Bleomycin-induced skin toxicity: a case of flagellate dermatitis.

Monique Pretorius[1] MBChB, Ilana Steenkamp[1] MBChB FCDerm, Leana Spies[2] MBChB Dip Pall Med MPhil Pall Med, Gerhard van der Linde[3] MBChB MMed (Anat Path)

Affiliations: [1]Department of Dermatology, Department of Oncology, Northern Cape, Robert Mangaliso Sobukwe Hospital, Kimberley, Northern Cape, South Africa, [2]Department of Oncology, Northern Cape, Robert Mangaliso Sobukwe Hospital, Kimberley, Northern Cape, South Africa, [3]Anatomical Pathology, Lancet Laboratories, Kimberley, Northern Cape, South Africa

Corresponding Author: Monique Pretorius, MBChB, Medical Officer, Department of Dermatology, Robert Mangaliso Sobukwe Hospital, 114 – 148 Du Toitspan Road, Kimberley, Northern Cape 8301, Tel: 27-053 802 9111, Email: monique.visser2x@gmail.com

Abstract

Bleomycin, an antineoplastic, glycopeptide antibiotic is commonly used to treat several malignancies, in particular, lymphomas, testicular carcinoma, and squamous cell carcinoma. As bleomycin degradation by enzyme hydrolase is less in the skin and lungs, a higher likelihood of cutaneous toxicity exists. We present a case of bleomycin-induced flagellate dermatitis, a characteristic cutaneous eruption that occurred as a result of bleomycin administration. A 58-year-old man with Stage 4 diffuse large B-cell lymphoma presented with sudden onset of skin lesions that appeared five weeks after initiation of third-line bleomycin-containing palliative chemotherapy. The whip-like, linear, hyperpigmented plaques were indicative of flagellate dermatitis. We aim to present the natural course of bleomycin flagellate dermatitis and its natural course.

Keywords: bleomycin, cutaneous eruption, flagellate dermatitis, large B-cell lymphoma

Introduction

Drug eruptions are an important component of clinical dermatology. The mucocutaneous side-effects of bleomycin are well described in the literature. Flagellate and diffuse hyperpigmentation are pigmentary changes associated with bleomycin use [1-7]. Mucosal side-effects include stomatitis and buccal ulceration [1-3,6]. Adnexal structures such as hair and nails can be involved in the form of alopecia and nail-bed changes [1-6,8]. Vascular toxicity such as Raynaud phenomenon, sclerodermoid changes, and digital gangrene can occur [1,3-6,8]. Notwithstanding the fact that most cancers are resistant to bleomycin and its toxicity has been well described [1], bleomycin still forms part of many current chemotherapy regimens [4]. In this case report we review a case of flagellate dermatitis, a characteristic cutaneous eruption that was triggered by bleomycin.

Case Synopsis

A 58-year-old man presented to the department of general surgery at Robert Mangaliso Sobukwe Hospital with upper gastro-intestinal bleeding, anemia, and a palpable abdominal mass. A gastric biopsy was performed in March 2019 and revealed a diagnosis of diffuse large B-cell lymphoma (CD20 positive). Further diagnostic work-up showed Stage four disease. Rituximab 375mg/m^2 IV day one (D1), cyclophosphamide 750mg/m^2 IV D1, doxorubicin 50mg/m^2 IV D1, vincristine 1.4mg/m^2 IV D1, prednisone 100mg PO daily D1-D5 (R-CHOP) chemotherapy regimen was initiated in April 2019. The patient received a total of seven cycles after which chemotherapy was terminated because of poor cardiac function (left ventricular ejection fraction 44%). A repeat computerized tomography scan showed residual disease and second-line

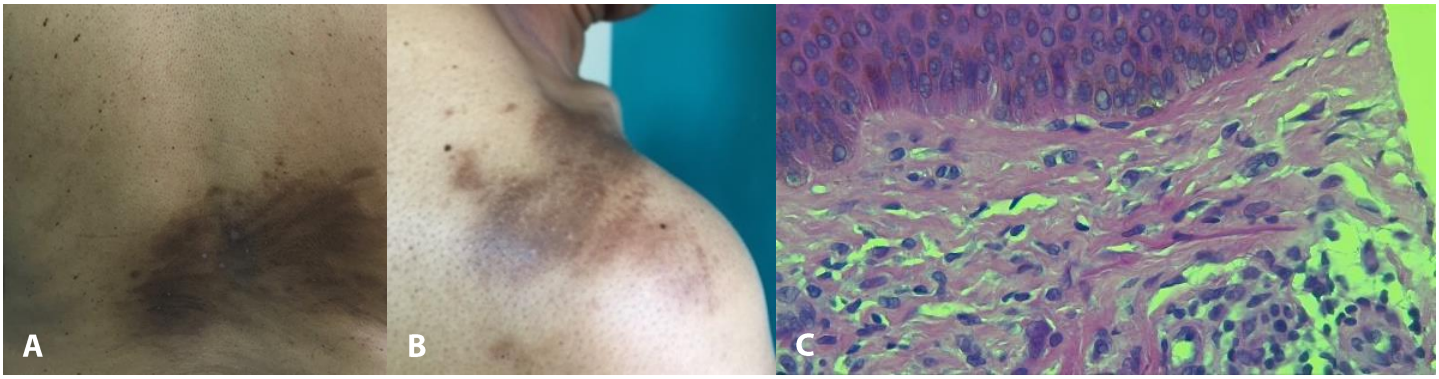

Figure 1. ***A, B)*** *Hyperpigmented flagellate plaques.* ***C)*** *Biopsy specimen. Hydropic degeneration at the dermoepidermal junction. H&E, 10×.*

chemotherapy was planned. Owing to severe neutropenia, the decision was made to initiate weekly bleomycin 10mg/m^2 IV D1, vincristine 1.4mg/m^2 IV D1, and prednisone 100mg PO D1,3,5 (BOP) chemotherapy.

Five weeks after initiation of BOP chemotherapy, the patient was referred to the dermatology department with a history of sudden onset of skin lesions. He reported pruritic skin lesions on his body and scalp with an initial parallel, erythematous, and linear appearance that changed to a darker color over 24 hours. He reported no systemic symptoms such as fever or muscle weakness. Apart from the chemotherapy drugs, no other drug history including alternative or over-the-counter medication was evident. He denied the ingestion of shiitaki mushrooms.

On physical examination multiple areas of hyperpigmented, linear plaques with excoriations were noted on the torso, upper extremities, and scalp. (**Figure 1**)

A skin biopsy was performed and revealed a relatively atrophic epidermis with focal areas of basal cell hydropic degeneration (**Figure 1C**) and cytoid body formation. The basement membrane appeared thickened and the dermis showed a polymorphic perivascular inflammatory infiltrate comprising of lymphocytes, histiocytes, and sporadic eosinophils. Pigmentary incontinence was noted in the dermis.

In addition to the diagnosis of flagellate dermatitis, the patient developed chemotherapy-induced bone marrow suppression. Subsequently, the bleomycin-containing chemotherapy regimen was stopped as per patient preference. Thereafter, the acute reaction resolved over a 12-week period with complete resolution of pruritis and excoriations. At a 13-month follow-up visit, post-inflammatory hyperpigmentation persisted, but showed significant improvement. (**Figure 2**).

Case Discussion

Flagellate dermatitis refers to cutaneous lesions with a characteristic whip-like appearance caused by the following antineoplastic and targeted therapies: bleomycin, peplomycin, docetaxel, doxorubicin, cisplatin, bendamustine, and trastuzumab. Other causes include adult-onset Still disease, dermatomyositis, ingestion of undercooked shiitake mushrooms, and human immunodeficiency virus with hypereosinophilic syndrome [1,4,6,7,9-13]. Furthermore, mycoplasma pneumonia-induced rash and mucositis has also been associated with flagellate dermatitis [11].

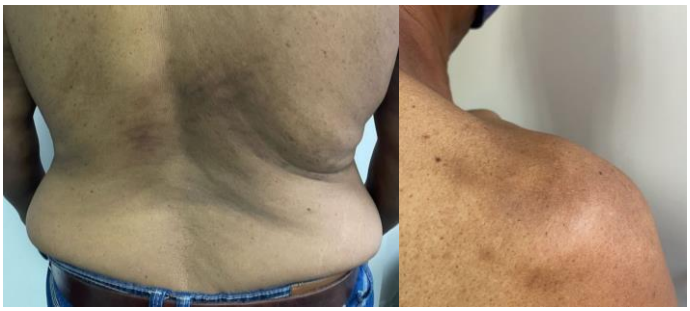

Figure 2. *Visible improvement in flagellate hyperpigmentation at 13-month follow-up.*

Table 1. *Clinical and histological features of bleomycin-induced flagellate dermatitis [1].*

History	Follows bleomycin administration
Symptoms	Pruritis
Onset	1 day to 9 weeks
Physical examination	Linear, whip-like, erythematous plaques, hyperpigmentation
Histology	Acute phase: Vacuolization at the dermoepidermal junction, melanin incontinence, scattered dyskeratotic keratinocytes Late phase: post-inflammatory hyperpigmentation

Bleomycin is a cytotoxic antibiotic used in oncology for the treatment of Hodgkin lymphoma, squamous cell carcinoma, and germ cell tumors. It is also used for sclerosis of pleural effusions [1-7]. It is isolated from the soil fungus *Streptomyces verticillus* [1-4,7,8,12]. In low doses it inhibits mitosis and at higher concentrations blocks DNA uptake of thymidine in the synthesis phase of the cell cycle [2,3,5,6,8,12]. It is metabolized by the enzyme bleomycin hydrolase that is deficient in the lung and skin. This results in increased concentrations and may explain predominant adverse reactions in these tissues [1-9,12].

An incidence of 8-22% of flagellate dermatitis has been reported in patients treated with bleomycin [2,4,6-8,10]. Bleomycin-induced flagellate dermatitis is largely independent of the dose and route of administration of bleomycin [2,4-8,10]. It commonly occurs after cumulative doses of 100-300mg of bleomycin [1,3,8]. Nonetheless, it can occur at doses as low as 14-15 units [1,3,5,8]. Lesions start as pruritic, linear, erythematous, urticarial plaques and later hyperpigmentation [1-12]. There seems to be no specific distribution pattern [4,5,7]. Onset of the characteristic lesions can occur between one day to nine weeks after bleomycin administration [1,2,4,5,7-9,13].

The pathogenesis of flagellate dermatitis remains unknown but theories such as fixed drug eruption, micro-trauma such as scratching, increased melanogenesis, heat recall, and reduced epidermal turnover allowing prolonged melanocyte and keratinocyte contact, have been described [1-9,12]. The histopathology is non-specific and depends on the stage of the disease. Vacuolization at the dermoepidermal junction, melanin incontinence, and scattered dyskeratotic keratinocytes are seen in the acute phase. Post-inflammatory changes can be found in the later stages [1-3,7-9]. Other findings include perivascular infiltrate consisting of lymphocyte and neutrophil granulocytes [1,7-9]. The clinical and histological characteristics of bleomycin-induced flagellate dermatitis are summarized in **Table 1**.

Flagellate dermatitis is usually self-limiting and may last several weeks-to-months provided that the use of bleomycin has been terminated [1–10]. Permanent hyperpigmentation in affected areas can occur [5]. In some cases oral antihistamines, topical corticosteroids and oral corticosteroids are required [1,2,4–8,10,12]. Applying heat to previously affected areas can lead to the recurrence of flagellate lesions known as heat-induced recall [1,7]. Cooling prior to chemotherapy can be used as a preventative measure [4,7]. However, a subsequent decrease in perfusion can lead to a reduction in drug exposure [14,15]. Cooling is contraindicated in patients with extensive hematological malignancies when curative chemotherapy is used [15].

Conclusion

This case report highlights the importance of knowledge regarding adverse drug-induced skin reactions and in particular that of bleomycin. Withdrawal of bleomycin will lead to improvement in most cases of bleomycin-induced flagellate dermatitis. Our case report is unique as it illustrates the clinical improvement following cessation of bleomycin.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Grynszpan R, Niemeyer-Corbellini JP, Lopes MS, Ramos-e-Silva M. Bleomycin-induced flagellate dermatitis. *BMJ Case Rep*. 2013; bcr2013009764. [PMID: 23814202].
2. Mota GD, Penna AM, Soares RC, Baiocchi OC. Bleomycin-induced flagellate dermatitis. *Rev Bras Hematol Hemoter*. 2014;36:297-299. [PMID: 25031171].
3. Abess A, Keel DM, Graham BS. Flagellate hyperpigmentation following intralesional bleomycin treatment of verruca plantaris. *Arch Dermato*l. 2003;139:337-339. [PMID: 12622626].
4. Agrawal C, Talwar V, Saini R, Babu P. Flagellate rash: an unusual complication of bleomycin therapy - a case report with brief review of literature. *Indian J Med Paediatr Oncol*. 2017;38:548-551. [PMID: 29333029].
5. Lee HY, Lim KH, Ryu Y, Song SY. Bleomycin-induced flagellate erythema: a case report and review of the literature. *Oncol Lett*. 2014;8:933-935. [PMID: 25009666].
6. Basu D, Podder I, Das A. Bleomycin-induced flagellate hyperpigmentation: a case report with review of literature. *Pigment Int*. 2016;3:40-42. [DOI: 10.4103/2349-5847.184260].
7. Changal KH, Raina H, Changal QH, Raina M. Bleomycin-induced flagellate erythema: a rare and unique drug rash. *West Indian Med J*. 2014;63:807-809. [PMID: 25867573].
8. Boussios S, Moschetta M, McLachlan J, Banerjee S. Bleomycin-induced flagellate erythema in a patient diagnosed with ovarian yolk sac tumor. *Case Rep Oncol Med*. 2015;2015:574708. [PMID: 26798532].
9. Loo HV, Oon HH. Flagellate dermatitis following consumption of shiitake mushroom. *Dermatol Reports*. 2011;3(2):e21. [PMID: 25386273].
10. Imhof RL, Tollefson MM. Bleomycin-induced flagellate dermatitis. *Mayo Clin Proc*. 2019;94:371-372. [PMID: 30711138].
11. Meyer Sauteur PM, Theiler M. Mycoplasma pneumoniae–associated flagellate erythema. *JAAD Case Rep*. 2020;6:1283-1285. [DOI: 10.1016/j.jdcr.2020.09.029].
12. Cohen PR. Trastuzumab-associated flagellate erythema: report in a woman with metastatic breast cancer and review of antineoplastic therapy-induced flagellate dermatoses. *Dermatol Ther (Heidelb)*. 2015;5:253-264. [PMID: 26506993].
13. Cohen PR. Antineoplastic therapy-associated flagellate dermatoses. *Int J Dermatol*. 2017;56:1490-1491. [PMID: 28681544].
14. Munzone E, Bagnardi V, Campennì G et al. Preventing chemotherapy-induced alopecia: a prospective clinical trial on the efficacy and safety of a scalp-cooling system in early breast cancer patients treated with anthracyclines. *Br J Cancer*. 2019;121:325-331. [PMID: 31303642]**.**
15. Grevelman EG, Breed WP. Prevention of chemotherapy-induced hair loss by scalp cooling. *Ann Oncol*. 2005;16:352-358. [PMID: 15642703].