Flagellate dermatitis in a patient with testicular germ cell neoplasia on bleomycin

Konstantina Mavridou,[1] Aggeliki Karakasi,[1] Evangeli Lampri,[2] George Gaitanis,[1,3] Ioannis D. Bassukas[3]

[1]Department of Dermatology, University Hospital of Ioannina; [2]Department of Pathology and [3]Department of Skin and Venereal Diseases, Faculty of Medicine, School of Health Sciences, University of Ioannina, Ioannina, Greece

Abstract

Bleomycin, an antineoplastic antibiotic that inhibits DNA synthesis, is used to treat various malignant tumors such as Hodgkin's lymphoma, squamous cell carcinoma, and germ cell tumors. Flagellate erythema is a rare rash with a linear pattern that has been observed in association with bleomycin treatment. Herein, we present a 43-year-old patient with metastatic testicular cell neoplasms who developed a whiplash rash during treatment with a chemotherapy regimen that included bleomycin. A typical case of bleomycin-related flagellate dermatitis has been diagnosed and the main features of this characteristic adverse drug event are briefly discussed.

Correspondence: Konstantina Mavridou, Department of Skin and Venereal Diseases, Faculty of Medicine, School of Health Sciences, University of Ioannina, University Campus, GR45110 Ioannina, Greece.
Tel.: +30.2651099721.
E-mail: mavridounantia@gmail.com

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Introduction

Cutaneous adverse drug events related to treatment with bleomycin are frequent and vary from common eruptions, such as erythema and urticaria to fewer common conditions, like onycholysis, Steven-Johnson syndrome and flagellate dermatitis.[1] Flagellate dermatitis, a rare, patterned skin eruption characterized by erythematous patches and papules that merge to multiple linear and whip-like hyperpigmented streaks,[1] was originally described in 1970 by Moulin *et al.* as a characteristic *bleomycin-induced linear hyperpigmentation*.[2] Since then, however, similarly patterned rashes have been linked to a variety of other causes, including consumption of Shiitake mushrooms and treatment with chemotherapy drugs other than bleomycin, such as docexatel. Moreover, *flagellate* eruptions have been also described independently of an exogenous eliciting factor in association with different clinical entities like adult-onset Still's disease, phytophotodermatitis, factitious dermatitis, dermographism and dermatomyositis.[1-4] Herein, we report the *classical* case of a 43-year-old patient with metastatic testicular germ cell neoplasia (GCN), who developed a whiplash-like rash while treated with a chemotherapy regimen including bleomycin and discuss the management of this alarming side effect manifestation of certain oncological treatments.

Case Report

A 43-year-old patient under chemotherapy with the BEP scheme [bleomycin 30 units (16 units/m^2)] i.v. on days 1, 8 and 15, etoposide 100 mg/m^2 i.v. on days 1-5 and cisplatin 20 mg/m^2 i.v. on days 1-5, per treatment cycle) for a metastatic testicular GCN, stage IIIb (pTisN3M0S2) was referred to the Dermatology Department for the evaluation of a pruritic rash on the chest, back, upper limbs, left thigh and neck (Figure 1). The patient, currently on the 3rd cycle of his treatment, reported that he had noticed this rash already after the first cycle of chemotherapy (corresponding to onset of the rush after a cumulative bleomycin dose of 90 units or about 50 units/m^2 body surface). The physical examination revealed linearly arranged, pigmented papules, and elongated, cordlike plaques that confluenced to form a *whip-like* eruption pattern (Figure 1). There was no evidence of nail or mucosal involvement, and he did not suffer of arthritis, fever, or muscle weakness. His medical history did not reveal atopy, allergies, immunological disorders, consumption of Shiitaki mushrooms, or conditions of self-injury.

A lesional skin biopsy showed under mild acanthosis and hyperkeratosis, a relatively prominent, peri-vascularly aggregated, eosinophils-enriched lympho-histiocytic infiltrate, which spanned the entire dermis and focally extended down to the layer of the subcutaneous fat (Figure 2), histopathology findings suggestive of a drug eruption. Taking the chemotherapy history and the clinical and histopathological findings together, a bleomycin-induced flagellate dermatitis was diagnosed.

Based on cost-benefit considerations, and in line with the chemotherapy protocol, the BEP scheme was continued until completion of 4 treatment cycles. For the management of the eruption the patient was given antihistamines (levocetirizine dihydrochloride twice a day) and topical corticosteroids (mometasone furoate twice daily). The skin lesions did not worsen further and resolved one month after the last bleomycin dose. Notably, withdrawal of bleomycin during the last, 4th cycle and continuing with only cisplatin and etoposide was discussed; however, the cutaneous adverse reaction was staged as mild, and the antineoplastic treatment was completed as planned.

Discussion

Herewith we presented a typical case of a bleomycin-induced flagellate dermatitis in a patient treated with the BEP chemotherapy scheme for a metastatic testicular germ cell neoplasia. Notably, in the present case the causative role of bleomycin is further supported by the highest degree of association (probable) for bleomycin among all used drugs according to both the Naranjo Probability Scale (score 7) and the WHO-UMC causality criteria.[5] Flagellate dermatitis is a well-characterized cutaneous adverse drug reaction to bleomycin,[1,3,6-9] that may affect in a rather dosage independent pattern, up to 20% of bleomycin-treated patients.[6] As also in this case, the eruption usually begins as urticarial pruritic lesions on the back and thorax which rapidly progress into multiple, linearly arranged, hyperpigmented papules and plaques.[7]

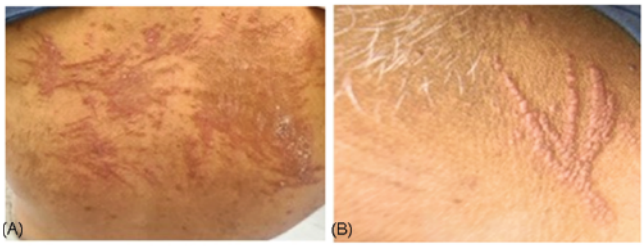

Figure 1. Linearly arranged pigmented papules on (**A**) back, and (**B**) neck.

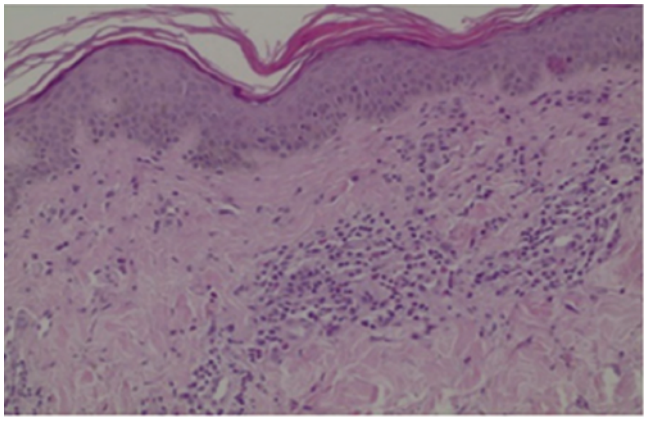

Figure 2. Flagellate dermatitis lesional skin biopsy (neck): A perivascularly attenuated inflammatory dermal infiltrate with prominent eosinophils admixture under an orthohyperkeratotic, slightly acanthotic, hyperpigmented epidermis (Hematoxylin & Eosin; initial magnification: 200x).

Considering the pathophysiological mechanism of flagellate dermatitis, it is widely accepted that the eruption is triggered by bleomycin accumulation in the skin. After i.v. administration, approximately 50% of the injected bleomycin is excreted unchanged in the urine, while most of the remaining is inactivated in various tissues by a hydrolase enzyme (bleomycin hydrolase). However, this enzyme is not present in the skin and the lungs, with the consequence that the drug is accumulated in these organs provoking tissue specific cutaneous and pulmonary toxicities (dermatitis and pneumonitis).[6,10] In the skin, the accumulation of the drug is regarded to elicit pruritus, which by triggering excoriations and skin microtraumas results into enhanced blood flow in the affected skin areas, which in turn intensifies local bleomycin delivery and deposition. In this way, a pathogenic vicious cycle is established, which perpetuates the accumulation of the drug in the skin so-long the treatment with bleomycin continues. Decisive for the translation of the drug accumulation into cutaneous inflammation and enhanced pigmentation is thought to be the ability of bleomycin to harm endothelial cells through the upregulation of transforming growth factor-beta (TGF-β), heralding apoptosis of keratinocytes and cytotoxic effects on melanocytes.[1,8,11] In addition, melanogenesis is induced, either by direct pharmacologic stimulation of the melanocytes or indirectly through mediators released by the adjacent keratinocytes.[6] The bleomycin-induced flagellate dermatitis was initially considered a dose-dependent skin condition.[9] Meanwhile, many case reports have demonstrated that this adverse event may emerge after cumulative bleomycin doses, varying widely between 5 IU and 465 IU.[1,9,12] Accordingly, the lesions may appear as early as 24 hours to up to six months after first bleomycin dose administration.[9] In the present case, the lesions begun about one month after the onset of the BEP chemotherapy scheme.

The histopathological findings of flagellate dermatitis include hyperkeratosis, parakeratosis, inconspicuous spongiosis, vacuolization in the *stratum basale* of the epidermis, and sometimes lymphocytic vasculitis. In the acute phase of the eruption plentiful neutrophils and eosinophils are admixed to the lympho-monocytic inflammatory skin infiltrate. Later, as the lesions mature, only a few inconspicuous post inflammatory tissue changes are found in biopsy specimens.[13] Altogether, there are no diagnostic histopathological hallmarks for the differentiation of bleomycin-induced flagellate dermatitis from other drug eruptions.

As a rule, the lesions of bleomycin-induced flagellate dermatitis are self-limited and resolve gradually six to eight months after drug discontinuation, leaving longer persisting hyperpigmentation of the affected areas. However, regardless of any bleomycin re-exposure, flagellate dermatitis can flair again with various stimuli, notably heat exposure, in the previously affected skin areas, even months after discontinuation of bleomycin administration.[9]

In the international literature, an individualized approach to the clinical management of patients with bleomycin-induced flagellate dermatitis is favored. Discontinuation of bleomycin is recommended only in patients with particularly severe skin symptoms and when adequate chemotherapy alternatives are available.[14] In most cases, however, continuation of bleomycin treat-

ment is recommended for as long as necessary to complete the antineoplastic regimen, with adjuvant oral or topical corticosteroids and antihistamines to adequately control skin symptoms.

Conclusions

In conclusion, we reported the typical case of a bleomycin - induced flagellate dermatitis which evolved in a patient with metastatic testicular GCN in the framework of a BEP scheme therapy after a cumulative bleomycin dose of 90 IU. In the present case, bleomycin was not discontinued, and the patient received adjuvant treatment to cope with the associated cutaneous symptoms during bleomycin treatment. The eruption resolved after the bleomycin-including chemotherapy scheme was completed.

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