

Bleomycin-induced Flagellate Erythema: A Rare and Unique Drug Rash

KH Chungal¹, H Raina¹, QH Chungal², M Raina¹

ABSTRACT

Bleomycin-induced flagellate erythema is a rare rash associated with the use of the drug. The rash has a characteristic and intermingled lacy appearance as if it has been whipped. Lack of detoxifying enzymes for bleomycin in the skin makes it a vulnerable site for the adverse effects of bleomycin, along with the lungs. We report the case of young girl with germ cell tumour who developed bleomycin-induced flagellate erythema.

Keywords: Bleomycin, exanthema, drug rash

Eritema Flagelado Inducido por Bleomicina: Un Rash Medicamentoso Raro y Único

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RESUMEN

El eritema flagelado inducido por bleomicina es una erupción rara asociada con el uso de este medicamento. La erupción tiene una característica y un aspecto de encajes entretejidos, como producidos con latigazos. La falta de enzimas de desintoxicación debido a la bleomicina en la piel, hace que esta sea un sitio vulnerable frente a los efectos adversos de la bleomicina, al igual que los pulmones. Reportamos el caso de una joven con tumor de células germinales, que desarrolló un eritema flagelado inducido por bleomicina.

Palabras claves: Bleomicina, exantema, rash medicamentoso

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INTRODUCTION

Bleomycin-induced flagellate erythema is a rare rash with a characteristic intermingled lacy appearance. We report the case of a young girl with germ cell tumour who developed bleomycin-induced flagellate erythema.

CASE REPORT

A 10-year old female presented to us with lower abdominal swelling associated with bilateral flank pain. An ultrasonogram showed a large left adnexal mass. Contrast enhanced computed tomography (CT) scan showed a large heterogeneously enhancing left adnexal mass with no hepatic metastasis, ascites, lymphadenopathy or any distant metastasis. Elective laparotomy with left salpingo-oophorectomy with pelvic lymphadenectomy was done. Omentectomy was also done as the growth was found to be adherent to the

omentum. Histopathology was suggestive of a mixed germ cell tumour with metastasis to the omentum. Preoperatively, serum alpha fetoprotein (AFP) was raised (> 2000 ng/mL) and postoperatively it decreased, although not to a significant level.

The patient was started on chemotherapy with BEP (bleomycin, etoposide and cisplatin; bleomycin 30 000 IU IV D1, D8 and D15 and etoposide 100 mg/m² IV D1–D5 and cisplatin 20 mg/m² IV D1–D5; five-day BEP regimen). Three days after receiving the first cycle of chemotherapy, the patient developed a rash on her left upper abdomen, right flank and right hand (Figs. 1–2). The rash began with an itch coinciding with the appearance of red linear streaks. Erythematous, linear, intermingled streaks were formed by rows of adjoining firm papules. There was evidence of dermatographia as well.

With the characteristic appearance of the rash coinciding with the use of bleomycin, a diagnosis of bleomycin-induced flagellate erythema was made. The patient was started on antihistamines and local topical steroids to which she responded well. The pruritus settled

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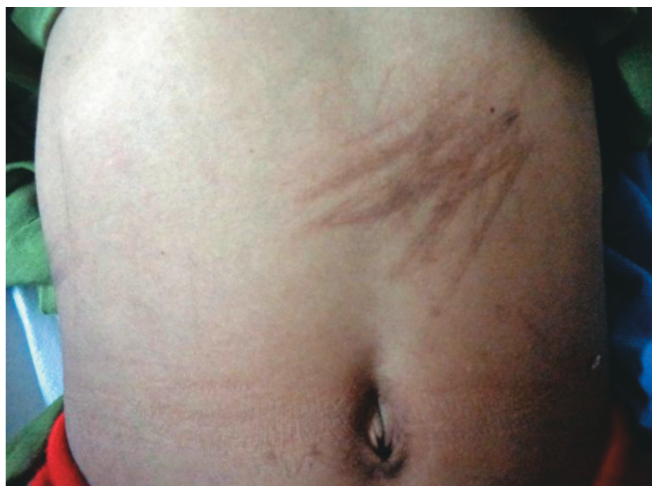


Fig. 1: The rash in the left upper quadrant of the abdomen shows characteristic interlacing flagellate erythema.



Fig. 2: The flagellate rash on the right flank.

and the erythema also decreased but subsequently had post inflammatory hyperpigmentation. As the rash was not severe, bleomycin was continued in subsequent cycles and in the second cycle, there was a slight worsening of the rash. The third cycle of BEP was given without causing any exacerbations of the rash. Heat in an area previously affected by flagellate erythema has been known to cause recurrence, called heat-induced recall. Therefore cooling before chemotherapy administration was used.

To date, the patient has received three cycles of BEP without any severe exacerbations of the rash. Her AFP levels have come down to 200 ng/mL from an initial > 2000 ng/mL and she is also doing clinically well. The patient is planned to receive six cycles of BEP after which her disease extent and response will be reassessed.

DISCUSSION

Bleomycin is an anti-neoplastic antibiotic used most commonly in malignancies like Hodgkin's lymphoma, germ cell

tumours and also for chemical pleurodesis in non-malignant diseases with recurrent pleural effusions. Bleomycin was first discovered in 1966 when the Japanese scientist Hamao Umezawa found anticancer activity while screening culture filtrates of *S. verticillus*. Umezawa published his discovery in 1966 (1). The drug is metabolized by bleomycin hydrolase, but it has been shown to have adverse effects in tissues with relatively low levels of this enzyme, such as the lungs and skin (2, 3). Flagellate dermatitis and subsequent hyperpigmentation in the skin in patients receiving bleomycin has a reported incidence between 8% and 22% (4). The decreased use of bleomycin in clinical practice has made this rash rare. Flagellate erythema was first reported as an adverse effect of bleomycin use in 1970 by Moulin *et al* (5).

In bleomycin-induced flagellate erythema, the patient appears to have been whipped over multiple body areas (6). Erythematous, linear, intermingled streaks are formed by rows of adjoining firm papules (7). There can be evidence of punctuate haemorrhages or pustular lesions. There does not seem to be a characteristic distribution as cases have shown involvement of the face, trunk and extremities. Dermato-graphia is present to a limited extent and the role of scratching in producing the linear shape of the lesions has been debated (7).

Though initially believed to be associated with a cumulative bleomycin dosage, several reports have shown that severe reactions can occur even during the initial doses. Onset of the characteristic lesions can occur anywhere from day one to nine weeks after bleomycin administration (8). This characteristic rash may appear following administration of bleomycin by any route: intravenous, intramuscular and topical, and has been reported even after intrapleural administration of the drug for management of malignant pleural effusion (6). Males and females were found to be equally affected, but in patients developing flagellate dermatitis early (within 72 hours of administration of bleomycin), there was a female preponderance (4).

Ziemer *et al*, in their report, summarized the common histological changes associated with the rash which include inconspicuous epidermal or spongiotic dermatitis, superficial lymphocytic infiltrate with neutrophil and eosinophilic granulocytes, dermal oedema, melanophages in papillary dermis and epidermal hyperpigmentation. Occasionally, necrotic keratinocytes and vacuolar degeneration at dermo-epidermal junction may be discerned. Focal acantholysis and leucocytoclasia are rare histopathological findings (4). Later on, the eruption shows only postinflammatory changes (9). Studies indicate that the number of melanocytes do not increase, although electron microscopy identified increased melanosomes (10).

The plausible mechanisms for this adverse effect include localized increase in melanogenesis, pigmentary incontinence secondary to inflammation, alterations in normal pigmentation patterns and toxic effects of the drug itself, inducing neutrophilic eccrine hidradenitis (11). Flagellate

dermatitis has also been reported in patients receiving other chemotherapeutic agents such as peplomycin, a bleomycin derivative, and docetaxel (12, 13). Flagellate dermatitis can also occur in association with consumption of shiitake mushroom, dermatomyositis, adult-onset Still's disease and infection with human immunodeficiency virus (4, 6).

In most cases, the rash resolves spontaneously. Addressing the symptom of itch is the main treatment measure (14). Treatment with antihistamines and topical and oral corticosteroids may be required (4). Severe rash requires discontinuation of bleomycin (4). Heat in an area previously affected by flagellate erythema has caused recurrence, called heat-induced recall. Therefore cooling before chemotherapy administration might prevent it (15). In our case, the patient had a mild rash which did not warrant the removal of bleomycin from chemotherapy and the patient showed good response to supportive therapy for the rash.

CONCLUSION

Bleomycin-induced flagellate rash is a very rare and unique drug rash. Severe rash may warrant cessation of the drug, but in mild cases the drug can be continued with regular monitoring and precautions. Lack of detoxifying enzymes for bleomycin in the skin makes it a vulnerable site for the adverse effects of bleomycin. These effects may also be seen in the lungs.

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