a cytostatic antibiotic extensively used in cancer therapy. The substance is derived from *Streptomyces verticillus*, and its potential as an antitumour drug was described by Umezawa in 1965.¹

Bleomycin consists of cytotoxic glycopeptides, which function as mininucleases. After binding to DNA, single-strand and double-strand breaks are produced due to the formation of an activated oxygen complex. Bleomycin is effective against several human cancers, in particular lymphomas, testicular and ovarian germ cell tumours and squamous cell carcinomas.²⁻³

If side effects occur, they are preferably seen on the skin and in the lungs. On one hand, the cutaneous and mucosal toxicity of bleomycin includes alterations commonly observed after treatment with other chemotherapeutics, for example, alopecia, stomatitis and nail changes. On the other hand, less common but more characteristic skin findings have been described in the course of bleomycin treatment. Among those are the development of painful inflammatory nodules on the fingers, warty hyperkeratotic plaques on the knees and elbows, digital gangrene, blisters, infiltrated violaceous plaques and hyperpigmentation that may be diffuse, patched or flagellated.³⁻⁷

To date a number of cases with bleomycin-induced flagellate erythema have been reported.⁸⁻²⁶ Additionally, an unusual case of reticular and linear hyperpigmentation has been reported.²⁷ Some studies have shown an incidence rate of 8–66% in patients treated with bleomycin.⁴

CASE PRESENTATION

A patient in her 40 s was undergoing chemotherapy with adriamycin, vinblastine, dacarbazine and bleomycin, due to a Hodgkin's lymphoma.

She presented for the evaluation of pruritic, erythematous lesions on the lower limbs and the back. Old lesions evolved with hyperpigmentation while new lesions appeared.

On examination, light-brown macules, with a distinct linear aspect, could be seen on the legs, ankles and on the upper back (figures 1–3).

INVESTIGATIONS

The diagnosis is made by the clinical picture during the administration of bleomycin, and also by the disappearance of the lesions after medication suspension.

DIFFERENTIAL DIAGNOSIS

The lesions associated with use of bleomycin are very characteristic but in an initial view without any patient's history some diagnosis that may be supposed as scabies, dermatographism, dermatitis factitia, among others.

TREATMENT

No treatment is necessary since the lesions usually disappear when the administration of bleomycin is stopped.

OUTCOME AND FOLLOW-UP

Lesions disappeared with the suspension of the medication.

DISCUSSION

Bleomycin is a cytostatic, antineoplastic antibiotic that inhibits the incorporation of thymidine into DNA and is widely distributed throughout the

Figure 1 Linear hyperpigmented lesions on the upper back.

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Figure 2 Detail of the right shoulder in figure 1.

body. It has to be pointed out, however, that most human cancers are resistant to bleomycin and, unfortunately, in those which are initially sensitive, the development of resistance to the drug during therapy is frequently observed.^{2 3}

Hydrolase inactivates bleomycin in all organs except the skin and the lungs. This is considered to be the reason why most side effects of bleomycin preferably manifest in these organs.¹⁹

Beside cutaneous side effects common to other chemotherapeutic agents, the spectrum of skin alterations induced by bleomycin also includes less commonly observed but highly characteristic cutaneous manifestations, in particular the occurrence of linear or flagellate erythema and hyperpigmentation that, to date, has not been reported from any other chemotherapeutic regimen.^{2-7 12 28}

Thus, these cutaneous side effects seem to be specific for bleomycin exclusively. The so-called flagellate erythema after bleomycin therapy was originally described by Moulin *et al*²⁸ in 1970 as bleomycin-induced linear hyperpigmentation.⁶

It is considered that the reaction is dose-dependent and usually occurs in total doses above 100 U and often higher than 200 U. In contrast, it has been reported after small doses as low as 14–15 U.^{14-16 19 26} Interestingly, in some patients, these characteristic skin symptoms can even develop when bleomycin was administered for purposes of scintigraphy^{7 15} using doses as low as 15 mg, which equals 15 U.¹⁵

Although the typical routes of administration are intravenous and intramuscular, intrapleural,^{8 9 17 25} intraperitoneal²⁰ and intracutaneous²⁶ injections can also induce flagellate erythema. It is supposed to be caused by a microtrauma, such as scratching, which causes the drug to leak out of the blood vessels;

Figure 3 Light-brown macules, with a distinct linear aspect, on the thigh.

however, some patients lack itching. Thus, its precise mechanism remains uncertain.

Patch tests with bleomycin are negative, but flagellate erythema may recur on a rechallenge.¹⁹ A peculiar heat-induced recall phenomenon has been reported, which showed recurrence of reticular hyperpigmentation in the area of the heating pad applied after a few months of stoppage of bleomycin owing to linear hyperpigmentation.²⁹ This phenomenon may be explained by the previous observations that hyperthermia enhances the toxicity of bleomycin.³⁰

The time span between administration of the drug and onset of clinical symptoms usually varies between 1 day and 9 weeks.^{3 4 12 28} The rash usually subsides 3–4 months following discontinuation of the drug.

The typical clinical symptoms consist of pruritic linear pigmented lesions arranged in a flagellate pattern, mainly occurring on the thorax and back. Likewise, linear urticarial lesions have been described to precede the stage of pigmentation.^{6 11}

In the acute phase, the histopathological findings in flagellate dermatitis share similarities with those observed in fixed drug eruption. These include vacuolisation in the basal layer of the epidermis, melanin incontinence and scattered dyskeratotic keratinocytes.¹⁹

In later stages of the cutaneous eruption, merely postinflammatory changes are observed.¹²

Analysis of electron microscopy demonstrated increased melanogenesis within the melanocytes and many melanosomal complexes in the surrounding keratinocytes,^{8 27 31} and the presence of intracytoplasmic vacuoles in the epidermis that probably resulted from damage to mitochondria.²⁷

To date, different hypotheses have been postulated to explain this uncommon cutaneous side effect of bleomycin. Histological and ultrastructural studies indicated that bleomycin reduced the epidermal turnover, resulting in a prolonged contact between melanocytes and keratinocytes. Polla *et al*⁷ found spongiosis mainly localised in the basal layer of the epidermis together with a perivascular infiltrate consisting of lymphocytes and neutrophil granulocytes as well as pigmentary incontinence.

These authors postulated that the hyperpigmentation is rather postinflammatory than a primary sign. Lindae *et al*¹¹ observed histological similarity to the findings in fixed drug eruption and, thus, suggested that the absence of hydrolase leads to an accumulation of bleomycin, which is associated with an inflammatory dermal infiltrate.

Apart from ceasing administration of the drug, no treatment is available for bleomycin-induced flagellate dermatitis. Treatment includes topical or systemic corticosteroids and oral antihistamines. The length of treatment depends on clinical response. Although the eruption is self-limiting and usually clears within 6–8 months, it can reoccur with even increased intensity after new treatment with bleomycin.^{19 24}

Learning points

- ▶ Adverse reaction of bleomycin has to be suspected in cases of sudden onset of linear lesions of erythema or hyperpigmentation in several areas of the skin.
- ▶ In these cases of flagellate dermatitis, questions about cancer and its therapy, use of immunosuppressive drugs, in particular bleomycin, have to be asked by the dermatologist.
- ▶ All physicians must be aware of this type of adverse event induced by bleomycin so they can suspend the drug fast after the onset of this collateral reaction.

Contributors All authors have contributed significantly for the collection of data about the patient, the drug and for the preparation of the manuscript.

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